2022
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, HDR]

- Irene Vignon Clementel [INRIA, Senior Researcher, HDR]

## Post-Doctoral Fellows

- Lorenzo Sala [INRIA]

- Jieling Zhao [IFADO]

## PhD Students

- Omar Ali [INSERM]

- Jérôme Kowalowski [Inria, from Dec 2022]

- Mahdi Rezaei Adariani [INRIA]

- Raoul Salle De Chou [INRIA]

## Technical Staff

- Elena Cutri [INRIA, Engineer, until Aug 2022]

- Mathieu De Langlard [INRIA, Engineer]

- Jules Dichamp [INRIA, Engineer]

- Weiqiang Liu [INRIA, from Oct 2022]

- Jiri Pesek [INRIA, Engineer]

- Paul Van Liedekerke [T-INSIL, Engineer, until Mar 2022]

## Interns and Apprentices

- Darius Dabert [ECOLE POLY PALAISEAU, from Nov 2022]

- Axel De Sinzogan [HEC Paris, from Sep 2022]

- Richard Hruby [HEC Paris, from Sep 2022]

- Peter Kottman [UNIV CHARLES - PRAGUE, from Aug 2022]

- Jerome Kowalski [Inria, from May 2022 until Oct 2022]

- Weiqiang Liu [Inria, from Mar 2022 until Sep 2022]

- Diane Penin De La Raudiere [HEC Paris, from Sep 2022]

## Administrative Assistant

- Hanadi Dib [INRIA]

**External Collaborators**

- Nicolas Golse [AP/HP]

- Lazaros Papamanolis [Heartflow]

- Eric Vibert [APHP]

## 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). 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. 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 aims at better understanding by in-silico modeling how non-invasive imaging reflects the underlying organ architecture, perfusion and function. In synergy with the first aim, SIMBIOTX aims at guiding clinical decisions by mathematical models integrating the data to inform clinicians and build predictions of possible therapy consequences. Both, models and software generated in that process will pertain to standardization. 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. SIMBIOTX aims at building models explaining the outcome of in vitro experiments and guiding in vivo toxicity predictions from in vitro toxicity data, eventually by building spatial-temporal in silico abstractions of the in vitro and in vivo systems. 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.

   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 [27]. For networks of thousands of small conduits, resistance (0D) models are typically solved, where a finer rheology can be incorporated [29]. 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] [28]. 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 [29], [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 [34]. 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. [31]).

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. A second approach is to perform quantitative image analysis and correlation of different image modalities [42]. 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.

Biophysical models can also be complemented by machine-learning approaches [5, 38].

# 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. [30]). 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 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. [36]). 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) 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 ([35], 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    Highlights of the year

- SIMBIOTX is part of a new European project: H2020 EDITH, Ecosystem for Digital Twins in Healthcare, Coordination and Support Action (CSA).

- Elena Cutri received a position as MCF (assistent professor) at Université de Technologie de Compiegne (France).

- Nicolas Golse received a position as MCU (assistant professor in the school of medicine) at Université Paris-Saclay.

- Lorenzo Sala received a position as CRCN (permanent researcher position) at INRAE (L'INSTITUT NATIONAL DE RECHERCHE POUR L'AGRICULTURE, L'ALIMENTATION ET L'ENVIRONNEMENT) (France).

- Paul Van Liedekerke received a possition as assistent professor as University of Ghent (Belgium).

## 5.1   Awards

- Weiqiang Liu, research assistant in the team received a travel grant: EUR Bertip BME awards for conferences from École Polytechnique, IP Paris (France).

- Lorenzo Sala, postdoc in the team received an invitation to the research program SQuaREs (1 week) at the American Institute of Mathematics in San José, California (USA) [October 2022].

- Omar Ali, PhD candidate in the team received the best poster award at the Engineering4Health Symposium organized at Ecole Polytechnique, IP Paris [July 2022].

## 5.2 Patents

- Patent 'Dispositif d'imagerie tumorale'- FR2006763, accepted July 2022 (France) + international request June 2021 PCT/FR 2021/051168, extension to Europe, USA, Canada, Japan, Dec 2022. Inventors: Dirk Drasdo, Irene Vignon-Clementel, Yi Yin.

> **Participants:** Dirk Drasdo, Irene Vignon-Clementel.

- Patent application for the invention titled "Computer-implemented method of liver resection planning" was filed on July 29 2022, with the European Patent Office as patent application number EP22306150.8.

> **Participants:** Omar Ali, Irene Vignon-Clementel.

# 6 New software and platforms

## 6.1 New software

### 6.1.1 LumpedFlow

**Keywords:** Ordinary differential equations, Kalman filter, Hemodynamics, Model, Pharmacokinetics

**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

**Authors:** Irene Vignon Clementel, Sanjay Pant, Chloé Audebert, Jean-Frederic Gerbeau, Quentin Nicolas, Florian Joly

**Contact:** Irene Vignon Clementel

### 6.1.2 TiSim

**Name:** Tissue Simulator

**Keywords:** Systems Biology, Bioinformatics, Biology, Physiology

**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 ($\tilde{6}0$ MMs) + model development time ($\tilde{2}64$ 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

**Partner:** IZBI, Université de Leipzig

### 6.1.3 TiQuant

**Name:** Tissue Quantifier

**Keywords:** Systems Biology, Bioinformatics, Biology, Physiology

**Functional Description:** Systems biology and medicine on histological scales require quantification of images from histological image modalities such as confocal laser scanning or bright field microscopy. The latter can be used to calibrate the initial state of a mathematical model, and to evaluate its explanatory value, which hitherto has been little recognized. We generated a software for image analysis of histological material and demonstrated its use in analysing liver confocal micrografts, called TiQuant (Tissue Quantifier). The software is part of an analysis chain detailing protocols of imaging, image processing and analysis in liver tissue, permitting 3D reconstructions of liver lobules down to a resolution of less than a micrometer.

