RESEARCH CENTRE

Inria Saclay Centre

2024 ACTIVITY REPORT

Project-Team SIMBIOTX

SImulations in Medicine, BIOtechnology and ToXicology of multicellular systems

DOMAIN

Digital Health, Biology and Earth

THEME

Modeling and Control for Life Sciences

Inria

Contents

Project-Team SIMBIOTX

Creation of the Project-Team: 2021 March 01

Keywords

Computer sciences and digital sciences

A3.4.1. – Supervised learning

A3.4.8. – Deep learning

A6.1.1. – Continuous Modeling (PDE, ODE)

A6.1.2. – Stochastic Modeling

A6.1.3. – Discrete Modeling (multi-agent, people centered)

A6.1.4. – Multiscale modeling

A6.3.2. – Data assimilation

A6.3.5. – Uncertainty Quantification

A6.5.1. – Solid mechanics

A6.5.2. – Fluid mechanics

A6.5.3. – Transport

Other research topics and application domains

B1.1.7. – Bioinformatics

B1.1.9. – Biomechanics and anatomy

B1.1.10. – Systems and synthetic biology

B2.2. – Physiology and diseases

B2.4.1. – Pharmaco kinetics and dynamics

B2.4.3. – Surgery

B2.6.3. – Biological Imaging

B5.10. – Biotechnology

1 Team members, visitors, external collaborators

Research Scientists

- Dirk Drasdo [Team leader, INRIA, Senior Researcher]
- Irene Vignon Clementel [INRIA, Senior Researcher]

Post-Doctoral Fellows

- Morgane Garreau [INRIA, Post-Doctoral Fellow]
- Marie Haghebaert [INRIA, Post-Doctoral Fellow, from Feb 2024]
- John Hanna [INRIA, Post-Doctoral Fellow, from Feb 2024]
- Roel Meiburg [INRIA, until Nov 2024]
- Jieling Zhao [IFADO, Post-Doctoral Fellow]

PhD Students

- Peter Kottman [INRIA]
- Jerome Kowalski [INRIA]
- Matteo Pedrazzi [INRIA, from Nov 2024]
- Mahdi Rezaei Adariani [UNIV MONTREAL]
- Raoul Salle De Chou [INRIA]
- Francesco Songia [INRIA, from Oct 2024]
- Pavlos Varsos [INRIA]

Technical Staff

- Ramdane Bessaid [INRIA, Engineer]
- Charles Boulitrop [INRIA, Engineer]
- Jules Dichamp [INRIA, Engineer]
- Sylvain Freud [INRIA, Engineer, from Oct 2024]
- Jiri Pesek [INRIA, Engineer]
- Tobias Schnirer-Nedjar [INRIA, Engineer, from Nov 2024]

Interns and Apprentices

- Clemence Finotto [CentraleSupelec, Intern]
- Kevin Hakkakian [AP/HP, Intern, until Oct 2024]
- Matteo Pedrazzi [INRIA, Intern, from Apr 2024 until Aug 2024]
- Maha Sakli [INRIA, Intern, from Mar 2024 until Sep 2024]
- Tobias Schnirer-Nedjar [INRIA, Intern, from Mar 2024 until Sep 2024]
- Francesco Songia [INRIA, from Mar 2024 until Aug 2024]

- Mohamed Ali Srir [INRIA, Intern, until Jan 2024]
- Ana Vlasceanu [CHU Tours, Intern, until Oct 2024]
- Amine Zannane [INRIA, Intern, from Mar 2024 until Sep 2024]

Administrative Assistant

- Anna Dib [INRIA]

External Collaborators

- Nicolas Golse [AP/HP]
- Lorenzo Sala [INRAE]
- Pascalle Wijntjes [UNIV EINDHOVEN]

2 Overall objectives

The overall objective of SIMBIOTX is the implementation of computational models and tools in systems medicine, systems toxicology and systems biotechnology to guide clinical and experimental designs and decisions. As many of the models are very close to their "real" counterpart ("Twins"), and so complex that they need to be implemented on the computer to be studied (translating the models into "digits" on the computer), they are, once they sufficiently display the systems behavior of their real counterpart, very well characterized by "Digital Twin Models" (DTMs) or "virtual twins". One important challenge is the systems behavior at the microscale and at the macroscale scale. In medicine, clinical decisions are still largely guided by clinical experience, as completely standardized workflows and protocols are hampered the complexity of the human body and the variety of patient responses on therapeutic approaches. Moreover, clinicians are partially guided in their decisions by experimental findings in animal models or in vitro systems, while the direct extrapolation from these systems to human is often unclear. Medicine permits acquisition of an increasing amount of data on the individual patient at all levels, which requires correct interpretation and processing to ensure the optimal decisions for each patient are taken. SIMBIOTX attempts to ongoingly adapt its strategy to capture the possible needs and benefits of novel developments on the medical, biological, and biotechnological side. In systems medicine, SIMBIOTX aims at guiding clinical decisions by mathematical models integrating data from multiple sources to inform clinicians and build predictions of possible therapy consequences. Both, models and software generated in that process will pertain to standardization. More specifically, SIMBIOTX aims at better understanding by in-silico modeling how non-invasive imaging reflects the underlying organ architecture, perfusion and function. Systems toxicology aims at grasping the complexity of a substance-system interaction, ideally by direct extrapolation from in vitro toxicological experiments to human toxicity, thereby reducing animal experiments. Biotechnology increasingly develops sophisticated experimental set ups that more and more resemble in vivo systems to permit realistic experiments with human material in vitro that otherwise cannot be performed, and to generate replacement tissue to long-term replace donor organs in transplantations. SIMBIOTX aims at calibrating models with this data, to explain the underlying processes, which may contribute to a better control of experiments, and to guide their designs by mimicking bioengineering process scenarios. Particular emphasis of SIMBIOTX is on liver and liver cells.

3 Research program

SIMBIOTX's research addresses research topics in three main related subject areas, on systems medicine, systems toxicology and systems biotechnology, and in addition a complementary subject image analysis as one major interface between modeling and data. The choice and the development of a method or model (the "theoretical technology" or "methodology") are in most cases driven by a specific application. Most of the methods and models address within a specific application specific sub-components of the

system (e.g. cells, flow, transport), that may occur also in other applications. Accordingly, the development of methods and models that was originally driven by one guiding application can later often be adapted to another application. While so far the modeling activities focussed on mechanistic models, these are now partially complemented by AI-technologies.

Based on this line of argument, we present our research lines within the prescribed scheme by describing the methodology with illustrating examples under the rubric "research program" and specify the examples as applications under the rubric "Application domains".

3.1 Methodology 1: Agent-based models

Agent-based models in which each basic modeling units are represented as individual agent are mainly used to simulate the spatial-temporal dynamics of biological cells when the cell population sizes are moderate and/or the spatial architecture of the system of interest does not favor averaging. In addition, they are applied to mimic networks of filaments, whereby filaments can for example be blood vessels, long molecules (e.g. collagen) or molecule bundles (e.g. bundles of collagen fibres).

3.1.1 Cells

Several of our applications in systems medicine and systems biotechnology address questions at the tissue micro-architecture at cell-and sub-cellular spatial scale. In these applications we present each cell as individual unit ("agents") in continuum space using mainly two modeling technologies, which we have co-developed: center-based models (CBMs) and deformable cell models (DCMs) [8], [40], [41].

In CBMs, cells are parameterized by a few geometric parameters such as the cell radius, and axis length (e.g. to mimic cell elongation prior to undergoing mitosis), material parameters and cell-kinetic parameters, and forces between cells are approximated as forces between cell centers. CBMs have no explicit notion of shape, the volume occupied by a cell is approximated by a geometric body (usually a sphere or dumb-bell) that specifies the approximate position and shape. Hence despite its geometric representation may indicate a rigid cell body, the cells are usually not rigid, represented by that their geometric representations can overlap depending on the forces between them.

In DCMs, cells are mimicked as deformable objects with an explicit representation of cell surface on a mesoscopic level, usually by triangulation of the cell surfaces. The DCM can further represent cell organelles. As in the CBM, the presented structures are parameterized by material parameters that are either directly represented or be inferred from the cells' response on experimental perturbations. Both CBM-and DCM-cells move according to force-balance equations that account for all passive forces on the cell plus active forces mimicking the cell movement. For CBM this is usually one equation for a translatory cell movement, while for DCM, it is one equation for each node of its triangulation. For different applications, the CBM/DCM-models have to be adapted, which in particular includes the force terms in the force balance equation(s) (the "equation of motion"). Each time, the model parameters have to be identified.

3.1.2 Other structures: networks of ellongated components

In certain diseases collagen networks form representing architectural and functional obstacles. Collagen bundles or fibers are mimicked as semiflexible chains with each node on the chain being mimicked by a force balance equation as for CBMs. The same approach is partially used to represent capillary networks as this permits to approximate network distortions upon physical forces on the capillaries in a simple and computationally efficient way. Alternatively, vessels may be triangulated as cells in the DCM.

3.2 Methodology 2: Flow models

Flow of mainly blood and bile is an important component to model for applications in systems medicine, toxicology or biotechnology. If the flow structure is intrinsically 3D, then the fluid is modelled by the incompressible 3D Navier-Stokes equations in multi-branched networks, which blood or bile conduit geometry comes from imaging data.

At the macroscale, for hemodynamics in the larger vessels, this typically entails coupling with the rest of the circulation, which is lumped into a 0D model (no dimension in space). Such ODE-based electric

analog is constructed to represent as necessary for the application the downstream vascular bed, other organs, the heart, etc. Part of the research consists in adapting its parameters based on subject-specific data (e.g. [6]).

An in-between model, typically to take into account the effect of a varying vessel cross-sectional area in space and time, is the 1D (Euler) equations of flow. It is solved here in small networks of vessels [24]. For networks of thousands of small conduits, resistance (0D) models are typically solved, where a finer rheology can be incorporated [26]. Geometry comes either from synthetically generated branching trees (mesocirculation) and networks representative of the organ functional unit architecture (microcirculation), or if available directly from imaging data of the blood or bile system.

3.3 Methodology 3: Transport and intra-cellular models

Multilevel and multi-scale models of biological tissues often include the transport of molecular species and chemical reactions at many different scales, sometimes up to the entire body.

3.3.1 Transport

Major fluxes considered are those inside the blood vessels and bile conduits, and between blood vessels or bile conduits and their adjacent structures (cells, extracellular, extravascular space).

Currently two major model types are used to mimic transport phenomena. The first one are compartment models where concentrations are assumed to be homogeneous in a certain spatial compartment and change upon transport into or from another compartment [39] [25]. In such models, we usually apply ordinary differential equations (ODEs) for the compartment concentration as a function of time. The second type emerges if concentrations can vary in space (e.g. along a blood vessel) in which case usually partial differential equations (PDEs) for the local concentrations depending on space and time are considered [26], [9]. In both cases, the equations can be derived from mass balance. The equations require the knowledge of the flow rate (ODs) or local flow velocity (PDE models), which emerge from the flow models (section 3.2).

3.3.2 Reactions

Besides fluxes, the mass balance can be modified as a consequence of chemical reactions. In our applications modifications by chemical reactions mostly occur inside cells, which we mostly mimic by ODE equations assuming the number of molecules inside the cell is sufficiently large to neglect stochastic fluctuations (e.g. [2]). If the latter is not the case, we develop master equation approaches to cope for fluctuations. In such an approach, the multivariate probability of a certain chemical species composition is tracked in time, and, if necessary, in space by subdividing the space into small reaction volumes (compartments) much smaller than the cell or other local volumes. The main work is the simulation of different reaction networks that are believed to represent alternative hypotheses on the reaction dynamics. The simulation results are usually compared to experimental readout observables [3].

3.4 Complementing methodologies

3.4.1 Image analysis

Many parameters used to calibrate the models have to be inferred from images [31]. For this purpose, the team has been repeatedly performing image analysis. As free tools are usually not suited for the images used, tools to analyze images of multiple modalities (e.g. light sheet microscopy, confocal laser scanning microscopy, MRI) to extract information from images are developed. This partially includes new and refined algorithms to better bridge the gap between experimental images and computational models (e.g. [30, 29]).

For patients, model parameterization needs to occur from non-invasive or moderately invasive modalities, e.g. from biomarkers or non-invasive imaging. While non-invasive functional imaging has been a very active field of research, its translation to the clinics is impeded by a good understanding of how the extracted parameters relate to the underlying tissue characteristics. A first approach consists in constructing in-silico models of such tissue images and study how model parameter changes relate to

these in-silico images [10]. A second approach is to perform quantitative image analysis and correlation of different image modalities [43]. One can then study how non-invasive imaging, a macroscale information, relates to organ microscale architecture, perfusion or function.

3.4.2 Integrative, multiscale, multilevel and multicomponent models

In a number of models the three methodology axes are combined to a multi-level multi-scale model (for example, those aiming at a virtual liver at microscale), which raises the challenge how to choose each of the model components and parametrise them (e.g. [1]).

So far the mostly chosen method is a systematic simulated parameter sensitivity analysis by variation of each model parameter within its physiological range and studying how this modifies the agreement between model simulation result and data from experiments for patients. A sensitivity analysis performed on such models would be crucial in order to (i) identify the most significant parameters to influence the desired output, (ii) test the robustness of a model in the presence of uncertainties, (iii) determine the interactions among parameters, and (iv) unveil the optimal regions within the parameters space for optimization studies. An example is the Saltelli algorithm to compute the Sobol' indices, a variance-based sensitivity analysis that exploits the variance decomposition (ANOVA) also in non-linear and non-monotonic cases. An example of such sensitivity analysis applied to our virtual human twins is [38].