**Authors:** Dirk Drasdo, Stefan Hoehme, Adrian Friebel

**Contact:** Dirk Drasdo

### 6.1.4 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.

**Authors:**  Jiri Pesek, Jules Dichamp, Dirk Drasdo

**Contact:**  Dirk Drasdo

**Partner:**  T-INSIL

# 7    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 2022, 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.

## 7.1    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 in 2022.

### 7.1.1    Digital twin model of paracetamol toxicity *in vitro* to *in vivo* extrapolation

**Participants:**    Jules Dichamp, Dirk Drasdo, Geraldine Celiere, Noemie Boissier.

This work addresses a digital twin model of the process of acute drug-induced liver injury (DILI). Paracetamol (acetaminophen, APAP) is a widely used drug but hepatotoxic (damaging the hepatocytes, i.e. the parenchymal cells of the liver) at high doses generating a characteristic spatial tissue damage pattern at the level of tissue microarchitectucture. Paracetamol was thus considered as a model drug to study to what extent one can extrapolate from in vitro to in vivo hepatotoxicity, which represents a critical challengeD in toxicology to minimize or circumvent animal experiments. In the paper [1] we explore *in vitro* to *in vivo* extrapolation strategies for paracetamol hepatotoxicity, comparing the classical common extrapolation strategy based on blood concentration estimates of the drug, to homogeneous (well-mixed) compartment pharmaco-dynamic models and to a multiscale digital twin model resolving liver micro-architecture at cellular resolution. For the sake of validation, in vitro and in vivo mouse experiments have been performed for the project by our experimental collaborators. The models integrate consensus detoxification reactions in each individual hepatocyte. We study the consequences of the two model types, well-mixed vs. spatial-temporal digital twin model of an entire liver lobule (that constitutes the smallest repetitive functional and anatomic unit of liver) on the extrapolation and show in which cases these model types perform better than the classical extrapolation strategy. We find that (1.) a classical model based on a well-mixed blood compartment is sufficient to correctly predict the in vivo toxicity from in vitro data if the model is fitted on in vitro hepatotoxicity data and the pharmacokinetic data of the drug blood concentration simultaneously. (2.) The digital twin model, that integrates more experimental information, performs equally well, but does not fit the data with precisely the same parameter choice as

the well-mixed model. This indicates a potentially important role of the spatial liver microarchitecture. (3.) This argument was supported by the observation of a non-negligible drug gradient in the liver lobule. In conclusion, the work proposes a mechanism-based, digital liver twin model - based strategy to outperform classical strategies of in vitro to in vivo drug toxicity extrapolation. **Collaborators: J.G. Hengstler, A. Ghallab and coworkers from Leibnitz Institute IFADO, Dortmund, Germany.**

### 7.1.2   Digital twin model of liver regeneration

**Participants:**   Jieling Zhao, Dirk Drasdo.

This work addresses a digital twin model of the regeneration process that follows the acute DILI caused by paracetamol described in the previous subsection, for consistency again in the mouse model. Accordingly, a mathematical mechanism-based digital twin model of the regenerating liver after drug-induced pericentral lobule damage resolving tissue microarchitecture was developed using the same liver microarchitectucture as in the previous subsection [23][25]. Many different cell types tightly orchestrated in time and space permit in most cases a restorage of liver mass and architecture after 1-2 weeks. These cell types were implemented as part of the liver microarchitecture inside a network of liver capillaries (so called sinusoids). The shape of cells in that model was approximated by center-based models (CBMs), whereby complex cell shapes were mimicked as objects composed of many spheres. However, the precise interplay of cell types is debated. Hence the consequence of alternative mechanistic hypotheses about the interplay of different cell types on regeneration were simulated. We used deviations of the simulated systems dynamics from the experimentally observed trajectories to identify branching points, at which the systems behavior cannot be explained by the underlying set of hypotheses anymore. In this way, our digital twin approach permitted to identify three sets of hypotheses that were incompatible with the experimentally observed regeneration process i.e., disqualify as a digital twin of regeneration. In a next step one of the digital twin models was used to virtually test a type of perturbations from the molecular up to the tissue scale of a type that experimentalists frequently apply to study mechanisms. The digital twin model predicted those perturbations that would be expected to change the regeneration process. Such perturbations would be prime candidates for new, future experiments. Hence our procedure reflects a successful strategy for generating a fully digital liver-twin model that, among others, permits identifying gaps in mechanistic relationships and guiding the system towards the most informative (lacking) experiments and parameters that can be experimentally addressed.

**Collaborators: J.G. Hengstler, A. Ghallab and coworkers from Leibnitz Institute IFADO, Dortmund, Germany; S. Dooley from University Clinics Mannheim, Germany**

### 7.1.3   Digital twin models of liver metabolism after toxic damage and in disease, and disease progression.

**Participants:**   Jules Dichamp, Dirk Drasdo, Jieling Zhao, Paul Van Liedekerke.

The two former paragraphs address first a digital twin model (DTM) of acute drug induced liver injury (DILI), then a digital twin model of the subsequent regeneration process. Both DTMs form bricks of a bigger DTM addressing acute DILI, regeneration, its impact on liver function and degeneration towards chronic liver disease. Accordingly, the missing bricks have been advanced as briefly summarized hereafter. A DTM for ammonia detoxification after DILI has been developed using the same liver microarchitecture as the other two DTMs described above. Ammonia detoxification is an important process, which is compromised after DILI, leading to encephalopathy and frequently death through acute liver failure. The simulation results with the DTM for DILI accurately agree with experimental data. The DTM was used to predict ammonia detoxification in fibrosis, where the liver microarchitecture is compromised by deposition of extracellular matrix in a characteristic spatial pattern. The digital liver twin of liver regeneration have been advanced to explain a possible scenario of how this characteristic spatial pattern may occur [24]. **Collaborators: J.G. Hengstler, A. Ghallab and coworkers from Leibnitz**

**Institute IFADO, Dortmund, Germany; S. Dooley, S. Hammad and co-workers from University Clinics Mannheim, Germany**

### 7.1.4  Guided interactive image segmentation using machine learning and color-based image set clustering

> **Participants:**    Tim Johann, Dirk Drasdo.

To create the spatial tissue arrangement for the digital liver twin model image data have to be processed and analyzed (e.g. ([33]; [32]; [31]). So far this requires image analysis experts, and a close interaction between the experts and the experimental group performing the imaging, to permit a correct calibration of the image analysis procedures and algorithms. To facilitate this iteration, a guided interactive image segmentation pipeline has been built into the former software TiQuant (Friebel et. al., 2015, which uses machine learning and color-based image set clustering ([13]). This methodology has been found to be efficient in case only a few images are available, which is a situation frequently met for histologiacal images, so that the applicability of deep learning is limited. The approach combines machine learning-based interactive image segmentation using supervoxels with a clustering method for the automated identification of similarly colored images in large image sets which enables a guided reuse of interactively trained classifiers. The presented methods are applicable for almost any image type and represent a useful tool for image analysis tasks in general. **Collaborators: S. Hoehme and A. Friebel, Institute for Computer Science, and Interdisciplinary Center for Bioinformatics (IZBI), University of Leipzig, Germany**

### 7.1.5  Physics informed tissue architecture reconstruction

> **Participants:**    Jiri Pesek, Mathieu de Langlard, Dirk Drasdo.

The above Digital twin models study processes in a statistically representative liver tissue microarchitecture, that has been constructed by statistical sampling from geometrical parameter distributions obtained from image analysis of 3D reconstructed confocal laser scanning micrographs from many tissue blocks . Such an approach does by construction not permit simulations out of concrete specific 3D tissue reconstructions, which would be necessary to study the effect of variations of tissue blocks at different positions in the liver, or to perform simulations right out of a concrete tissue sample e.g. obtained from a biopsy. Hence we developed a cell-model-based method to start digital twin model simulations directly out of 3D image reconstructions. The method refines 3D image reconstructions obtained from a classical image analysis by ensuring that the obtained cell shapes and other tissue microarchitectural elements comply with the mechanical and several other physical properties of the cells and other tissue elements. We demonstrate that such a method offers a higher accuracy of reconstructed cell shapes and tissue organization as, for example, the morphological watershed algorithm that has previously been demonstrated to in general perform well surface reconstruction within image stacks of tissue samples . The developed methodology is not limited to liver tissue but can equally be applied to other tissue microarchitectures as well as to in vitro multi-cellular arrangements. **Collaborators: This study was inspired by requirements inside the ANR-projects iLite and STEDI-NASH, as well as in the BMBF project LiSyM-Cancer.**

## 7.2  Liver: From the micro- to the mesoscale 3D

### 7.2.1  Reconstruction of the human liver architecture at the interface of micro-and mesoscale

> **Participants:**    Mathieu de Langlard, Irene Vignon-Clementel, Dirk Drasdo.

So far the digital twin models focused on tissue samples from the mouse model. This was partially caused by the need of model validation, which is in most cases by ethical reasons not possible in human, and partially by a lack of human liver tissue. As a first step we here study human tissue organisation, capturing elements of microarchitectucture, and of tissue architecture at a mesoscopic level, which is necessary to prospectively study if, when and how disease-related processes and microarchitectural alterations translate into macroscopic observables, that can be minimal-invasively be detected in patients within the clinical workflow.

Histopathology based on 2D tissue samples is the common basis for the diagnosis and study of diseases of the liver tissue. However, the complexity of the liver organization calls for richer and more consistent data representation, hence leading to spatially resolved 3D visualization and analysis. This would enable better understanding of how processes at different scales influence and are influenced by the liver tissue anatomy and microanatomy and hence facilitate a better understanding and earlier diagnosis of liver diseases.