3.4.3 Artificial intelligence

Biophysical models have also been complemented by machine-learning [5, 37], replaced by [23] or mixed with [16] deep-learning approaches.

4 Application domains

4.1 Systems Medicine

4.1.1 Liver

The objective is to establish models at multiple scales and multi-scale models (i.e. linking intracellular functional units up to the whole organ scale) of the different liver subsystems, aiming finally at a digital liver model (e.g. [28]). Prospectively the models should be implemented within a single or within linked software tools permitting systematic hypothesis testing with small extra effort. Applications in liver concern liver tissue architecture and function in the healthy liver serving as a reference state, as well as acute liver damage, disease development and its functional consequences, as well as treatment of aberrant states, for which a prominent example is liver surgery. The computational models integrate information from in vitro experiments, animal models and human data. At the methodology level, liver modeling requires all elements introduced in the previous section, integrating agent-based modeling approaches for cells and molecules, ODE/PDE models of molecular transport, flow, as well as inter-cellular and intra-cellular reactions (which can for example be signaling cascades, metabolic reaction networks or detoxification reactions) by ODE models or, if required, stochastic modeling methods.

The first step is to provide biologists, pharmacologists, toxicologists, and clinicians with a better understanding of the interplay of the many components pertaining to liver function, injury, and the disease progression in a systems approach. In a further step, modeling is increasingly used to guide the design of experiments and data acquisition. While a number of aims and concepts can be developed based on animal models, where mechanisms may be validated, a key challenge will be to develop strategies and concepts for model and parameter identification in human. The long-term aim is to support clinicians in diagnosis by informing about disease progression, possible disease origin, disease reversal, and predict the possible consequences of therapy options. An important example for a therapy studied in SIMBIOTX is liver surgery [4].

Liver disease partially impacts on other organs such as heart, kidney and lung, which might therefore be addressed if required by the clinical questions.

4.1.2 Congenital heart disease

Congenital Heart Disease (CHD) consists in diseases that affect children born with heart or connecting large vessel abnormalities. Pulmonary hypertension is a disease that has several etiologies, one of which is CHD.

While great advances have been made in the last decades in their clinical treatment (mainly through surgery), these patients still suffer from significant mortality and morbidity, due in part to interactions between heart, systemic circulation, pulmonary circulation and other components such as implanted graft or devices. The goal here is to perform patient-specific modeling to better understand such interactions (e.g. [34]). Choosing the treatment option (surgical, interventional, drug) and optimizing it based on modeling opens up several research directions.

4.1.3 In vitro cell populations, tumors and cancer

A tumor can be malign (cancerous) or benign. A malign tumor can grow and spread to other parts of the body. A benign tumor can grow but will not spread. Benign tumors sometimes degenerate into malign tumors (cancer). Cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020 (WHO) and therefore a major subject of research worldwide. Both, benign and malign tumors are characterized by being largely unstructured compared to highly structured organs like liver, lung or kidney, which simplifies the modelling and model implementation effort at the histological scale compared to highly structured tissues. In vitro growing cell populations are often derived from tumor cell lines, and are due to the population sizes usually well amenable to agent-based models with each agent being a single-cell. Modeling of growing cell populations, early tumor growth, different phases in tumor development (e.g. invasion and intravasation), have hence been a regular work subject of SIMBIOTX members as it does not only provide interesting insight into the biological processes underlying cancer development, but also permits to study and develop the modeling concepts and methodology. Many cell-mechanisms are first studied in-depth in in vitro cell populations such as the effect of mechanical stress on cell growth and proliferation [7], which makes them prone to be implemented first in models of the in vitro setting before integrating them into in vivo tumor growth models.

4.2 Systems Biotechnology and Systems Toxicology

In vitro systems are increasingly developed to more closely resemble their in vivo counterparts. This prospectively permits creation of bio-engineered tissues as replacement of cancerous or non-functional tissues as well as of in vitro test systems for realistic in vitro - in vivo extrapolation of drug effects, in particular adverse effects. SIMBIOTX develops computational (digital) twin models of in vitro systems for growth and toxicology. An example is paracetamol (acetaminophen, APAP) - overdosing - induced hepatotoxicity that is the major cause for acute liver failure in many countries.

Part of our activity is to establish computational models for simulating detoxification processes in in vitro and in vivo situations and implementing them in software. These models shall mimic both, processes in digital in vitro experiments and drug effects in digital organs, eventually in time and space. An important example is drug action of paracetamol ([32], sect. 4.1.1, Dichamp et al., 2023).

The simulation methods at all scales put us in an good position to develop models to guide experimental designs (which experiment to perform, and how to perform it), and assist in design devices in biotechnology. The developed models furthermore contain significant information on cell and multicellular properties and behavior, that often can be used to parameterize models mimicking in vivo disease or repair processes hence importantly pertain to the systems biology projects in liver (sect. 4.1.1). The most frequent current culturing methods are monolayers and spheroids and have been studied by computational agent-based models of different types.

5 Social and environmental responsibility

5.1 Impact of research results

The virtual human twins developed in SIMBIOTX aim on the long run at improving health of patients. For this reason, we work hand in hand with biologists and clinicians. (E.g.LeMonde Informatique)

6 Highlights of the year

6.1 Awards

- Jérôme Kowalski, PhD student in the team, was awarded the 3rd Jury Prize for "Ma Thèse en 180s" at Institut Polytechnique de Paris [March 2024]
- Morgane Garreau, postdoctoral researcher in the team, was awarded the Best PhD thesis award from the Société Française de Résonance Magnétique en Biologie et Médecine (SFRMBM, French Society of Magnetic Resonance in Biology and Medicine) [May 2024].
- Pavlos Varsos, PhD student in the team, was awarded the Visiting Student Researcher fellowship from the France-Stanford Center for Interdisciplinary Studies [June 2024].
- Morgane Garreau, postdoctoral researcher in the team, was awarded the Best PhD thesis award from the Société de Biomécanique (French Society of Biomechanics) [October 2024].
- Pavlos Varsos, PhD student in the team, was awarded the BME Conference fellowship from IP Paris at the Engineering for Health Annual Forum [November 2024].
- John M. Hanna, Postdoctoral researcher in the team, was awarded a grant from the Inria startup studio to participate in the incubation program for his project aiming to improve composite manufacuring using AI [December 2024].
- Roel Meiburg, Postdoctoral researcher in the team, was awarded the 'Team Science' grant of the Dutch Heart Foundation of 650.000,- euro for his proposal of the COMPUTE-HF study, which aims to use patient specific models of heart failure patients and AI to optimize cardiac resynchronization therapy [December 2024].

7 New software, platforms, open data

The team implements its models regularily in software tools, from which some are available or will be made available together with the publications that present the models. As as partially significant progress in a number of key software tools have not been made available so far we briefly report the progress here:

Lumped flow:

- Updating the numerical method libraries used in the software, along with developing new features and components, fixing bugs and cleaning up the repository.
- Setting up a CI/CD pipeline, including configuring servers for GitLab runners, writing tutorials, containerising into development and user versions, and implementing tests.
- Writing and structuring technical, physical and mathematical documentation.
- Merging the system's different architectures to simplify its use.
- Drawing up a transition plan towards a code base in C++ (previously in C) for developers and Python for researchers, in order to increase modularity and genericity, improve numerical methods and enable possible coupling with external modules or functions.

- Hiring and training a C++ developer on LumpedFlow to help develop the new software.
- Addition of identifiability and UQ methods

A number of smaller codes will be shared open-source associated with their respective papers (see sections 8.2.3, 8.2.4, 8.4.2, 8.4.3, 8.4.4).

TiSim:
During the implementation phase for CompuTiX, the digital twin liver models so far were implemented and executed with the 3rd generation software tool TiSim, the precursor of CompuTiX. This concerns disease progression (section 8.1.2) and fibrotic scar formation (section 8.1.3). In future steps the final digital twin models should be implemented in CompuTiX.

CompuTiX:
Motivation: The models at histological level have become so complex that it is not possible anymore to implement them de-novo in reasonable time. Implementing one model de-novo takes approximately the duration of a PhD thesis. As a consequence, novel digital twin models that should built upon existing models are either not performed or are implemented in an simplistic way that often does not reproduce the results of the existing models. Hence, "standard" models do not develop. Based on its 30 years of experience in generating and coding agent-based models of multicellular systems, the 4th generation code CompuTiX has been designed to serve as a community tool and to meet the conditions to be transferrable to companies for simulation applications in biomedicine. It is highly modular and extensible. This code should prospectively contain the basis of a virtual liver twin, integrating and extending all liver models that so far has been modelled with the 3rd generation code TiSim. CompuTiX is an agent-based library for simulations of biological, biomedical and biophysical systems. Its data oriented and functional design provides a great range of flexibility and permits to target new applications in reasonable time. CompuTiX has been greatly extended in 2024 and moved from the technology demo stage to the production stage, as it was/is an integral part of the projects EDITH, STEDI-NASH and the ongoing ARTEMIS project. Overall, the changes included more than 200 merge requests and closed issues, more than 140 000 new lines of code, and 30 000 deleted lines of old code, with more than 270 000 lines of C++ code in total at the end of 2024.
The most significant improvements of the previous year included:

- Completion of implementation and largely of validation of the center-based models. Implementation of monolayer and spheroid growth.
- The deformable cell model implementation is approaching its completion. Final validation is foreseen in first half of 2025.
- Blood flow simulation in a micro-vascular network is largely implemented, and proof of concept simulations of a transport (advection) equation in a network with a finite volume scheme has been performed.
- By code improvements, the initial performance was improved by 10% on small systems, and up to 50% on larger simulation setups. Additional improvements included implicit numerical schemes, which allow to increase time-step yielding further speed-up; extended slicing of data to traverse the hierarchy sideways, improved flexibility of the code, and faster contact detection algorithm, providing significant (up to 200-times) speed-up for 2D and 3D systems.

CompuTiX is planned to be available to close collaborators early in 2025, serving as "test users and developpers", followed by public release later the same year.

(Some complementary information can be found in section 8.5)

7.1 New software

7.1.1 LumpedFlow

Functional Description: Forward and inverse mathematical models (ODEs) for biomedical applications (lumped parameter models of the entire blood circulation and pharmacokinetic models)

Publications: hal-01093879v1, hal-01404771v1, hal-01696064v1, hal-01954783v1

Contact: Irene Vignon Clementel

7.1.2 TiSim

Name: Tissue Simulator

Scientific Description: TiSim (Tissue Simulator) is a versatile and efficient simulation environment for tissue models. TiSim is a software for agent-based models of multicellular systems. It permits model development with center-based models and deformable cell models, it contains modules for monolayer and multicellular spheroid simulations as well as for simulations of liver lobules. Besides agent-based simulations, the flow of blood and the transport of molecules can be modelled in the extracellular space, intracellular processes such as signal transduction and metabolism can be simulated, for example over an interface permitting integration of SBML-formulated ODE models. TiSim is written in modern C++ , keeping central model constituents in modules to be able to reuse them as building blocks for new models. For user interaction, the GUI Framework Qt is used in combination with OpenGL for visualisation. The simulation code is in the process of being published. The modeling strategy and approaches slowly reach systems medicine and toxicology. The diffusion of software is a fundamental component as it provides the models that are complex and difficult to implement (implementing a liver lobule model from scratch takes about 2-2.5yrs) in form of a software to the developer and users who like to build upon them. This increases significantly the speed of implementing new models. Moreover, standardization is indispensible as it permits coupling different software tools that may have implemented models at different scales / levels.

Functional Description: TiSim is a software that permits agent-based simulations of multicellular systems. - center-based lattice-free agent-based model - modular - C++, Qt, OpenGL, GUI, batch mode - permits multiscale simulations by integration of molecular pathways (for signaling, metabolisms, drug) into each individual cell - applications so far: monolayer growth, multicellular spheroids - Boolean networks (development time = coding time (̃60 MMs) + model development time (̃264 MMs)) - in follow-up version 1: - liver lobule regeneration - SBML interface - in follow-up version 2: - deformable cell model (by triangulation of cell surface) - deformable rod models - extracellular matrix - vascular flow and transport TiSim can be directly fed by processed image data from TiQuant.

Contact: Dirk Drasdo

Participants: Andreas Buttenschoen, Dirk Drasdo, Eugenio Lella, Géraldine Cellière, Johannes Neitsch, Margaretha Palm, Nick Jagiella, Noémie Boissier, Paul Van Liedekerke, Stefan Hoehme, Tim Johann

7.1.3 CompuTiX

Name: Computational Tissue

Keywords: Single cell, Multi-agent, Modularity, Biophysics, Biological tissue, Cell cultures, Physical simulation, Digital twin

Scientific Description: Establishment of a code architecture to integrate functional modules that represent computational models, or their components, for digital twin simulations of cell culture experiments (monolayer, organoids, bioreactors, ...), and of processes in biological tissues (liver, ...).

Functional Description: CompuTiX is a simulational framework for performing and designing physical simulations of biological cells, organoids, liver and other tissues and for investigation of biological processes. It is designed as user-extensible and flexible software package which also permits integration to other software packages.

Release Contributions: It is the first version published on BIL.

Contact: Dirk Drasdo

7.2 Open data

We have released our dataset of 77 cases annotating both veinous trees of the liver and of their "sub-annotations" according to anatomical nomenclature on Zenodo. See section 8.2.1 for more information.

We made the code for simulation of liver regeneration after drug-induced paracetamol damage accessible on: Zenodo.

8 New results

The results are organized by application theme but many of the concepts range beyond the specific application. For example, the methodology demonstrated in subsection can be applied to any histology.

The results section is subdivided in a liver section composed of different subsections reflecting that this is the backbone of the SIMBIOTX team, and some other sections. The subsections on liver are ordered in a way that they represent a zooming out from smaller to larger lengths scales, while the other subjects that follow are rather on larger scales.

The paragraphs summarize results from 2024, some of which are accessible at least as preprints, which are described in more detail, some which are part of projects with sufficient maturity but yet with no preprint, which are hence only briefly summarized.

In the last paragraph we update developments of our novel softare COMPUTIX in greater detail as in the BIL-website.

8.1 Liver: micro-architecture

At the microarchitectural level important bricks towards a digital liver twin model prototype for the entire drug induced liver injury (DILI) circle that includes the drug action on the liver, the regeneration process, and the effect of DILI on the liver metabolic function have been significantly advanced.

8.1.1 Mathematical modeling of steatotic liver cell metabolic network

Participants: Matteo Pedrazzi, Dirk Drasdo, Jieling Zhao.

Metabolic dysfunction–associated steatotic liver disease (MASLD), previously known as non alcoholic fatty liver disease (NAFLD), is a chronic liver disease characterized by excessive fat accumulation in the hepatocytes, leading to liver steatosis and potential progression to more severe

liver conditions, annually responsible of 1 out of every 25 deaths worldwide. Due to the lack of pharmacological and targeted treatments, this study aims to build a liver numerical digital twin, reproducing the kinetic model of hepatic lipid droplet metabolism, encompassing free fatty acid (FFA) uptake, triglyceride (TAG) esterification, and lipid droplet dynamics, based on experimental in vitro and in vivo findings. By simulating lipid droplets size distributions in hepatocytes under varying conditions, one of the goals is to highlights the role of regulatory surface proteins (RSPs) in cellular lipid accumulation. Additionally, a novel approach has been employed by utilizing sensitivity analysis methods to identify the most significant input parameters. These parameters were then used as key features in the integration of a neural network, enhancing the numerical solution of the model's ordinary differential equations (ODEs) to improve both predictive accuracy and computational efficiency in modeling hepatocyte lipid content [PedrazziMasterThesis]. The next objective will be to integrate the intracellular model into each cell of the multicellular tissue liver model.

8.1.2 Modeling of liver disease progression from liver steatosis to cirrhosis and HCC: digital twins

Participants: Jieling Zhao, Dirk Drasdo.

Metabolic Dysfunction-associated Steatotic Liver Disease (MASLD) (see previous paragraph) can progress to fibrosis, cirrhosis, and eventually hepatocellular carcinoma (HCC). Digital twin (DT) models enable simulation of disease progression by integrating hypothesized cellular interactions and extracellular matrix (ECM) dynamics. We developed a first DT model prototype permitting to simulate entire disease scenarios from MASLD to HCC to better understand disease progression, and in particular, how interactions between the different cell types, the cellular activation and de-activation pattern of cells, and the generation and degradation of ECM determine histology. Cellular behaviors and fate transitions were modeled and simulated to assess key modulatory impacts during disease progression. The model integrates biological mechanisms and biomechanics, informed by spatial transcriptomics of human and mouse liver tissue and co-culture experiments with HepaRG cells and LX2/HSC supernatants.

Collaborators: S. Hammad, S. Dooley (Heidelberg University), S. Wolf, J. Bode, A (Dusseldorf University Hospital), A. Friebel, S. Hoehme (Leipzig University)

8.1.3 Modeling liver the generation of fibrotic scar formation

Participants: Jieling Zhao, Dirk Drasdo.

We extended our digital liver twin model of the formation of fibrotic scars in septal fibrosis by a model reproducing the spatial collagen distribution in biliary fibrosis. While in septal fibrosis the scars are sharply located at the connecting line between central veins of neighboring liver lobules, in biliary fibrosis, they are scattered at the portally located borders between neighboring lobules.

Main collaborators: S. Hammad, S. Dooley (Heidelberg University), J.G. Hengstler, IfADo, Dortmund.

8.1.4 Multilevel modeling of flow and transport in liver lobules in health and disease

Participants: Peter Kottman, Irene Vignon-Clementel, Dirk Drasdo.

The liver guarantees its function as main detoxifying organ by a complex microarchitecture that permits a perfect exchange of metabolites between blood and hepatocytes, whereby some molecular species are secreted into the biliary system [9]. However, how critical the microarchitecture is for liver function is largely unclear. This is also reflected in computational models of liver metabolism or liver toxicology. Most of these make the assumption of a well-mixed liver compartment or well-mixed liver subcompartments but a systematic study is missing.

We formulated a consistent model of lobular transport in sinusoidal (blood) and biliary networks. Starting from a 3D transport equation, the lobule was decomposed into structurally relevant subdomains (sinusoids, hepatocytes, bile canaliculi), on which the model was reduced into 1D or 0D based on subdomain specifics. The resulting model allows to describe transport in sinusoids and bile canaliculi, as well as uptake and secretion by surrounding hepatocytes. Thanks to its reduced 1D-0D-1D nature, it promises reasonable computational cost once implemented, as well as ability to communicate with other models on the cell level (e.g. metabolic networks).

To further study the impact of microarchitecture on liver function, compartment models of liver clearance were studied. The initial ideas formulated by Géraldine Cellière in her PhD thesis ([CellierePhDThesis]) were generalized into an analytical study of multi-compartment models of clearance at steady state for certain type of reactions. Such models can be seen as a bridging point between the spatially resolved models that represent each cell individually and well-mixed single-compartment models that disregard completely the spatial heterogeneity of liver.

Collaborators: E. Rohan, UWB Pilsen, Czech Republic

8.1.5 Temporal diffusion spectroscopy for the characterization of MASH

Participants: Charles Boulitrop, Jiří Pešek, Dirk Drasdo.

The gold standard in the staging of many liver diseases is the evaluation of a histological sample of the patient. Obtaining tissue material for histopathological evaluation requires invasive interventions such as taking biopsies, which underlies strict criteria due to the possible adverse effects. The objective is hence to gather knowledge on histopathological characteristics non-invasively, as this not only minimizes size effects but also permits longitudinal follow-ups. A typical use case is the classification of metabolic dysfunction-associated steatohepatitis (MASH), which includes hepatocyte ballooning. Ballooning is characterized by accumulation of lysis vesicles in the cytoplasmic space, hepatocyte swelling and alterations of the intermediate filament cytoskeleton. Temporal diffusion spectroscopy (TDS), a development of Diffusion-Weighted-Magnetic Resonance Imaging (DW-MRI), has recently enabled identification of apparent diffusion coefficients that may permit to probe ballooning non-invasively.

Using the team's novel simulation software CompuTiX, agent-based models simulating the DW-MRI process have been developed. The main physical processes at stake in DW-MRI, diffusion of magnetic moments and magnetic precession, were simulated in CompuTiX and have been verified against the conventional continuum-based approach (namely finite-element method), with good agreement. Additionally, models of DW-MRI in a constrained synthetic microarchitecture have been developed in CompuTiX, including specific gradient pulse sequences used for *in vitro* experiments with "phantoms". Apparent diffusion coefficients are then derived from the simulation results. These display the expected behavior with regard to theory. The final goal is to study how changes in the liver tissue microarchitecture may impact on MRI-signals.

Collaborators: P. Garteiser, B. Van Beers (Inserm)

8.1.6 Microvascular modeling for medical imaging and toxicity assessment

Participants: Jérôme Kowalski, Dirk Drasdo, Peter Kottman, Jules Dichamp, Irene Vignon-Clementel.

Dynamic-contrast-enhanced medical imaging can be used to detect non-invasively tissue abnormalities like tumors, to evaluate organ function, or to assess drug efficacy. Tracers injected into the body may reflect tissue perfusion and function, depending on whether they are taken up and/or metabolized by the cells or not. Distinguishing spatial and functional contributions to the signal obtained from *in-vivo* analyses is challenging, which is why we develop *in-silico* models for better image interpretation, again following a conceptual strategy as in ref. [42].
In organs such as the liver, cells are nourished by networks of capillaries, small fenestrated vessels called sinusoids. Remodeling of liver microarchitecture during chronic liver disease may modify the fenestration of the network resulting in an impaired liver function, such as the modification of detoxification of the blood from potentially hepatotoxic drugs. On the other hand, hepatotoxicity of most drugs is dose-dependent, which requires to determine the critical concentration of no-observed-adverse-effect levels (NOAEL) at the location of the hepatocytes. Recent findings indicate that the tissue microarchitecture and the spatial-temporal distribution of the drug may play an important role in the determination of the NOAEL [27]. *In-vitro* experiments permit to determine the concentration at which a substance a cell is exposed to is hepatotoxic (the pharmadynamics), but to know the concentration distribution, information on the microarchitecture of the liver, the drug kinetics, and the distribution of a drug in the liver needs to be known. This seems feasible with the help of mathematical models addressing flow and transport in liver tissue microarchitecture.
We assessed three *in-silico* models that, based on a common mathematical framework, simulate blood flow and drug transport in and out of a diseased micro-vascular network, and their effect on cells [18] . To that end, the main pillars of multi-phase multi-species flow and transport models are first derived from primary principles and then transcribed for a vascularized tissue. The chapter provides overall a methodology to link changes in vascular network architectures, microcirculation consequences and some macroscale biomarkers relevant for dynamic medical imaging or toxicity predictions.

8.1.7 A digital liver twin to demonstrate the significance of disease-related remodeling of liver architecture in ammonia detoxification

Participants: Jules Dichamp, Dirk Drasdo, Geraldine Cellière, Noémie Boissier.

Hyperammonemia i.e., a critically elevated ammonia blood concentration, can lead to encephalopathy and patients' death and constitutes the major reason for acute liver failure. We introduce a digital liver twin that reflects the remodeling of architecture and all key processes relevant in ammonia detoxification during fibrosis development. We demonstrate, that the architectural changes alone can explain most of the experimentally observed changes in ammonia detoxification during fibrosis. Our findings suggest a novel modeling strategy in toxicology modeling in tissues during acute liver tissue damage or disease development, by first studying the effect of tissue remodeling of a toxic substance, and subsequently adapt intracellular processes to capture the observed concentrations of toxic substances. Earlier results have been completed and a first draft of the manuscript has been written.

Collaborators: J.G. Hengstler, A. Ghallab and coworkers from Leibnitz Institute IFADO, Dortmund, Germany.

8.2 Liver: Organ-scale

In this section, we present a number of computational modeling results of flow and transport of particles or injected substances. Such biophysical approach is complemented by AI approaches.

The common goal is to create digital twins to help design or assess the risk of liver cancer treatment.

8.2.1 Enhancing the automatic segmentation and analysis of 3D liver vasculature models

Participants: Yassine Machta, Omar Ali, Kevin Hakkakian, Ana Vlasceanu, Amaury Facque, Nicolas Golse, Irene Vignon-Clementel.

Surgical assessment of liver cancer patients requires identification of the vessel trees from medical images. Specifically, the venous trees - the portal (perfusing) and the hepatic (draining) trees are important for understanding the liver anatomy and disease state, and perform surgery planning. In this study, we aim to enhance the identification and analysis of venous trees in liver cancer patients through advanced 3D segmentation and skeletonization techniques. We propose an automatic pipeline that leverages deep learning and image processing to improve vessel tree connectivity and segmentation. Initially, we investigate the impact of differentiable skeletonization methods, such as ClDice and morphological skeletonization loss, on the performance of liver vessel segmentation. Subsequently, we extend the segmentation approach from a single-class model to a multi-class model, distinctly identifying the portal and hepatic venous trees. This method not only improves the clarity of vessel tree outputs but also enables detailed morphometric analysis by sub-labeling specific anatomical branches. Our approach is validated by surgeons and supported by a new high-quality liver vessel dataset of 77 cases, providing a robust framework for precise liver vessel morphometry analysis.

We have published our work on HAL [15] and Arxiv. We have also released our dataset of 77 cases annotating both veinous trees of the liver and of their "sub-annotations"according to anaotmical nomenclature on Zenodo.

8.2.2 Geometric and Hemodynamic Study of the Portal Vein: Identification of Predictive Factors for Portal Thrombosis through 3D Numerical Simulation after Extended Liver Resection

Participants: Ana Vlasceanu, Morgane Garreau, Amaury Facque, Weiqiang Liu, Irene Vignon-Clementel.

Hepatocellular carcinoma, cholangiocarcinoma and liver metastases of colorectal cancer account for the vast majority of liver tumor lesions. Cholangiocarcinoma (CK) is the most common biliary malignancy. It accounts for 3% of all digestive tumors, with an incidence of 5,000 new cases per year in France. Apart from liver transplantation, which is currently not an option for the majority of patients (organ shortage, risk of recurrence), surgical resection is considered the main curative treatment. Long-term survival is between 3 and 6 months without resection, 12 months with chemotherapy alone, 24 months with resection and positive margins, and between 36 and 48 months with resection and negative margins. In most surgical series, 5-year survival is between 10 and 40%.

In this work, extended liver resection for perihilar CK is considered, as these tumors require complex resections associated with high morbidity/mortality and, in particular, high risk of portal vein thrombosis. This complication occurs in approximately 10% of patients and can be fatal. 3 groups of patients are investigated: patients who underwent portal resection (PR) with consecutive thrombus formation, patients who underwent PR but without thrombus development and patients who did not undergo PR and did not develop a portal thrombus. Their portal vein geometries are reconstructed based on postoperative CT scans. A fourth group is built based on preoperative CT scans of patients who had PR and developed thrombus, where the surgery is replaced in silico by a virtual graft. Geometric analysis and CFD simulations are performed from these four groups of patient-specific geometries. Part of the work has been presented in a major clinical conference [14].