We proposed[1] with our collaborators at the hospital Kremlin-Bicêtre and hospital Paul Brousse a new approach to reconstruct and quantify the liver structures at the micro- and mesoscale. We called this methodology *3D histology reconstruction* and it encompasses technical advances in the preparation of the liver tissue (liver sectioning, staining and imaging) as well as methodological results in the field of image analysis and reconstruction. We showed that we are now able to analyse large and consistent liver sample volumes from the micro- to the mesoscale. We also obtained a morphological quantification of liver structures such as lobule size-shape distribution or the topology of the vascular system, which can furthermore inform the computational models we devise in the team to probe the possible functional consequences of architectural alterations. **Collaborators: Nassima Benzoubir, Anne Dubart Kupperschmitt, Jean-Charles Duclos-Vallee, Catherine Guettier, Antonietta Messina, Olivier Trassard**

## 7.3 Liver: macro-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.

### 7.3.1 Hemodynamics modeling for liver surgery: a sensitivity analysis study

**Participants:**    Lorenzo Sala, Irene Vignon-Clementel.

Recently a lumped-parameter model of the cardiovascular system was proposed to simulate the hemodynamics response to partial hepatectomy and evaluate the risk of portal hypertension due to this surgery, where model parameters are tuned based on each patient data. In [15], we focus on a global sensitivity analysis (SA) study of such model to better understand the main drivers of the clinical outputs of interest. The analysis suggests which parameters should be considered patient-specific and which can be assumed constant without losing in accuracy in the predictions. While performing the SA, model outputs need to be constrained to physiological ranges. An innovative approach exploits the features of the polynomial chaos expansion method to reduce the overall computational cost. The computed results give new insights on how to improve the calibration of some model parameters. Moreover the final parameter distributions enable the creation of a virtual population available for future works.
In this context, we share a virtual population that can represent well the behavior of a real population of patients (virtual population dataset available.) **Collaborators: N. Golse, A. Joosten, and E. Vibert at APHP-hopital Paul Brousse.**

### 7.3.2 Prediction of Liver Resection Complexity with a Machine Learning Framework

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[1]Manuscript in preparation.

**Participants:**    Omar Ali, Irene Vignon-Clementel.

Surgical interventions remain the most prevalent curative treatment for primary liver cancer. Tumors located in critical positions are known to complexify liver resections (LR). While experienced surgeons in specialized medical centers have the necessary expertise to anticipate LR complexity, an automatic preoperative method able to reproduce this behavior can improve the standard routine of care of patients attained of liver cancer. In [18], we propose CoRe, an automated medical image processing pipeline for predicting postoperative LR complexity from preoperative CT scans, using imaging biomarkers. The CoRe pipeline first segments the liver, lesions, and vessels with two deep-learning networks. The liver vasculature is then pruned based on a topological criterion to define the hepatic central zone (HCZ), a convex volume circumscribing the major liver vessels. This zone is patient specific and designed to reflect the critical zone for liver resections. Biomarkers are extracted and leveraged from the HCZ and the raw segmentations to train and evaluate a LR complexity prediction model. **Collaborators: A. Bone and M-M Rohe at Guerbet, C. Accardo, O. Belkouchi, and E. Vibert at APHP-hopital Paul Brousse.**

### 7.3.3   Joint Segmentation of the Liver Anatomy from Partially Annotated Datasets

**Participants:**    Omar Ali, Irene Vignon-Clementel.

The segmentation of the liver, lesions, and vessels from pre-operative CT scans is of major importance in hepatic surgery planning. However, large databases with reference segmentations for these regions of interest remain unavailable In [19], we propose the FuSe loss, a novel loss function for multi-task learning on datasets with partial annotations. By employing the nnU-Net's 3D full resolution pipeline to calibrate and train a deep network for the joint segmentation of the liver, lesions, and vessels, we show how the FuSe loss allows to learn from the differently annotated datasets. **Collaborators: A. Bone and M-M Rohe at Guerbet, and E. Vibert at APHP-hopital Paul Brousse.**

### 7.3.4   Whole body vascular transport model and applications to human liver diseases

**Participants:**    Jerome Kowalski, Lorenzo Sala, Irene Vignon-Clementel.

To understand the impact of partial hepatectomy or liver disease on the transport of a compound in the human body, a physical model of the blood circulation hemodynamics in the whole body with a focus on transport of a compound *to* the liver and the processing of it *by* the liver has been proposed. It consists in a closed-loop 1D-0D model of hemodynamics and transport. A deeper focus is put on conservation of the compound's mass and the reduction of numerical errors on the one hand ; transport in organs' main vasculature and liver's metabolism of a compound on the other hand.
A simple model for transport in the main vascular system of an organ is developed and helps to understand the transformation of a compound's concentration profile through such vasculature.

### 7.3.5   Optimization of the selective internal radiation therapy (SIRT) for the treatment of hepatocellular carcinoma

**Participants:**    Elena Cutri.

Hepatocellular carcinoma (HCC) is a primary malignancy of the liver. Selective internal radiation therapy (SIRT) has emerged as an effective and safe treatment for HCC. It consists in inter-arterial administration of radioactive microspheres, typically Yttirium-90, via catheter directly into the hepatic

artery. A pre-treatment assessment is routinely carried out prior SIRT to identify the injection site and for dosimetry evaluation. Nevertheless, a discrepancy between the pre-treatment assessment and the SIRT can occur thus resulting in a suboptimal outcome. A patient specific CFD workflow was developed to assess the microspheres distribution in the hepatic arterial tree and to identify the optimal injection site to selectively target the tumour while preserving the non-tumoral tissues. **Collaborators: LTSI - Université de Rennes 1; Centre Eugène Marquis, Rennes.**

### 7.3.6  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) has become a significant method to steer magnetized particles in medical applications by using MRI scanners. Dedicated MRN sequences have been successfully developed to track and drive such particle aggregates for selective chemoembolization of liver tumors. Particle aggregation is a complex process; a comprehensive study of its shape and motion is needed to avoid damaging healthy tissues. In this study [26], the forces acting on aggregates have been classified into four different categories including magnetic forces (gradient and dipole), gravitational forces (gravity and buoyancy), contact forces (normal and tangential forces) and fluid forces (drag, pressure gradient, virtual mass). The code is being developed in the OpenFOAM framework and each force is verified against exact solutions. Primary results are compared with experimental data of an in-vitro bifurcation. This research represents an initial step towards complex in-vitro phantoms and in-vivo models. **Collaborators: Gilles Soulez (CR-CHUM, Montreal, Canada), Charlotte Debbaut (group bioMMeda, UGent, Belgium).**

## 7.4   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, ...).

### 7.4.1   Patient-specific, noninvasive cardiovascular assessment via physiology-based modeling

**Participants:**    Lorenzo Sala
                                .

Left ventricular (LV) catheterization provides LV pressure-volume (P-V) loops and it represents the gold standard for cardiac function monitoring. This technique, however, is invasive and this limits its applicability in clinical and in-home settings. Ballistocardiography (BCG) is a good candidate for non-invasive cardiac monitoring, as it is based on capturing non-invasively the body motion that results from the blood flowing through the cardiovascular system. In [17] we aim at building a mechanistic connection between changes in the BCG signal, changes in the P-V loops and changes in cardiac function. A mechanism-driven model based on cardiovascular physiology has been used as a virtual laboratory to predict how changes in cardiac function will manifest in the BCG waveform. The reproducibility of BCG measurements has been assessed on repeated, consecutive sessions of data acquisitions on three additional swine. Overall, this study provides experimental evidence supporting the utilization of mechanism-driven mathematical modeling as a guide to interpret changes in the BCG signal on the basis of cardiovascular physiology, thereby advancing the BCG technique as an effective method for non-invasive monitoring of cardiac function. **Collaborators: group G. Guidoboni (University of Missouri).**

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

**Participants:** Raoul Sallé de Chou, Lazaros Papamanolis, Irene Vignon-Clementel.

Coronary arteries feed the heart muscles with nutrients and oxygen and as such are some of the most critical blood vessel in the entire body. Coronary disease is difficult to diagnose especially when it affects the smaller branches of these vessels, because direct imaging of these vessels is infeasible with current medical imaging technology. Instead, blood perfusion through the myocardium can be imaged and is correlated with both arterial and myocardium disease. However, blood perfusion imaging is challenging and expensive. The aim of this project is to replace the actual exam with a numerical twin and conduct it via simulations.

A previous model was developed for myocardial perfusion simulation for coronary artery disease in [37]. 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. One of the main challenges is the low resolution of the CT scans, which complexifies the inference of the micro-vascular parameters necessary for tuning the simulation. We developed a graph neural network in order to solve the Darcy equations on irregular shapes in order to replace the myocardium part of the simulation, modelled as a porous medium. This model reduces the computational burden at the cost of some inaccuracies, and facilitate the tuning of the simulation parameters. In parallel, sensitivity analysis on micro-vascular artery resistance computed from [15O]H2O PET exams were conducted. Based on these analyses, a machine learning model aiming to predict the biological parameter using only CT scans is being developed. **Collaborators: L. Najman (ESIEE - U Gustave Eiffel), H. Talbot (CentraleSupelec, INRIA OPIS) and the Heartflow company.**

### 7.4.3 3D blood flow simulations for understanding cerebral vasculopathy in sickle cell disease across ages

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

Sickle Cell Disease (SCD) is the most common severe inherited disease in the world. It is caused by a single mutation, leading to pathological hemoglobin called HbS. SCD represents a unique model of pathological interactions between blood and vessels, since it associates red blood cell (RBC) abnormalities with HbS and vascular alteration. Among severe complications, the cerebral vasculopathy, defined by stenosis on carotid termination and cerebral anterior and middle arteries, exposes patients to stroke, disability, cognitive impairment throughout life and premature death. The main risk factor for developing an SCD cerebral vasculopathy is the acceleration of cerebral arterial blood flow. These accelerations occur mainly in children aged from two to five years old and generally precede the appearance of arterial lesions, detected by magnetic resonance angiography. In this study [20], we proposed to evaluate potential determinants of abnormal velocities in 3D patient-specific cerebral artery geometries of sickle cell patients by modifying inlet flow in the carotids and viscosity. We also investigate the geometrical properties of the internal carotid arteries and hemodynamics differences in SCD patients across ages based on CFD 3D-0D simulations. **Collaborators: Pablo Bartolucci's group (Hôpitaux Universitaires Henri Mondor APHP, Créteil, France), Suzanne Verlhac (Hôpital Universitaire Robert-Debré APHP, Paris, France).**

### 7.4.4 Modeling the Pulmonary Circulation in Congenital Heart Disease: Clinical Concepts, Engineering Applications, and an Integrated Medico-Engineering Approach

**Participants:** Irene Vignon-Clementel.

We contributed to a book on Modelling Congenital Heart Disease based on on our expertise on computational hemodynamics modelling in the pulmonary circulation to understand associated diseases and treatment [21]. **Collaborators: Weiguang Yang and interventional cardiologist Jeffrey Feinstein, School of Medicine, Stanford University, USA.**

### 7.4.5 Quantitative analysis of 4D MRI to understand how pulmonary artery flow features relate to heart remodelling after surgical treatment of pulmonary hypertension