Collaborators: N. Golse, E. Vibert at APHP-hopital Paul Brousse.; L. Sala at INRAE

8.2.3 Hemodynamics modeling for liver surgery: digital twins

Participants: Roel Meiburg, Kevin Hakkakian, Ramdane Bessaïd, Clémence Finotto, Francesco Songia, Irene Vignon-Clementel.

To evaluate the risk of portal hypertension after partial hepatectomy, our team proposed the usage of a lumped parameter model to predict the hemodynamic response after surgery. This year, our clinical cohort was expanded by 26 patients with small hepatectomies, meaning the model can be verified versus a larger and more diverse patient group. For the modelling side, the model was expanded to include: 1) dynamic implementation of peroperative events, 2) upgrade of libraries, 3) automatization and speed up of the simulation pipeline to run on a database 4) implementation of physiological autoregulation mechanisms. These changes facilitate the simulation of hepatectomy patients under different hemodynamic states, such as blood loss, saline infusion and pharmacological effects, which in turn affect portal pressure and thus the prediction of portal pressure. Finally, further sensitivity and identifiability analyses demonstrated that time-series data (which are technically and clinically feasible) of portal pressure and flow pre-intervention potentially contain information on blood pressure inside the liver tissue, and may hence contain information on whether any obstruction is pre- or post-sinusoidal.

Collaborators: N. Golse, S. Roullet and E. Vibert at APHP-hopital Paul Brousse.; L. Sala at INRAE

8.2.4 Whole-body vascular transport and pharmacokinetics models: application to imaging, in particular of the liver

Participants: Jérôme Kowalski, Irene Vignon-Clementel, Dirk Drasdo, Maha Sakli, John Hanna.

A crucial aspect in the surgical decision process is organ perfusion and functional assessment. In this context, an active medical imaging field is dynamic functional imaging. Functional imaging often involves a tracer, which is transported in the blood circulation, with a certain time-dynamics as it goes through the different components of the circulatory system. However, following a disease or a major surgery, the time-dynamics of the different components is subject to change. A better knowledge of the impact of a disease on the time-dynamics of a tracer would enhance the interpretation of the tracer measured signals and thus help radiologists and surgeons to detect abnormal behaviors. We aim at understanding these dynamical signals, by a combination of mathematical modeling of flow and transport, numerical simulations, determination of model parameter from imaging data and machine learning.

One work has been done in the analysis of classical reduced transport models used in the medical imaging and pharmacokinetics communities. They have been thoroughly derived from the physical equations, and the derivation hypotheses have been tested for different possible regimes. This work outlined the different applicability zones of the reduced models in the parameter space and introduced diffusion as the main factor enabling the model applicability.

To permit comparison to data, software has been developed that extracts the centerline of a complex vascular tree structure. It enables to consider disconnected vascular trees and goes deeper in the hierarchy than traditional methods. This has been done in the context of the Master's internship of Maha Sakli. Thanks to this work, a first analysis of the corrosion casts of the human liver vascular networks made available by Gent University has been performed, highlighting the importance of the introduction of asymmetry to predict hemodynamics and transport with the model of vascular network.

The sensitivity of the closed-loop model for ICG transport developed last year to the patient's characteristics (body mass, cardiac output, etc.) was analyzed. The results show similarities with clinical practice. A synthetic cohort of patients has been simulated, using parameter ranges from

the literature and thanks to several discussions with and a visit to the collaborating surgeons in LUMC. The generated time-intensity curves have been used to train a recurrent neural network to predict the severity of the synthetic patient's stenosis. The model achieves good accuracy, which is promising for a future study of the measured signals.

Collaborators: L. Sala at INRAE; Charlotte Debbaut (group bioMMeda, UGent, Belgium)

8.2.5 Numerical investigation of particle aggregate steering with magnetic resonance navigation for targeted embolization

Participants: Mahdi Rezaei Adariani, Jiří Pešek, Irene Vignon-Clementel.

Magnetic resonance navigation (MRN) of medicinal substances is gaining popularity in the treatment of liver cancer. This method relies on a cluster of particles formed by dipole-dipole interaction; the latter originates from the magnetic moments generated by the MRI scanner static magnetic field. These aggregates are then injected into the controlled blood flow where they are steered into the target branch by the combination of the magnetic gradient force and gravity.

The success of the MRN procedure depends on the aggregates shape, which determines their mobility and stability. In this part of our research, we deploy a computational model to investigate the dynamics of MRN clusters and to optimize their design for improved treatment efficacy. Using a modified version of Maxey-Riley equation and the immersed boundary method, the hydrodynamic forces acting on clusters were simulated and validated against experimental data and the bead-chain drag model (BDM).

Preliminary results show that the immersed boundary method is suitable for determining the drag as its results are in a good agreement with the bead drag model and the experiments reported in the literature. However as the bead drag model is limited to a rigid chain of spherical particles, additional research is required to generalize the effect of the hydrodynamic force on aggregates of different shapes in a realistic arterial blood flow field.

Collaborators: Gilles Soulez (CR-CHUM, Montreal, Canada), Charlotte Debbaut (group bioMMeda, UGent, Belgium)

8.2.6 Computational modeling for TIPS shunt implantation and pre-operative planning

Participants: Pavlos Varsos, Irene Vignon-Clementel.

The Transjugular Intrahepatic Portosystemic Shunt (TIPS), is a well-established treatment tool in liver cirhossis, which has been proved to prolong transplant-free survival. It is a graft (usually out of PTFE) that interconnects, within the liver parenchyma, the portal vein to the hepatic vein, decreasing the portal pressure gradient. Depending on the diameter of the shunt, more or less blood will bypass the liver towards the systemic circulation. Greater shunt diameters, will thereby increase the levels of ammonia in the brain coming from the intestines, leading to the development of hepatic encephalopathy (HE). Therefore, computational modelling could help as a predictive tool for patient selection and pre-operative planning, with regards to shunt size selection and portosystemic pressure gradient assessment. We have started to reconstruct patient-specific 3D geometries from CT scans, and perform CFD simulations based on realistic boundary conditions. Flow distributions (e.g., shunt index) and pressure levels can then be evaluated in collaboration with clinicians.

Collaborators: N. Golse, APHP - Hôpital Paul Brousse

8.3 Digital twins of blood flow for disease or treatment assessment

In the section below, we first present two studies where the aim is to replace invasive or challenging medical exams of the heart by computational modeling. The heart often adjusts to diseases. Numerical results are then presented to better understand vasculopathy in sickle-cell patients, whose cardiac output typically increases to compensate for insufficient oxygen delivery in the brain. Finally, diseases in the pulmonary circulation and their pallation typically affect the right pump of the heart. Different aspects are presented in a bookchapter, an imaging study and a proof-of-concept multiscale digital twin study. All these studies are conducted in collaboration with clinicians (radiologists, cardiologists, surgeons, ...).

8.3.1 Myocardial perfusion simulation for coronary artery disease: combination of Machine Learning and physical simulation

Participants: Raoul Sallé de Chou, Francesco Songia, Tobias Schnirer, Irene Vignon-Clementel.

Blood perfusion imaging is a challenging and expensive imaging modality for the analysis of myocardial perfusion and the diagnosis of coronary artery diseases (CAD). A previous model was developed for myocardial perfusion simulation for coronary artery disease in [36] to replace the actual imaging exam with a numerical twin and conduct it via simulations. The model aims at reproducing [15O]H2O PET imaging exam using only CT scans as input. However, in addition to a high computational cost, the simulation fails to accurately reproduce some diseases, particularly those that affect medium-size coronary branches. The main goal of this project is to combine Machine Learning (ML) methods with physical simulations in order to improve the current simulation pipeline while diminishing the dependency on patient data for the ML models. To achieve this, each part of the simulation is to be replaced by an ML model.

The perfusion model integrates a 1D Navier-Stokes (NS) model for the coronary arteries coupled with a Darcy model to simulate perfusion within the myocardial volume. To address the myocardium component, we developed a finite volume informed Graph Neural Network (GNN) [16]. To predict the solution of the 1D NS equations, a transformer encoder model was employed to estimate the pressure distribution from a given flow distribution within the coronary network.

The second key component of the simulation involves the generation of synthetic vascular trees based on the “Constructive Constrained Optimization” (CCO) method [17]. However, this method method has notable limitations, including high computational costs, a tendency to produce suboptimal solutions. To address these limitations, our work focuses on developing more optimal synthetic trees by generating them directly from terminal points uniformly sampled within the myocardial volume. We developed a gradient-based method to construct optimized binary trees. In our new approach, instead of minimizing total volume, our approach minimizes a transport cost [17]. Preliminary results indicate that this method generates trees more efficiently and achieves more globally optimal solutions than the CCO method. Additionally, this approach paves the way for integrating deep learning methods into tree generation.

Currently, the simulation relies on an estimate of the total blood flow in the coronary arteries for a healthy patient, derived from myocardial mass. A more accurate estimation of a patient’s total blood flow can be obtained using PET images, which provide insights into the state of blood flow in the microvascular network. As a final component of the project, we trained a Machine Learning model to predict total blood flow as measured by PET images. While the model improved total flow prediction on a test set compared to the mass-based estimate, further investigation was undertaken to identify better features derived from coronary artery geometries and their relationship to CAD using GNN. Current results show that correlating plaque location with morphometry remains complex and requires deeper investigation.

Collaborators: L. Najman (ESIEE - U Gustave Eiffel), H. Talbot (CentraleSupelec, INRIA OPIS), L. Papamanolis (Stanford university, USA, California) Heartflow inc. (USA, California).

8.3.2 Potts Shunt as a palliative treatment option for suprasystemic idiopathic Pulmonary Arterial Hypertension: an in-silico modelling study

Participants: Pavlos Varsos, Irene Vignon-Clementel.

The Potts shunt emerges as a palliative treatment option for pediatric patients, facing unsuccessful drug treatments for suprasystemic Pulmonary Arterial Hypertension, and for whom lung transplantation is not yet feasible. Despite its intent, a considerable number of surgeries prove unsuccessful, leading eventually to mortality, with the failure mechanism still eluding comprehension. This study aims to investigate the underlying factors that influence the success or failure of the procedure, while exploring various shunt designs, ranging from anastomoses to conduits, and with or without the integration of a unidirectional valve. A multiscale model (0D-3D) was orginially developed Pant et al. [35], for which, an extensive sensitivity analysis was conducted. Meta-modelling techniques were also applied to perform both sensitivity analysis and uncertainty quantification. Preliminary findings reveal that patient-specific parameters, such as systemic and pulmonary vascular resistances, along with cardiac characteristics like wall volumes and contractility, significantly impact surgical outcomes, and can consequently act as biomarkers for patient stratification. Additionally, shunt parameters, such as diameter and shape, also play a considerable role, emphasizing their importance in pre-operative planning. In collaboration with leading hospitals in France (Marie Lannelongue Hospital) and the United States (Stanford University Hospital), we are expanding our patient cohort to further explore the model and gain deeper insights into disease mechanisms.

Collaborators: S. Pant; E. Valdeolmillos, S. Hascoet, Hôpital Marie Lannelongue

8.3.3 In-silico modeling in deciphering stroke risk factors in children with sickle cell disease

Participants: Morgane Garreau, Weiqiang Liu, Lazaros Papamanolis, Irene Vignon-Clementel.

Sickle cell disease (SCD) is the most common inherited blood disorder in the world. It is associated with serious complications such as cerebral vasculopathy (CV). CV is characterized by remodeling of the intracranial carotid arteries (ICA), resulting in stenosis and occlusion that can lead to stroke, most commonly in young patients aged 2 to 5 years. A proven method for screening patients at high risk for stroke is transcranial Doppler. A time-averaged maximum velocity (TAMV) greater than 200 cm/s has been proposed as an effective threshold for identifying patients at highest risk. However, the causes of these pathological blood flow velocities remain unclear. In [33], hemodynamic metrics obtained from blood flow CFD simulations are investigated to understand the development of arterial luminal narrowing.

Collaborators: Saskia Eckert (PhD student, ENSAM, IMRB, EFS, Créteil), Kim-Anh Nguyen-Peyre (PhD, IMRB, EFS, Créteil), Suzanne Verlhac (MD, Hôpital Robert Debré AP-HP), Pablo Bartolucci (MD, Univ Paris Est Créteil/Hôpitaux Universitaires Henri Mondor AP-HP, Créteil)

8.3.4 Multiscale modeling of feto-placental hemodynamics

Participants: Amine Zannane, Irene Vignon-Clementel.

The simulation of feto-placental vasculature is vital for understanding nutrient and gas exchange during pregnancy, yet current models face significant computational challenges. This report focuses on reducing the computational time of a 1D blood flow model, which presently requires

approximately 56 hours to simulate hemodynamics in a placental vasculature consisting of over 98,000 vessels. To address this limitation, this work explores methodologies to significantly reduce computation time without sacrificing accuracy. The hybridization approach selectively replaces 1D elements with computationally simpler 0D components, reducing simulation time to as little as 10 hour (a reduction of over 80) when all vessels below a defined radius are replaced. In parallel, the ablation strategy eliminates terminal branches and replaces them with equivalent resistances, achieving a reduction of over 90% in computation time while ensuring that critical hemodynamic characteristics of the larger vessels are preserved. A detailed analysis of the Womersley number and component contributions (inductance, capacitance, and convection) informs the optimization of the 0D models. Results demonstrate that both strategies can maintain hemodynamic fidelity while achieving substantial time savings, establishing a robust framework for future applications in both healthy and pathological placenta studies.

Collaborators: Pascalle Wijntjes, Beatrijs van der Hout, Wouter Huberts, Frans Van de Vosse, TU Eindhoven

8.4 Methodology on blood flow model parameter estimation

8.4.1 In-silico modeling of Hypoplastic Left Heart Syndrome patient as a clinical tool for stage one treatment planning

Participants: Marie Haghebaert, Irene Vignon-Clementel.