Four-dimensional flow cardiovascular magnetic resonance imaging (4D flow CMR) allows comprehensive assessment of pulmonary artery (PA) flow dynamics. Few studies have characterized longitudinal changes in pulmonary flow dynamics and right ventricular (RV) recovery following a pulmonary endarterectomy (PEA) for patients with chronic thromboembolic pulmonary hypertension (CTEPH). This can provide novel insights of RV and PA dynamics during recovery. In [12], we developed a semi-automated pipeline to investigate the longitudinal trajectory of 4D flow metrics following a PEA including velocity, vorticity, helicity, and PA vessel wall stiffness. The results showed that PEA was associated with changes in 4D flow metrics of PA flow profiles and vessel stiffness. Longitudinal analysis revealed that PA helicity was a positive factor: it was associated with pulmonary remodeling and RV reverse remodeling following a PEA. **Collaborators: Marsden lab, Stanford University; Different MDs from the School of Medicine, Stanford University, USA; Different MDs from Hosp. Marie-Lannelongue, Groupe Hospitalier Saint Joseph, France.**

### 7.4.6 Multiscale hemodynamics modelling of a pulmonary hypertension palliative treatment

**Participants:**    Irene Vignon-Clementel.

The Potts shunt (PS) was suggested as palliation for patients with suprasystemic pulmonary arterial hypertension (PAH) and right ventricular (RV) failure. The shunt is an artificial conduit that allows blood to go from the higher pressure pulmonary arteries (PA) to the lower pressure descending aorta (DAo). PS however, can result in poorly understood mortality. In [14], a patient-specific multiscale model of PAH physiology and PS was developed, with the major vessels represented in 3D coupled to a reduced model of the rest of the circulation. The results show that PS produces near-equalisation of the DAo and PA pressures, as was seen for the patient with the same PS diameter. Changes in key local and global quantities of interest were quantified for different shunt sizes. For example RV work increased but without increasing RV end-diastolic volume. Overall, this model reasonably represents patient-specific haemodynamics pre- and post-creation of the PS, providing insights into physiology of this complex condition, and presents a predictive tool that could be useful for clinical decision-making regarding suitability for PS in certain PAH patients. **Collaborators: Sanjay Pant, Swansea U., UK; and interventional cardiologists Aleksander Sizarov, MUMC, The Netherland and Younes Boudjemline, Sidra Heart Center, Quatar**

## 7.5   Micro-to-macroscale behavior

### 7.5.1   Sperm motility pattern formation study via a swimmer-obstacle interactions model

**Participants:**    Lorenzo Sala.

In [10] we investigate the collective motion of self-propelled agents in an environment filled with obstacles that are tethered to fixed positions via springs. The active particles are able to modify the environment by moving the obstacles through repulsion forces. This creates feedback interactions between the particles and the obstacles from which a breadth of patterns emerges (trails, band, clusters, honeycomb structures,...). We focus on a discrete model first introduced in [Aceves2020] and derived into a continuum PDE model. As a first major novelty, we perform an in-depth investigation of pattern

formation of the discrete and continuum models in 2D: we provide phase-diagrams and determine the key mechanisms for bifurcations to happen using linear stability analysis. As a result, we discover that the agent-agent repulsion, the agent-obstacle repulsion and the obstacle's spring stiffness are the key forces in the appearance of patterns, while alignment forces between the particles play a secondary role. The second major novelty lies in the development of an innovative methodology to compare discrete and continuum models that we apply here to perform an in-depth analysis of the agreement between the discrete and continuum models. **Collaborators: group P. Degond (CNRS, Institut de Mathématiques de Toulouse).**

# 8    Bilateral contracts and grants with industry

## 8.1    Bilateral contracts with industry

### 8.1.1    Guerbet

> **Participants:**     Omar Ali, Irene Vignon-Clementel *(correspondant)*.

This project led by E. Vibert (APHP-Hop Paul Brousse, France) is on AI as a decision support tool for the curative treatment of primary liver cancer.

### 8.1.2    Heartflow

> **Participants:**     Raoul Sallé de Chou, Lazaros Papamanolis, Irene Vignon-Clementel *(correspondant)*.

This project is in collaboration with Hugues Talbot (CentraleSupelec & INRIA OPIS) and Laurent Najmann (ESIEE/G Eiffel University). The goal is to generate heart perfusion maps by machine learning.

# 9    Partnerships and cooperations

## 9.1    International research visitors

### 9.1.1    Visits of international scientists

#### Prof. Jonathan Butcher

**Status** Professor

**Institution of origin** Cornell University

**Country** USA

**Dates** 11 feb. 2022

**Context of the visit** BME faculty seminar at IP Paris and visit of the team

**Mobility program/type of mobility** Lecture

#### Prof. Eduard Rohan

**Status** Professor

**Institution of origin** West Bohemia University

**Country** Czech Republic

**Dates**  2 days (July 2022, Dec 2022)

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

**Mobility program/type of mobility**  Discussions

### 9.1.2  Visits to international teams

**Research stays abroad**    Mahdi Rezaei Adariani visited the group of C. Debbaut, BIOMMEDA, U. of Ghent (2 weeks, Winter 2022) in the context of the ERC MoDeLLiver.

Dirk Drasdo, Jieling Zhao did multiple visits of IfADo Leibniz Institute, Dortmund, Germany (groups Professor J.G. Hengstler, Dr. Ahmed Ghallab, Dr. Natiket Vartak).