The MEDITWIN project aims to develop a preoperative surgical planning tool to support the medical team in managing single ventricle patients. The task focuses on creating a 0D digital twin that integrates morphological changes from the 3D preoperative planning tool and functional patient data, such as pulse wave Doppler echocardiography. This 0D digital twin will be calibrated using either 3D digital twin data or patient-specific measurements. Ultimately, the model will help predict post-operative outcomes and assist in optimizing surgical planning. Additionally, the 0D model will be used for monitoring patients after surgery, helping to detect potential issues and inform clinical staff. It will also be employed to track the patient's condition at home until the second stage of the procedure, scheduled 4 months later.

Over the past year, a literature review on single-patient modeling was conducted, and discussions with the clinical staff were initiated to align the project with medical needs. Two different heart models were compared through sensitivity and identifiability analysis to understand their differences and to determine when to use one model or the other, depending on the available data. A first model of an HLHS patient was proposed, which is currently in the parameterization phase. **Collaborators: M Fernandez (Inria COMMEDIA team), 3DS, D. Bonnet & team (AP-HP Necker-enfants malades Hospital)**

8.4.2 A comparative study of lumped heart models for personalized medicine through sensitivity and identifiability analysis

Participants: Marie Haghebaert, Pavlos Varsos, Roel Meiburg, Irene Vignon-Clementel.

Numerical modelling of the heart is becoming an increasingly accepted tool for clinical applications, with the ultimate goal of personalized medicine. Lumped parameter models are attractive due to their low computational cost but often do not directly incorporate physical properties, thus requiring calibration to (often sparse) clinical data. Furthermore, there exists a trade-off between physiological relevance and model complexity, making the choice of cardiac model non-trivial.

For two established cardiac chamber models embedded in a hemodynamics whole circulation model, we perform sensitivity and identifiability analyses to examine the possibility of finding a unique subset of important parameters with varying levels of clinically measurable data, thereby examining their applicability in personalized medicine [20]. To give a concrete clinical context, the case of treatment planning for a young pulmonary arterial hypertension patient is considered. The methodology is however relevant for other pathophysiologies. The results suggest that the single-fibre model, although a priori more complex than the time-varying elastance model, is more amenable for patient-specific modelling. This was found for representing the patient state from clinical data, defining parameter ranges for sensitivity analysis and in the results of the identifiability analysis. Moreover the sensitivity analysis revealed the most influential parameters. These parameters for the right (resp. left) heart chambers, mostly affect the hemodynamics of these chambers and the pulmonary (resp. systemic) circulation but also the ones of the left (resp. right) side. This highlights the importance of studying the whole circulation, especially in the context of disease a priori thought to affect one side.

8.4.3 A comparative analysis of metamodels for 0D cardiovascular models with applications to sensitivity analysis, parameter estimation and uncertainty quantification

Participants: John M. Hanna, Pavlos Varsos, Jérôme Kowalski, Roel Meiburg, Irene Vignon-Clementel.

Despite the low computational cost of 0D cardiovascular models, tasks as sensitivity analysis, parameter estimation or uncertainty quantification remain an issue since thousands of simulations are needed which can take several hours to days. To alleviate this issue metamodels can always be used to speed up these tasks. In this work, three different metamodels are assessed: neural networks (NN), polynomial chaos expansion (PCE), and Gaussian processes (GP) [21].

A pipeline is developed from the data collection to the building of metamodels and performing sensitivity analysis, parameter estimation and patient specific uncertainty quantification. The 3 metamodels strategies are tested on 3 different 0D models and it was seen that in general neural networks have the best performance, accuracy and easy to use practically. The framework of automatic differentiation available in common machine learning libraries allows the easy development of inverse problems and uncertainty quantification tasks.

Collaborators: L. Sala (Inrae)

8.4.4 A novel loss function based on the standard deviation to improve regularization: applications in physics-informed neural networks

Participants: John M. Hanna, Irene Vignon-Clementel.

Classical loss functions are usually the mean of a chosen error metric as the squared or absolute error. Depite being the state of the art, outliers are usually ignored and not captured by minimizing such loss. However, sometimes these outliers represent a physical phenomenon or feature in the data. In this work, we introduce a new loss function that gives more importance to outliers [22].

The new loss function is a combination of the mean term and a term representing the standard deviation of the chosen error metric. By minimizing such combined loss, we ensure a more uniform error distribution and reduce the localized error regions. This new loss function is tested on 3 different physics-informed neural networks problems: Burger's problem, 2D linear elasticity, and 2D flow governed by Navier-Stokes equations. The solutions are greatly improved when compared to using the classical mean loss, while ensuring the same weight initialization , number of iterations and optimizer.

8.5 Towards standardisation: Models and Software

8.5.1 Towards standardisation of center-based models

Participants: Jieling Zhao, Jiri Pesek, Jules Dichamp, Dirk Drasdo.

There is a wide agreement for models and simulation tools at the level of intracellular models and at the level of continuum descriptions (organ level, body level, flow, transport, biomechanical models, ...). At the histological scale between the intracellular and the organ level, tissues are modelled increasingly by agent-based models, that display each individual cell. While models displaying cells on space-fixed lattices cannot capture the biomechanics correctly by construction (Van Liedekerke et. al., 2015), center-based models (CBMs), in which forces between cells are modelled as forces between cell centers in continuum space are increasingly used to simulate growth and re-organisation processes in multicellular tissue (as for example in the cancer use-case in EDITH). Conceptually, CBMs mimic cells similarly as active slightly deformable adhesive colloidal particles.

Several software tools are being used for this purpose (e.g. Chaste, Physicell/Physiboss, Biodynamo, TiSim, CompuTiX). The problem is that there is no standard on how to formulate the CBMs even at a basic level as for example for the Navier-Stokes Equations in fluid mechanics that form an accepted basis for the simulation of isotropic homogeneous fluids. As a consequence, the different CBMs implemented in different software tools would lead to different answers for the same question.

In a collaboration with Arnau Montagud and other partners representing the software tools enumerated above, a set of basic simple model unit problems and use cases were developed for which different tools should give the same answers and interpretations, and simulations were performed to compare and, as far as possible, unify the simulation results.

Main collaborators: Arnau Montagud (CSIC), Alfonso Valencia (Barcelona Supercomputing Center.), Paul Van Liedekerke (University of Ghent)

8.5.2 CompuTiX

Participants: Jiri Pesek, Jules Dichamp, Charles Boulitrop, Peter Kottman, Dirk Drasdo.

Information on progress see section 7.

8.5.3 TiSim

Participants: Jieling Zhao, Dirk Drasdo.

Information on progress see section 7.

9 Bilateral contracts and grants with industry

9.1 Bilateral contracts with industry

9.1.1 Heartflow

Participants: Francesco Songia, Tobias Schnirer-Nedjar, Raoul Sallé de Chou, Irene Vignon-Clementel *(correspondant)*.

This project is in collaboration with Hugues Talbot (CentraleSupelec & INRIA OPIS), Laurent Najmann (ESIEE/G Eiffel University) and the company Heartflow. The goal is to generate heart perfusion maps by machine learning. See the PhD thesis of Raoul Sallé de Chou for more information [ThesisSalleDeChou].

10 Partnerships and cooperations

10.1 International research visitors

10.1.1 Visits of international scientists

Prof. Eduard Rohan

Status Professor

Institution of origin West Bohemia University

Country Czech Republic

Dates 3 days (February 2024) + 1 day (December 2024)

Context of the visit co-advising of PhD of Peter Kottman, ERC MoDeLLiver

Prof. Jessica Oakes

Status Associate Professor

Institution of origin Northeastern University

Country USA

Dates 5 days (January 2024)

Context of the visit ERC MoDeLLiver

10.1.2 Visits to international teams

Jérôme Kowalski, Irene Vignon-Clementel

Visited institution: Leiden University Medical Center

Country: Netherlands

Dates: 1 day (April 2024)

Context of the visit: ERC MoDeLLiver

Irene Vignon-Clementel

Visited institution: Northeastern University

Country: USA

Dates: 1 day (June 2024)

Context of the visit: ERC MoDeLLiver

Type of mobility: Research exchange

Irene Vignon-Clementel

Visited institution: Boston Children's Hospital

Country: USA

Dates: 1 day (June 2024)

Context of the visit: ERC MoDeLLiver

Type of mobility: Research exchange

10.2 European initiatives

10.2.1 Horizon Europe

ARTEMIS ARTEMIS project on cordis.europa.eu

Title: AcceleRating the Translation of virtual twins towards a pErsonalised Management of fatty lIver patients

Duration: From January 1, 2024 to December 31, 2027

Partners:

- INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET AUTOMATIQUE (INRIA), France
- MEDIZINISCHE UNIVERSITAET WIEN, Austria
- IMPERIAL COLLEGE OF SCIENCE TECHNOLOGY AND MEDICINE, United Kingdom
- FONDATION CARDIOMETABOLISME NUTRITION, France
- ASSISTANCE PUBLIQUE HOPITAUX DE PARIS, France
- ALBERT-LUDWIGS-UNIVERSITAET FREIBURG (ALU-FR), Germany
- DEUTSCHES KREBSFORSCHUNGSZENTRUM HEIDELBERG (GERMAN CANCER RESEARCH CENTER), Germany
- CLINIQUES UNIVERSITAIRES SAINT-LUC ASBL, Belgium
- BETTHERA SRO (BETTHERA), Czechia
- FUNDACION PARA LA INVESTIGACION DEL HOSPITAL UNIVERSITARIO LA FE DE LA COMUNIDAD VALENCIANA (HULAFE), Spain
- UNIVERSITAET LEIPZIG (ULEI), Germany
- MEDICAL RESEARCH INFRASTRUCTURE DEVELOPMENT AND HEALTH SERVICES FUND BY THE SHEBA MEDICAL CENTER (Sheba Research Fund), Israel
- BOURNEMOUTH UNIVERSITY, United Kingdom
- CHARITE - UNIVERSITAETSMEDIZIN BERLIN, Germany
- UNIVERSITATSKLINIKUM HEIDELBERG (UKHD), Germany
- EUROPEAN LIVER PATIENTS ASSOCIATION (ELPA), Belgium
- MEDEXPRIM (MEDEXPRIM), France
- FUNDACIO HOSPITAL UNIVERSITARI VALL D'HEBRON - INSTITUT DE RECERCA (VHIR), Spain
- UNIVERSITA DEGLI STUDI DI ROMA LA SAPIENZA (UNIROMA1), Italy
- MATICAL INNOVATION SL, Spain
- UNIVERSITATSKLINIKUM JENA, Germany

Inria contact: Dirk Drasdo

Grant Coordinator MATICAL INNOVATION SL

*(Clinical Coordinator:)*Vlad Ratziu

Clinical Data Coordinator: Raul Herance

Scientific Coordinator: Irene Vignon-Clementel

Summary: The ARTEMIs project aims to consolidate existing computational mechanistic and machine-learning models at different scales to deliver 'virtual twins' embedded in a clinical decision support system (CDSS). The CDSS will provide clinically meaningful information to clinicians, for a more personalised management of the whole spectrum of Metabolic Associated Fatty Liver Disease (MAFLD). MAFLD, with an estimated prevalence of about 25%, goes from an undetected sleeping disease, to inflammation (hepatitis), to fibrosis development (cirrhosis) and/or hepatocellular carcinoma (HCC), decompensated cirrhosis and HCC being the final stages of the disease. However, many MAFLD patients do not die from the liver disease itself, but from cardiovascular comorbidities or complications.

The ARTEMIs will contribute to the earlier management of MAFLD patients, by prognosing the development of more advanced forms of the disease and cardiovascular comorbidities, promoting active surveillance of patients at risk. The system will predict the impact of novel drug treatments or procedures, or simply better life habits. The system will therefore not only serve as a clinical decision aid tool, but also as an educational tool for patients, to promote better nutritional and lifestyle behaviors.

In more advanced forms of the disease, therapeutic interventions include TIPPS to manage portal hypertension, partial hepatectomy, partial or complete liver transplant. ARTEMIs will contribute to predict per- or post-intervention heart failure, building on existing microcirculation hemodynamics models.

The model developers will benefit from a large distributed patient cohort and data exploration environment to identify patterns in data, draw new theories on the liver-heart metabolic axis and validate the performance of their models.

The project includes a proof-of-concept feasibility study assessing the utility of the integrated virtual twins and CDSS in the clinical context.

10.2.2 H2020 projects

- **EDITH**

Participants: Dirk Drasdo, Maxime Sermesant *(INRIA Sophia-Antipolis)*, Irene Vignon Clementel, Jules Dichamp, Charles Boulitrop, Matteo Pedrazzi.

H2020 EDITH, Ecosystem for Digital Twins in Healthcare, Coordination and Support Action (CSA). This project aims at developing a vision for the integrated human digital twin, based on standardised (meta-)data and models, and a roadmap to realise that vision, together with concrete proof-of-concept examples. 10/2022-09/2024

- **MoDeLLiver**

Participants: Amine Zannane, Jules Dichamp, Dirk Drasdo, Sylvain Freud, Kevin Hakkakian, Peter Kottman, Jérôme Kowalski, Roel Meiburg, Ramdane Bessaid, Jiří Pešek, Mahdi Rezaei Adariani, Maja Sakli, Tobias Schnirer-Nedjar, Francesco Songia, Pavlos Varsos, Ana Vlasceanu, Irene Vignon Clementel *(correspondant; grant holder)*.

H2020 ERC consolidator grant MoDeLLiver is about 'Numerical modelling of hemodynamics and pharmacokinetics for clinical translation'. Surgical interventions are based on patient data, and although they require careful planning, they may be revised during surgery. To better predict surgery outcome, several aspects must be considered, including the local point of intervention, whole organ perfusion and function as well as their interaction with the entire circulation. To

address this complexity, the EU-funded MoDeLLiver project aims to develop a haemodynamic model to guide surgical interventions in the lung and liver. Researchers will also employ an injected substance model to unravel the link between non-invasive medical imaging and organ perfusion and function: this will be very useful to parameterise the model prior to the patient's intervention. The new modelling tool is expected to bring personalised surgical simulation a step closer to reality. 10/2020-09/2025

Collaborators are the groups of E. Vibert, N. Golse (Chair BOPA and APHP-Hop. P Brousse, France), E. Rohan (U of West Bohemia, Czech Republic), G. Soulez (CHUM, Canada), C. Debbaut (U. Ghent, Belgium), J.r. Van der Vorst (LUMC, The Netherlands), W. Huberts & F. Van de Vosse (TuE, The Netherlands), S. Hascoet & O. Mercier (Marie Lannelongue Hosp, France).

10.2.3 Other european programs/initiatives

- **BMBF-LiSyM-Cancer-2**

  Participants: Jieling Zhao, Dirk Drasdo *(Correspondant)*.

BMBF "LiSyM-CANCER-2" (liver systems medicine of cancer-2). This project followed the project LiSyM-Cancer and establishes liver systems medicine approaches to understand progression in chronic liver disease towards Hepatocellular cancer. The project is a large network project linking many partners all over Germany, and was prolonged after a new grant application round in 2024.

Collaborators include the groups of Steven Dooley (University Hospital Mannheim, Germany), Jan Hengstler (Leibniz Institute IFADO, Dortmund, Germany), Johannes Bode (University Hospital Düsseldorf, Germany)

10.3 National initiatives

- **MEDITWIN**

  Participants: Marie Haghebaert, Irene Vignon Clementel *(Correspondant)*.

The MEDITWIN project is a large French Consortium. In the UseCase on cardiopediatry, Simbiotx and Commedia Inria teams in collaboration with 3DS and Necker Enfants Malades Hospital, aim to develop a preoperative surgical planning tool to support the medical team in managing single ventricle patients. 11/2024-2029

11 Dissemination

11.1 Promoting scientific activities

11.1.1 Scientific events: organisation

General chair, scientific chair

- Organized 1-day course on biomechanics (modeling, imaging, AI) & collaboration experience for clinicians with D. Garcia (Inserm), A. Vlasceanu (CHU Tours & Inria) and K. Hakkakian (APHP & Inria) [l'Art de Soigner, la Science de Comprendre], Dec 2nd 2024, Paris, France

Member of the organizing committees

- I. Vignon-Clementel, Member of the organizing committee of the French working group GDR mecabio santé
- I. Vignon-Clementel, hosted the first EU EDITH project workshop open to a general audience & lead discussion group, Ecole Polytechnique - Saclay, France, Jan 18-19th 2024

11.1.2 Scientific events: selection

Member of the conference program committees

- Irene Vignon-Clementel, Program committee member, Computational and Mathematical Biomedical Engineering Conference
- Dirk Drasdo, Program committee for "Systems Biology of Mammalian Cells" 2024

Reviewer

- I. Vignon-Clementel, reviewer for CMBE, SBM conferences
- I. Vignon-Clementel, ESB2024, Best PhD in Biomedical Engineering award committee

11.1.3 Journal

Member of the editorial boards

- Irene Vignon-Clementel is Associate Editor of the International Journal for Numerical Methods in Biomedical Engineering and Royal Society Open Science
- Dirk Drasdo is Associated Editor for Journal of Theoretical Biology.

Reviewer - reviewing activities Journal reviewing not listed.

- I. Vignon-Clementel, European Research Council
- I. Vignon-Clementel, DFG (Germany)
- I. Vignon-Clementel, Single Ventricle Research Fund (USA)
- D. Drasdo, DFG (German Research Society) (Germany)

11.1.4 Conferences and invited talks

- Roel Meiburg, Attended, Innovaheart workshop, Paris, February 2024.
- Roel Meiburg, Oral presentation, SIAMUQ 24, Trieste, February 2024.
- Roel Meiburg, Attended, EDITH ecosystem meeting, Amsterdam, July 2024.
- Roel Meiburg, Oral Presentation, Virtual Physiological Human, Stuttgart, September 2024.
- John M. Hanna, Oral presentation, Research group "Ingénierie augmentée par la donnée, l'Apprentissage et l'IA" (GDR I-GAIA), December 2024.
- John M. Hanna, Oral presentation, Image-based Simulation for Industry conference in London, October 2024.
- John M. Hanna, Oral presentation, Virtual Physiological Human Conference, Stuttgart, September 2024.

- Pavlos Varsos, Oral presentation, Cardiogen, French National Days for Rare Cardiac Diseases, Paris, April 2024.
- Pavlos Varsos, Poster presentation, 57th Annual Meeting of the Association for European Paediatric and Congenital Cardiology, Porto, May 2024.
- Pavlos Varsos, Attended, Summer School in Percutaneous Interventions in Congenital Heart Diseases at IHU Liryc, Bordeaux, June 2024.
- Pavlos Varsos, Oral presentation, European Society of Biomechanics Conference, Edinburgh, July 2024.
- Pavlos Varsos, Poster presentation, Engineering 4 Health Annual Forum, Palaiseau, November 2024.
- Pavlos Varsos, Poster presentation, IP Paris PhD students' day, Palaiseau, December 2024.
- Marie Haghebaert, Attended, Cardiogen, French National Days for Rare Cardiac Diseases, Paris, April 2024.
- Marie Haghebaert & Morgane Garreau, Combined oral presentation, ateliers Inria x France BIOTECH, PariSanté Campus, April 2024
- Marie Haghebaert, Attended, Summer School in Percutaneous Interventions in Congenital Heart Diseases at IHU Liryc, Bordeaux, June 2024.
- Marie Haghebaert, Oral presentation, Virtual Physiological Human Conference, Stuttgart, September 2024.
- Marie Haghebaert, Attended, Kick-off MEDITWIN INRIA, PariSanté Campus, September 2024
- Marie Haghebaert, Oral presentation, INRIA Numerical Twin Workshop at INRIA Paris, October 2024
- Marie Haghebaert, Attended, 10th International Virtual Twin of Human Experience Symposium, Paris, November 2024
- Peter Kottman, Attended, Summer School "*Approches quantitatives et prédictives en biomécanique et mécanobiologie pour la santé*" organized by CNRS and GDR MécaBio Santé, Grenoble, June 2024.
- Peter Kottman, Oral presentation, Journées GDR MécaBio Santé, ENIM Metz, December 2024.
- Jérôme Kowalski, Oral presentation, Pre-clinical and clinical team meeting, Leiden University Medical Center, Leiden, The Netherlands, April 2024.
- Jérôme Kowalski, Oral presentation, World Congress of Computational Mechanics, Vancouver Canada, August 2024.
- Jérôme Kowalski, Oral presentation, Virtual physiological Human Conference 2024, Stuttgart Germany, September 2024.
- Jérôme Kowalski, Oral presentation, Journées GDR MécaBio Santé, ENIM Metz France, December 2024.
- Jieling Zhao, Oral presentation, LiSyM-Cancer Young Scientist Retreat, Huenfeld Germany, December 2024.
- Morgane Garreau, Poster presentation, 19th International symposium on Biomechanics in Vascular Biology and Cardiovascular Disease, Rotterdam, The Netherlands, May 2024.
- Morgane Garreau, Poster presentation, Journées Maths Bio Santé, Nantes, France, June 2024.
- Morgane Garreau, Oral presentations, 49ème congrès de la Société de Biomécanique, Compiègne, October 2024.

- Morgane Garreau & Ana Vlasceanu, Combined oral presentation, Journées GDR MécaBio Santé, ENIM Metz, France, December 2024.
- Morgane Garreau, Poster presentation, 3rd International School on HemoPhysics (Hemphys3), Montpellier, France, December 2024.
- Charles Boulitrop, Poster presentation, Virtual physiological Human Conference 2024, Stuttgart Germany, September 2024.
- Yassine Machta, Poster presentation, Medical Image Computing And Computer Assisted Intervention Workshop ADSMI, Marrakech Morroco, October 2024
- Raoul Sallé de Chou, Oral presentation, Discrete Geometry and Mathematical Morphology, Florence Italy, April 2024.
- Raoul Sallé de Chou, Oral and Poster presentation, Medical Imaging with Deep Learning, Paris France, July 2024.
- Jiří Pešek, Oral presentation, COMBINE-2024: Conference of the Computational Modeling in Biology Network, University of Stuttgart, September 2024
- Irene Vignon-Clementel, Seminar, ESMTB (European Society of Mathematics & Theoretical Biology), Jan 31rst, online
- Irene Vignon-Clementel, Oral presentation / video with N. Golse, Bernoulli Lab seminar, Paris, France, March 2024
- Irene Vignon-Clementel, Plenary talk, Math Num Mod conf, Roma, Italy, April 2024
- Irene Vignon-Clementel, Oral presentation, Cardiogen, French National Days for Rare Cardiac Diseases, Paris, April 2024.
- Irene Vignon-Clementel, Round table on Numerical twins & pediatric cardiology with Dr. Milani-Malekzadeh (APHP- Necker Sick Children), MediTwin kick-off, 3DS, June 5th 2024, Velizy, France
- Irene Vignon-Clementel, Invited talk, Scientific Days of Nantes U., June 11th 2024, Nantes, France
- Irene Vignon-Clementel, Invited presentation, CMBBE, June 24th-26th 2024, George Mason University, Arlington, Virginia, United States
- Irene Vignon-Clementel, seminar, Boston Children's Hospital, July 3rd 2024, Boston, United States
- Irene Vignon-Clementel, Round table, academia representative, EDITH, VPH conference, Sept 4th-6th 2024, Stuttgart, Germany
- Irene Vignon-Clementel, Invited presentation, VPH conference, Sept 4th-6th 2024, Stuttgart, Germany
- Irene Vignon-Clementel, Invited presentation, Societe de Biomécanique conference, Oct 29th 2024, Compiègne, France
- Irene Vignon-Clementel, Roundtable, 3DS 10th International Virtual Twin of Human Experience Symposium, Oct 31rst 2024, Paris, France
- Irene Vignon-Clementel, participated, INRIA Numerical Twin Workshop at INRIA Paris, October 2024
- Irene Vignon-Clementel, NRC2024 keynote (Nafems), Nov 20th 2024, CETIM, Senlis, France
- Dirk Drasdo, Plenary talk, VPH 2024, Stuttgart, 4th-6th Sept 2024.
- Simbiotx Team, Attended, Workshop for European project Edith, Palaiseau France, January 2024

11.1.5 Leadership within the scientific community

- Dirk Drasdo is associated with IfADo Leibniz Institute, having directed three research engineers/postdoccs from that institute.

11.1.6 Scientific expertise

- I. Vignon-Clementel is member of the Advisory Board, EPSRC Healthcare Technologies Network-Plus–BIOREME project (UK), since Sept 2021
- I. Vignon-Clementel is the academic presentative in Initiative Biomed in-silico France taskforce since 2023
- I. Vignon-Clementel is member of VPHi / EDITH clinical WG since 2023
- D. Drasdo, Selection committee DFG-Schwerpunktprogramm (SPP 2311) (26/06/2024, Bonn)

11.1.7 Research administration

- D. Drasdo is modeling coordinator of German LiSyM-Cancer-2 network project.
- D. Drasdo is associated with IfADo Leibniz Institute, having directed a postdocs from that institute.
- D. Drasdo is coordinator for EU-EDITH for INRIA.
- D. Drasdo is usecase1 co-leader of the EU ARTEMIS project.
- I.Vignon-Clementel is scientific coordinator & usecase3 co-leader of the EU ARTEMIS project (organizing kick-off agenda, several interventions-presentations on numerical twins & modelling, discussion group leader during workshops & meetings,...) since Jan 2024.

11.2 Teaching - Supervision - Juries

11.2.1 Teaching

Practical and lab work supervision:

- Bachelor: R. Salle de Chou, "Probability", 12h, L3, ESIEE, Universite Paris Gustave Eiffel, France.