## 9.2  European initiatives

### 9.2.1  H2020 projects

- **EDITH project**

  | Participants: | Dirk Drasdo, Maxime Sermesant *(INRIA Sophia-Antipolis)*, Irene Vignon-Clementel. |
  | --- | --- |

  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

- **H2020 ERC consolidator grant MoDeLLiver**

  | Participants: | Irene Vignon-Clementel *(correspondant; grant holder)*, Peter Kottman, Weiqiang Liu, Mahdi Rezaei Adariani, Jerome Kowalski, Elena Cutri, Mathieu De Langlard, Jules Dichamp, Jiri Pesek, Lorenzo Sala, Dirk Drasdo. |
  | --- | --- |

  This project 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) and C. Debbaut (U. Ghent, Belgium).

### 9.2.2  Other european programs/initiatives

**BMBF-LiSyM-Cancer**

> **Participants:**    Jieling Zhao, Dirk Drasdo *(correspondant)*.

BMBF "LiSyM-CANCER" (liver systems medicine of cancer). This project followed the project LiSyM and establishes liver systems medicine approaches to understand progression from chronic liver disease to Hepatocellular cancer. The project is a large network project linking many partners all over Germany.

## 9.3    National initiatives

- **RHU iLite**

> **Participants:**    Mathieu De Langlard, Dirk Drasdo *(correspondant)*, Jiri Pesek,
> Irene Vignon-Clementel.

The project iLite (Innovations for Liver Tissue Engineering) led by JC Duclos-Vallee (APHP-Hopital Paul Brousse, Inserm U1193) aims at establishing pipelines combining biotechnological experiments, image analysis and modeling to work out patient liver replacement. The starting points here are in vivo detoxification hepatocyte spheroid systems (organoids) and the direct comparison of their architecture and perfusion / detoxification properties compared to human in vivo tissue. For this 3D organoids and 3D human liver tissue will be reconstructed from microscopic images and models be executed right in these image reconstructions. The long-term objective is a pipeline that permits virtual tissue in vitro experiments representing the entire culture or biotechnological system for consultancy, generating of movies (as a physical based simulation alternative to animations), and transfer of user-adapted binaries to biotechnological labs and companies.

- **ANR ABM-EPISPREAD**

> **Participants:**    Jules Dichamp, Marwan Bourdim, Dirk Drasdo.

The project established a stochastic modeling framework of epidemic spread both individual agent-based and population-based in space of time. It permits to easily introduce many stratifications, super spreaders, traveling etc.

- **ANR STEDI-NASH**

> **Participants:**    Jiri Pesek, Irene Vignon Clementel, Dirk Drasdo *(Correspondant)*.

The project led by Philippe Garteiser (Inserm, Hopital Beaujon) aims at a non-invasive imaging approach to extract histological information in NASH (non-alcoholic steatohepatitis).

# 10    Dissemination

## 10.1    Promoting scientific activities

### 10.1.1    Scientific events: organisation

**General chair, scientific chair**

- I. Vignon-Clementel: WCB2022 (world conference of biomechanics, occurs every 4 years): co-chair of the track 'Cardiorespiratory: clinical applications' with M. Tawhai (New Zealand) (organizing around 12 sessions)

- I. Vignon-Clementel (co-chair): the organizing committee of VPH2020 wrote an editorial [16], for the special issue that was published in Annals of Biomedical Engineering following the conference.

**Member of the organizing committees**    I. Vignon-Clementel: GDR mecabio santé days, 3 days, Dec 2022: organization committee (program), around 100 participants

### 10.1.2    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"

**Reviewer**    I. Vignon-Clementel, reviewer for ESB, SBM conference.

### 10.1.3    Journal

**Member of the editorial boards**

- Dirk Drasdo is Associated Editor for Journal of Theoretical Biology, Royal Society Open Science,and The Scientific World Journal.

- Irene Vignon-Clementel is Associate Editor of the International Journal for Numerical Methods in Biomedical Engineering

**Reviewer - reviewing activities**    The most senior team members have reviewed articles for a number of journals.

### 10.1.4    Conferences and Talks

- Omar Ali, Oral Presentation, MICCAI 2022, Medical Image Computing and Computer Assisted Intervention, Singapore, September, 2022

- Omar Ali, Oral Presentation, VPH 2022, Virtual Physiological Human, Porto, September, 2022

- Omar Ali, Oral Presentation, ICIP 2022, International Conference on Image Processing, Bordeaux, October 2022

- Omar Ali, Oral Presentation, GDR Mécabio 2022, Paris, December, 2022

- Omar Ali, Poster Presentation, ISBI 2022, International Symposium on Biomedical Imaging, Kolkata, March, 2022

- Omar Ali, Poster Presentation, E4H 2022, Engineering for Health, Palaiseau, July, 2022

- Omar Ali, Poster Presentation, ILCA 2022, International Liver Cancer Association, Madrid, September, 2022

- Omar Ali, Poster Presentation, JFR 2022, Journées Francophones de Radiologie, Paris, October, 2022

- Omar Ali, Poster Presentation, ACHBT 2022, Association Chirurgie Hepato-Biolio-Pancréatique et Transplantation, Paris, December, 2022

- Mathieu de Langlard, Poster presentation, Engineering for Health. *3D reconstruction and morphological characterization of the human liver micro- and meso-structures*, École Polytechnique, Paris, July 2022.