Focused Interventions:

- M. Garreau, J. Dichamp. "Paraview Tutorial", 1h30, Joint training SIMBIOTX & Ladhyx (CNRS, Ecole polytechnique research unit), INRIA Saclay, France.
- I. Vignon-Clementel: “Numerical twin” conference (3h, Feb 29 2024), Master SIO, CentraleSupelec, France
- I. Vignon-Clementel: "Numerical simulations of blood flow" (1h30, Sept 12th 2024), undergraduate "continuum mechanics" class at AgroParisTech, Palaiseau, France
- I. Vignon-Clementel: Lecture (1h, Oct 4th 2024), Master, Biofluid Mechanics and Mass Transport, Ecole Polytechnique, France

11.2.2 Supervision

- CentraleSupélec Parcours Recherche project in progress: C. Finotto: "Improved personalization of a 0D hemodynamic model for liver surgery outcome", Oct. 2023 - present, supervisors: Roel Meiburg, I. Vignon-Clementel
- Master 2 Internship: K. Hakkakian, "Modeling portal hemodynamics using a 0D digital twin". Sept. 2023 - Sept. 2024, supervisors: I. Vignon-Clementel & N. Golse

- Master 2 Internship: A. Vlasceanu, "Geometric and Hemodynamic Study of the Portal Vein: Identification of Predictive Factors for Portal Thrombosis after Extended Liver Resection". Sept. 2023 - Sept. 2024, supervisors: I. Vignon-Clementel & N. Golse, informal supervisor: M. Garreau.
- Master Internship: A. Zannane, "Optimizing Computational Efficiency in Feto-Placental Vasculature Modeling", Apr. - Sept. 2024, supervisors: I. Vignon-Clementel & P. Wijntjes
- Master Internship: T. Schnirer, "Study on the correlation between arterial coronary morphometry and plague development using AI.", Apr. - Aug. 2024, supervisors: R. Sallé de Chou
- Master Internship: M. Pedrazzi, "Mathematical modeling of a steatotic liver cell metabolic network", Apr. - Aug. 2024, supervisors: D. Drasdo & J. Zhao
- Master Internship: M. Sakli, "Analysis of liver vascular tree architectures to characterize the development of a disease.", Mar. - Sep. 2024, supervisors: I. Vignon-Clementel & J. Kowalski
- Internship: F. Songia, "Generation of a two chambers mesh for the simulation of heart perfusion for coronary artery diseases", Mar. - Aug. 2024, supervisors: R. Sallé de Chou
- PhD in progress: M. Pedrazzi, "A model of liver disease progression", Nov. 2024 - present, supervisor: D. Drasdo.
- PhD in progress: F. Songia, "Reduced order modelling of hemodynamics for liver surgery procedure", Oct. 2024 - present, supervisors: I. Vignon-Clementel, N. Golse (AP-HP), H. Talbot (CentraleSupelec).
- PhD in progress: P. Kottman, "Multilevel modeling of flow and transport in liver lobules in health and disease", Sep. 2023 - present, supervisors: I. Vignon-Clementel, D. Drasdo & E. Rohan (UWB Pilsen, Czech Republic).
- PhD in progress: P. Varsos, "Multi-fidelity modelling of vascular shunts and clinical applications", Jul. 2023 - present, supervisors: I. Vignon-Clementel, S. Pant, N. Golse.
- PhD in progress: J. Kowalski, "Whole-body vascular transport and pharmaco-kinetics models: application to imaging, in particular of liver ", Dec. 2022 - present , supervisors: I. Vignon-Clementel, D. Drasdo & L. Sala (INRAE).
- PhD in progress: R. Sallé de Chou, "Machine Learning based prediction of heart perfusion maps", Oct. 2021 - present, supervisors: H. Talbot (CentraleSupelec and INRIA Opis team), I. Vignon-Clementel, L. Najman (ESIEE Paris)
- PhD in progress: M. Rezaei Adariani, "Flow Dynamic Modelling to Assess the Accurate Forces Scheme of Magnetic Drug Eluting Beads Navigated by Magnetic Resonance Imaging", Sep. 2021 - Aug. 2024, supervisors: G. Soulez (CR-CHUM, Montreal, Canada), I. Vignon-Clementel

11.2.3 Juries

- I. Vignon-Clementel, Hiring committee for Handicap CRCN (Junior permanent research position) for Inria, Rocquencourt, France
- I. Vignon-Clementel, Hiring committee for Professor position, Mathematics Department, U. of Côte d'Azur (Nice), France
- I. Vignon-Clementel, PhD defense committee: Ludovica Saccaro (referee), U. Bordeaux, Feb 20th 2024
- I. Vignon-Clementel, PhD defense committee: Aurèle Goetz (referee), Mines de Paris (Nice), Sept 2nd 2024
- I. Vignon-Clementel, PhD CSI: Quentin Vanderbecq, Paris May 17th 2024

- I. Vignon-Clementel, PhD CSI: Littisha Lawrance, U. Paris-Saclay, Sept 25th 2024
- I. Vignon-Clementel, Undergrad research project committee, CentraleSupelec, June 2024
- I. Vignon-Clementel, PhD defense committee: Ahmet Sen (member), Mines Saint-Etienne, Oct 1rst 2024
- I. Vignon-Clementel, HDR committee: Nathalie Poupin (member), U. Paul Sabattier (Toulouse), France, Oct 11th 2024
- I. Vignon-Clementel, PhD defense committee: Hang Jung Ling (president), INSA Lyon, Nov 7th 2024
- I. Vignon-Clementel, PhD CSI: Rodrigues Doamba, U. Paris-Saclay, Nov 14th 2024
- D. Drasdo, PhD, Friedrich-Schiller Universität Jena: Christoff Saffer, 13/12/2024 (Reviewer)

11.3 Popularization

11.3.1 Internal or external Inria responsibilities

I. Vignon-Clementel, scientific responsible of public outreach for the Inria Saclay IDF research center

11.3.2 Education

- Simbiotx group: Hosted at Inria a junior high school student (March 2024)
- J. Kowalski co-organized a week of hands-on for high-school students at Inria (June 2024)
- I. Vignon-Clementel: CHICHE !, meeting and presentation to high-school students. At Inria Rocquencourt, April 4th 2024
- J. Kowalski, M. Garreau, M. Haghebaert and I Vignon-Clementel: helped at the Fête de la Science events (Science days, 4-5th October 2024)

11.3.3 Article and contents

- M. Garreau. Interview for Studyrama website "Ils ont choisi de faire de la recherche leur métier - Témoignages", March 2024.
- I. Vignon-Clementel: Interview with journalist Catherine Decombe-Joulain on EU EDITH project for Inria web article, April 3rd 2024
- I. Vignon-Clementel: Interview by journalist Franck Niedercorn for journal Les Echos (Prospective), on EU EDITH project and Numerical Twins in Health, article out September 2024

11.3.4 Participation in Live events

- M. Garreau and M. Haghebaert: Rendez-vous des Jeunes Mathématiciennes et Informaticiennes (RJMI, Young mathematicians and computer scientists meeting). Young girls in high school speed meeting & supervision, Inria Saclay, Feb 22nd-23rd 2024.
- I. Vignon-Clementel: Rendez-vous des Jeunes Mathématiciennes et Informaticiennes (RJMI, Young mathematicians and computer scientists meeting). Young girls in high school scientific days organization, conference & speed meeting session, Inria Saclay, Feb 22-23rd 2024
- Jérôme Kowalski & Charles Boulitrop: Paris Saclay SPRING 7th edition's Innovation Tour, Inria Saclay, May 2024
- M. Garreau, M.Haghebaert, A. Vlasceanu, C. Boulitrop, M. Sakli, F. Songia, R. Bessaid : presenting the world of research to 1st year high school students in internships, Inria Saclay, June 18-19th 2024.

- I. Vignon-Clementel, 1rst year high-school student 2-weeks internship co-organization & discussion, Inria Saclay, June 17th-28th 2024
- Marie Haghebaert, Careers Conference for CSM master students, Rennes, December 2024
- Finale régionale IP Paris MT180 2024 | Jérôme Kowalski Live event & YouTube, March 2024.
- I. Vignon-Clementel: Round table intervention for Inria new comers day, Paris, France, June 4th 2024

11.3.5 Other science outreach relevant activities

- I. Vignon-Clementel: 2 videos for EU EDITH project (Jan 2024, Sept 2024)
- I. Vignon-Clementel: High school scientific girls interview, visio, May 20th 2024

12 Scientific production

12.1 Major publications

[1] J. Dichamp, G. Cellière, A. Ghallab, R. Hassan, N. Boissier, U. Hofmann, J. Reinders, S. Sezgin, S. Zühlke, J. Hengstler and D. Drasdo. 'In-vitro to in-vivo acetaminophen hepatotoxicity extrapolation using classical schemes, pharmaco-dynamic models and a multiscale spatial-temporal liver twin'. In: *Frontiers in Bioengineering and Biotechnology* (2023). URL: https://hal.science/hal-03941544 (cit. on p. 6).

[2] D. Drasdo, S. Hoehme and J. G. Hengstler. 'How predictive quantitative modeling of tissue organization can inform liver disease pathogenesis.' In: *Journal of Hepatology* 61.4 (Oct. 2014), pp. 951–956. DOI: 10.1016/j.jhep.2014.06.013. URL: https://hal.inria.fr/hal-01110644 (cit. on p. 5).

[3] A. Ghallab, G. Celliere, S. Henkel, D. Driesch, S. Hoehme, U. Hofmann, S. Zellmer, P. Godoy, A. Sachinidis, M. Blaszkewicz, R. Reif, R. Marchan, L. Kuepfer, D. Häussinger, D. Drasdo, G. Gebhardt and J. G. Hengstler. 'Model-guided identification of a therapeutic strategy to reduce hyperammonemia in liver diseases'. In: *Journal of Hepatology* 64.4 (27th Nov. 2015), pp. 860–871. DOI: 10.1016/j.jhep.2015.11.018. URL: https://hal.archives-ouvertes.fr/hal-01257127 (cit. on p. 5).

[4] N. Golse, F. Joly, P. Combari, M. Lewin, Q. Nicolas, C. Audebert, D. Samuel, M.-A. Allard, A. Sa Cunha, D. Castaing, D. Cherqui, R. Adam, E. Vibert and I. Vignon-Clementel. 'Predicting the risk of post-hepatectomy portal hypertension using a digital twin: A clinical proof of concept'. In: *Journal of Hepatology* 74.3 (Mar. 2021), pp. 661–669. DOI: 10.1016/j.jhep.2020.10.036. URL: https://hal.archives-ouvertes.fr/hal-03523641 (cit. on p. 6).

[5] F. Joly, G. Soulez, S. Lessard, C. Kauffmann and I. Vignon-Clementel. 'A cohort longitudinal study identifies morphology and hemodynamics predictors of abdominal aortic aneurysm growth'. In: *Annals of Biomedical Engineering* (1st Oct. 2019). DOI: 10.1007/s10439-019-02375-1. URL: https://hal.archives-ouvertes.fr/hal-02302464 (cit. on p. 6).

[6] S. Pant, B. Fabrèges, J.-F. Gerbeau and I. Vignon-Clementel. 'A methodological paradigm for patient-specific multi-scale CFD simulations: from clinical measurements to parameter estimates for individual analysis'. In: *International Journal for Numerical Methods in Biomedical Engineering* 30.12 (Dec. 2014), pp. 1614–1648. DOI: 10.1002/cnm.2692. URL: https://hal.inria.fr/hal-01093879 (cit. on p. 5).

[7] P. Van Liedekerke, J. Neitsch, T. Johann, K. Alessandri, P. Nassoy and D. Drasdo. 'Quantitative cell-based model predicts mechanical stress response of growing tumor spheroids over various growth conditions and cell lines'. In: *PLoS Computational Biology* 15.3 (8th Mar. 2019), e1006273. DOI: 10.1371/journal.pcbi.1006273. URL: https://hal.archives-ouvertes.fr/hal-02371813 (cit. on p. 7).

[8] P. Van Liedekerke, M. Palm, N. Jagiella and D. Drasdo. 'Simulating tissue mechanics with Agent Based Models: concepts and perspectives'. In: *Computational Particle Mechanics* 2.4 (25th Nov. 2015), pp. 401–444. DOI: 10.1007/s40571-015-0082-3. URL: https://hal.inria.fr/hal-01220539 (cit. on p. 4).

[9] N. Vartak, G. Guenther, F. Joly, A. Damle-Vartak, G. Wibbelt, J. Fickel, S. Jörs, B. Begher-Tibbe, A. Friebel, K. Wansing, A. Ghallab, M. Rosselin, N. Boissier, I. Vignon-Clementel, C. Hedberg, F. Geisler, H. Hofer, P. Jansen, S. Hoehme, D. Drasdo and J. Hengstler. 'Intravital dynamic and correlative imaging reveals diffusion-dominated canalicular and flow-augmented ductular bile flux'. In: *Hepatology* 73.4 (Apr. 2021), pp. 1531–1550. DOI: 10.1002/hep.31422. URL: https://hal.inria.fr/hal-03135253 (cit. on pp. 5, 13).

[10] I. Vignon-Clementel, N. Jagiella, J. Dichamp, J. Kowalski, W. Lederle, H. Laue, F. Kiessling, O. Sedlaczek and D. Drasdo. 'A proof-of-concept pipeline to guide evaluation of tumor tissue perfusion by dynamic contrast-agent imaging: Direct simulation and inverse tracer-kinetic procedures'. In: *Frontiers in Bioinformatics* 3 (13th Apr. 2023). DOI: 10.3389/fbinf.2023.977228. URL: https://hal.science/hal-04068296 (cit. on p. 6).

12.2 Publications of the year

International journals

[11] P. Kottman and O. Souček. 'On the pitfalls of diffuse interface methods in problems involving non-material interfaces'. In: *International Journal of Non-Linear Mechanics* 162 (June 2024), p. 104725. DOI: 10.1016/j.ijnonlinmec.2024.104725. URL: https://inria.hal.science/hal-04840702.

[12] I. Vignon-Clementel. 'Deep-learning and hemodynamics models: efficient complementarity for disease diagnosis and surgery planning'. In: *Multidisciplinary Biomechanics Journal* 49th congress of the Société de Biomécanique (31st Jan. 2025). DOI: 10.46298/mbj.14522. URL: https://hal.science/hal-04738004.

[13] J. Zhao, A. Ghallab, R. Hassan, S. Dooley, J. G. Hengstler and D. Drasdo. 'A liver digital twin for in silico testing of cellular and inter-cellular mechanisms in regeneration after drug-induced damage'. In: *iScience* 27.2 (Feb. 2024), p. 108077. DOI: 10.1016/j.isci.2023.108077. URL: https://inria.hal.science/hal-03738207.

International peer-reviewed conferences

[14] A. Facque, W. Liu, L. Sala, I. Vignon-Clementel and N. Golse. 'A new geometric and hemodynamic approach to understand post-operative portal thrombosis development based on in-silico modeling'. In: 16th World Congress of the International Hepato-Pancreato-Biliary Association. Vol. 26. Cape Town, South Africa, South Africa, 2024, S28. DOI: 10.1016/j.hpb.2024.03.052. URL: https://hal.science/hal-04869969 (cit. on p. 15).

[15] Y. Machta, O. Ali, K. Hakkakian, A. Vlasceanu, A. Facque, N. Golse and I. Vignon-Clementel. 'Enhancing the automatic segmentation and analysis of 3D liver vasculature models'. In: ADSMI @ MICCAI Workshop on Advancing Data Solutions in Medical Imaging AI. Marrakesh, Morocco, 6th Oct. 2024. URL: https://hal.science/hal-04854990 (cit. on p. 15).

[16] R. Sallé de Chou, M. Sinclair, S. Lynch, N. Xiao, L. Najman, I. E. Vignon-Clementel and H. Talbot. 'Finite Volume Informed Graph Neural Network for Myocardial Perfusion Simulation'. In: MIDL 2024 - Medical Imaging with Deep Learning 2024. Paris, France, 3rd July 2024. URL: https://inria.hal.science/hal-04828473 (cit. on pp. 6, 18).

[17] R. Sallé de Chou, M. A. Srir, L. Najman, N. Passat, H. Talbot and I. Vignon-Clementel. 'Convex optimization for binary tree-based transport networks'. In: *Lecture Notes in Computer Science*. International Conference on Discrete Geometry and Mathematical Morphology (DGMM). Vol. 14605. Florence, Italy, 2024, pp. 217–228. DOI: 10.1007/978-3-031-57793-2_17. URL: https://inria.hal.science/hal-04359833 (cit. on p. 18).

Scientific book chapters

[18] J. Kowalski, D. Drasdo, P. Kottman, J. Dichamp and I. Vignon-Clementel. 'Microvascular modeling for medical imaging and toxicity assessment'. In: *Quantitative approaches to microcirculation: mathematical models, computational methods, measurements and data analysis*. Vol. 36. SEMA SIMAI Springer Series. Springer; Springer Nature Switzerland, 2024, pp. 49–85. DOI: 10.1007/978-3-031-58519-7_3. URL: https://hal.science/hal-04465901 (cit. on p. 14).

Edition (books, proceedings, special issue of a journal)

[19] *CompuTiX: A library for agent based modeling (not only) at a tissue-scale*. COMBINE 2024 - Conference of the Computational Modeling in Biology Network : September 1-5, 2024, University of Stuttgart. COMBINE 2024 - Conference of the Computational Modeling in Biology Network : September 1-5, 2024, University of Stuttgart. COMBINE, 2024. DOI: 10.24407/KXP:1902121317. URL: https://hal.science/hal-04852174.

Reports & preprints

[20] M. Haghebaert, P. Varsos, R. Meiburg and I. Vignon-Clementel. *A comparative study of lumped heart models for personalized medicine through sensitivity and identifiability analysis*. 18th Dec. 2024. URL: https://hal.science/hal-04844897 (cit. on p. 21).

[21] J. M. Hanna, P. Varsos, J. Kowalski, L. Sala, R. Meiburg and I. Vignon-Clementel. *A comparative analysis of metamodels for lumped cardiovascular models, and pipeline for sensitivity analysis, parameter estimation, and uncertainty quantification*. 2024. URL: https://hal.science/hal-04829481 (cit. on p. 21).

[22] J. M. Hanna and I. Vignon-Clementel. *Variance-based loss function for improved regularization*. 18th Dec. 2024. URL: https://hal.science/hal-04846756 (cit. on p. 21).

12.3 Cited publications

[23] O. Ali, A. Bône, C. Accardo, O. Belkouchi, M.-M. Rohe, E. Vibert and I. Vignon-Clementel. 'CoRe: An Automated Pipeline for the Prediction of Liver Resection Complexity from Preoperative CT Scans'. In: *Artificial Intelligence over Infrared Images for Medical Applications and Medical Image Assisted Biomarker Discovery : First MICCAI Workshop, AIIIMA 2022, and First MICCAI Workshop, MIABID 2022, Held in Conjunction with MICCAI 2022, Singapore, September 18 and 22, 2022, Proceedings*. Vol. LNCS-13602. Lecture Notes in Computer Science. Singapore, Singapore: Springer Nature Switzerland, Sept. 2022, pp. 125–133. DOI: 10.1007/978-3-031-19660-7_12. URL: https://hal.science/hal-03919572 (cit. on p. 6).

[24] C. Audebert, P. Bucur, M. Bekheit, E. Vibert, I. Vignon-Clementel and J.-F. Gerbeau. 'Kinetic scheme for arterial and venous blood flow, and application to partial hepatectomy modeling.' In: *Computer Methods in Applied Mechanics and Engineering* 314 (Feb. 2017), pp. 102–125. DOI: 10.1016/j.cma.2016.07.009. URL: https://hal.archives-ouvertes.fr/hal-01347500 (cit. on p. 5).

[25] C. Audebert and I. Vignon-Clementel. 'Model and methods to assess hepatic function from indocyanine green fluorescence dynamical measurements of liver tissue'. In: *European Journal of Pharmaceutical Sciences* (2018). DOI: 10.1016/j.ejps.2018.01.008. URL: https://hal.archives-ouvertes.fr/hal-01696064 (cit. on p. 5).

[26] N. Boissier, D. Drasdo and I. Vignon-Clementel. 'Simulation of a detoxifying organ function: Focus on hemodynamics modeling and convection-reaction numerical simulation in microcirculatory networks'. In: *International Journal for Numerical Methods in Biomedical Engineering* 37.2 (2021). DOI: 10.1002/cnm.3422. URL: https://hal.inria.fr/hal-03135175 (cit. on p. 5).

[27] J. Dichamp, G. Cellière, A. Ghallab, R. Hassan, N. Boissier, U. Hofmann, J. Reinders, S. Sezgin, S. Zühlke, J. Hengstler and D. Drasdo. 'In-vitro to in-vivo acetaminophen hepatotoxicity extrapolation using classical schemes, pharmaco-dynamic models and a multiscale spatial-temporal liver twin'. In: *Frontiers in Bioengineering and Biotechnology* 11 (2023). DOI: 10.3389/fbioe.2023.1049564. URL: https://hal.science/hal-03941544 (cit. on p. 14).

[28] D. Drasdo, S. Hoehme and J. G. Hengstler. 'How predictive quantitative modeling of tissue organization can inform liver disease pathogenesis.' In: *Journal of Hepatology* 61.4 (Oct. 2014), pp. 951–956. DOI: 10.1016/j.jhep.2014.06.013. URL: https://hal.inria.fr/hal-01110644 (cit. on p. 6).

[29] A. Friebel, T. Johann, D. Drasdo and S. Hoehme. 'Guided interactive image segmentation using machine learning and color-based image set clustering'. In: *Bioinformatics* 38.19 (2022), pp. 4622–4628. DOI: 10.1093/bioinformatics/btac547. URL: https://inria.hal.science/hal-03702928 (cit. on p. 5).

[30] A. Friebel, J. Neitsch, T. Johann, S. Hammad, D. Drasdo and S. Hoehme. 'TiQuant: software for tissue analysis, quantification and surface reconstruction'. In: *Bioinformatics* 31.19 (June 2015), pp. 3234–3236. DOI: 10.1093/bioinformatics/btv346. URL: https://hal.inria.fr/hal-01257137 (cit. on p. 5).

[31] N. Jagiella, B. Müller, M. Müller, I. E. Vignon-Clementel and D. Drasdo. 'Inferring Growth Control Mechanisms in Growing Multi-cellular Spheroids of NSCLC Cells from Spatial-Temporal Image Data'. In: *PLoS Computational Biology* 12.2 (2016), e1004412. DOI: 10.1371/journal.pcbi.1004412. URL: https://hal.sorbonne-universite.fr/hal-01244593 (cit. on p. 5).

[32] M. Leist, A. Ghallab, R. Graepel, R. Marchan, R. Hassan, S. H. Bennekou, A. Limonciel, M. Vinken, S. Schildknecht, T. Waldmann et al. 'Adverse outcome pathways: opportunities, limitations and open questions'. In: *Archives of Toxicology* 91.11 (Nov. 2017), pp. 3477–3505. DOI: 10.1007/s00204-017-2045-3. URL: https://hal.inria.fr/hal-01968849 (cit. on p. 7).

[33] W. Liu, M. Garreau, L. Papamanolis, C. Kassasseya, K.-A. Nguyen-Peyre, N. Belkeziz, S. Verlhac, P. Bartolucci and I. Vignon-Clémentel. 'In-silico modelling of cerebral vasculopathy risk for children with sickle cell disease'. working paper or preprint. Oct. 2024. URL: https://hal.science/hal-04737957 (cit. on p. 19).

[34] S. Pant, C. Corsini, C. Baker, T.-Y. Hsia, G. Pennati and I. Vignon-Clementel. 'A Lumped Parameter Model to Study Atrioventricular Valve Regurgitation in Stage 1 and Changes Across Stage 2 Surgery in Single Ventricle Patients'. In: *IEEE Transactions on Biomedical Engineering* 65.11 (Nov. 2018), pp. 2450–2458. DOI: 10.1109/tbme.2018.2797999. URL: https://hal.inria.fr/hal-01954784 (cit. on p. 7).

[35] S. Pant, A. Sizarov, A. Knepper, G. Gossard, A. Noferi, Y. Boudjemline and I. Vignon-Clementel. 'Multiscale modelling of Potts shunt as a potential palliative treatment for suprasystemic idiopathic pulmonary artery hypertension: a paediatric case study'. In: *Biomechanics and Modeling in Mechanobiology* 21.2 (Apr. 2022), pp. 471–511. DOI: 10.1007/s10237-021-01545-2. URL: https://inria.hal.science/hal-03690837 (cit. on p. 19).

[36] L. Papamanolis, H. J. Kim, C. Jaquet, M. Sinclair, M. Schaap, I. Danad, P. van Diemen, P. Knaapen, L. Najman, H. Talbot, C. A. Taylor and I. Vignon-Clementel. 'Myocardial Perfusion Simulation for Coronary Artery Disease: A Coupled Patient-Specific Multiscale Model'. In: *Annals of Biomedical Engineering* 49 (May 2021), pp. 1432–1447. DOI: 10.1007/s10439-020-02681-z. URL: https://hal.science/hal-03036457 (cit. on p. 18).

[37] N. Pozin, S. Montesantos, I. Katz, M. Pichelin, I. Vignon-Clementel and C. Grandmont. 'Predicted airway obstruction distribution based on dynamical lung ventilation data: a coupled modeling-machine learning methodology'. In: *International Journal for Numerical Methods in Biomedical Engineering* 34.9 (May 2018). DOI: 10.1002/cnm.3108. URL: https://hal.archives-ouvertes.fr/hal-01568065 (cit. on p. 6).

[38] L. Sala, N. Golse, A. Joosten, E. Vibert and I. Vignon-Clementel. 'Sensitivity Analysis of a Mathematical Model Simulating the Post-Hepatectomy Hemodynamics Response'. In: *Annals of Biomedical Engineering* (Jan. 2023). DOI: 10.1007/s10439-022-03098-6. URL: https://hal.science/hal-03839072 (cit. on p. 6).

[39] F. Schliess, S. Hoehme, S. Henkel, A. Ghallab, D. Driesch, J. Böttger, R. Guthke, M. Pfaff, J. Hengstler, R. Gebhardt, D. Häussinger, D. Drasdo and S. Zellmer. 'Integrated metabolic spatial-temporal model for the prediction of ammonia detoxification during liver damage and regeneration'. In: *Hepatology* 60.6 (Dec. 2014), pp. 2040–2051. DOI: 10.1002/hep.27136. URL: https://hal.inria.fr/hal-01110646 (cit. on p. 5).

[40] P. Van Liedekerke, J. Neitsch, T. Johann, K. Alessandri, P. Nassoy and D. Drasdo. 'Quantitative cell-based model predicts mechanical stress response of growing tumor spheroids over various growth conditions and cell lines'. In: *PLoS Computational Biology* 15.3 (Mar. 2019), e1006273. DOI: 10.1371/journal.pcbi.1006273. URL: https://hal.archives-ouvertes.fr/hal-02371813 (cit. on p. 4).

[41] P. Van Liedekerke, M. Palm, N. Jagiella and D. Drasdo. 'Simulating tissue mechanics with Agent Based Models: concepts and perspectives'. In: *Computational Particle Mechanics* 2.4 (Nov. 2015), pp. 401–444. DOI: 10.1007/s40571-015-0082-3. URL: https://hal.inria.fr/hal-01220539 (cit. on p. 4).

[42] I. Vignon-Clementel, N. Jagiella, J. Dichamp, J. Kowalski, W. Lederle, H. Laue, F. Kiessling, O. Sedlaczek and D. Drasdo. 'A proof-of-concept pipeline to guide evaluation of tumor tissue perfusion by dynamic contrast-agent imaging: Direct simulation and inverse tracer-kinetic procedures'. In: *Frontiers in Bioinformatics* 3 (Apr. 2023). DOI: 10.3389/fbinf.2023.977228. URL: https://hal.science/hal-04068296 (cit. on p. 14).

[43] Y. Yin, O. Sedlaczek, B. Müller, A. Warth, M. González-Vallinas, B. Lahrmann, N. Grabe, H.-U. Kauczor, K. Breuhahn, I. Vignon-Clementel and D. Drasdo. 'Tumor cell load and heterogeneity estimation from diffusion-weighted MRI calibrated with histological data: an example from lung cancer'. In: *IEEE Transactions on Medical Imaging* (2017). DOI: 10.1109/TMI.2017.2698525. URL: https://hal.inria.fr/hal-01421398 (cit. on p. 6).