- Mathieu de Langlard, Oral presentation, GDR Mecabio Santé 2022, session *Physics Informed Tissue Architecture Reconstruction.* Paris, December 2022.

- Dirk Drasdo, Oral invited, Séminaire du métaprogramme DIGIT-BIO on Digital Twin in Biology, INRAE 2022, Lyon.

- Dirk Drasdo, speaker for INRIA at Webinar "Inria FC3R", 10.11.2022.

- Weiqiang Liu, Poster, IP Paris Engineering for Health (E4H) Annual Forum, Paris, July 2022.

- Weiqiang Liu, Oral presentation, VPH 2022, Virtual Physiological Human, Porto, September 2022.

- Weiqiang Liu, Oral presentation, 1ères Journées du GDR MÉCABIO Santé, Paris, December 2022.

- Weiqiang Liu, Oral presentation, LE STUDIUM Conference "Cardiovascular Modelling: Basic Science to Clinical Translation", Tour, December 2022.

- Mahdi Rezaei Adariani, Oral presentation, GDR Mecabio Santé 2022, session *Flow and transport modelling*. Paris, December 2022.

- Lorenzo Sala, Contributed talk, WCB 2022, session *Inverse Problems and Data Assimilation in the Circulatory System*. Online, July 2022.

- Lorenzo Sala, Invited talk, WCCM 2022, session *Efficiency and reliability in biomedical modeling: computational and mathematical advances*. Online, August 2022.

- Lorenzo Sala, Contributed talk, VPH 2022, session *Computational modeling in health and disease*. Porto, September 2022.

- Lorenzo Sala, Contributed talk, GDR Mecabio Santé 2022, session *Macroscale and multiscale biomechanics for Health*. Paris, December 2022.

- Raoul Salle de Chou, Oral presentation, Heartflow inc, *Neural Network for solving PDE*. Paris, October 2022

- Irene Vignon-Clementel, Invited talk, Virtual human modelling - liver session of Dassault Systeme's International Symposium on the Living Heart and Virtual Human Twin, New-York, online Dec 6th 2022

- Irene Vignon-Clementel, Invited speaker at the AI session, GDR mecabio santé days, Paris, Nov 31th-Dec 2nd 2022

- Irene Vignon-Clementel, Keynote speaker DLES, Udine Italy, Oct 26th-28th 2022

- Irene Vignon-Clementel, Invited talk, WCB (world congress of biomechanics), Taipei (online), July 11th-14th 2022

- Irene Vignon-Clementel, Roundtable, E4H (engineering for health), IP Paris, Ecole Polytechnique, July 6th 2022

- Irene Vignon-Clementel, Invited talk, CMBE conference, Milano Italy, 26th-29th 2022

- Irene Vignon-Clementel, Seminar at SIMULA Norway, Sept 1rst 2022

- Irene Vignon-Clementel, Invited speaker, RITS workshop, Brest May 23th-25th 2022

- Irene Vignon-Clementel, Invited speaker, 17th International symposium on Biomechanics in Vascular Biology and Cardiovascular Disease, Rotterdam, The Netherland, April 21-22nd 2022

- Irene Vignon-Clementel, Invited speaker, International workshop on reduced order modelling, Inria Bordeaux, March 30-31th/April 1rst 2022

- Irene Vignon-Clementel, Presentation of common work with APHP to CEO of APHP (M Hirsch), BOPA, Jan. 2022

- Jieling Zhao, Oral presentation, VPH 2022, Virtual Physiological Human, Porto, September 2022.

- Jieling Zhao, Oral presentation, WCB 2022, World Congress of Biomechanics, Taipei, July 2022.

- Jieling Zhao, Oral presentation, SBMC 2022, System Biology of Mammalian Cells, Heidelberg, May 2022.

### 10.1.5 Leadership within the scientific community

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

- I. Vignon-Clementel, Member of the Société de Biomécanique, the European Society of Biomechanics and VPH institute.

- I. Vignon-Clementel is a member of the Board of Directors, VPHi (virtual physiological human institute)

### 10.1.6 Scientific expertise

- I. Vignon-Clementel is member of the Advisory Board, EPSRC Healthcare Technologies NetworkPlus – BIOREME project (UK), since Sept 2021

- I. Vignon-Clementel is a member of the Scientific Advisory Board, FDA-Dassault Systèmes Enrichment project, since Feb. 2020

- I. Vignon-Clementel for INRAE in 2022: WG to write a report on the concept of 'digital twin' (métaprogramme DIGIT-BIO)

### 10.1.7 Research administration

- Dirk Drasdo is modeling coordinator of a project within the program LiSyM-Cancer that started 7/2021.

## 10.2 Teaching - Supervision - Juries

### 10.2.1 Teaching

**Full course:**

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

- Master: D. Drasdo, "Agent-based models of tissue organization", Paris 24 h / yr, M2 course, Sorbonne U., Paris, France

- Master: R. Salle de Chou, "Annual IT project", 10h, M1, Project supervision, ESIEE, Universite Paris Gustave Eiffel, France.

**Focused Interventions:**

- Master: D. Drasdo, "Modélisation cellulaire et moléculaire", Paris 1,5 h, UE Initiation à la bio-ingéniérie,master 3i, Master de Sciences, technologies et Santé Mention Biologie Integrative, Sorbonne U., France.

- Master: I. Vignon-Clementel, "Examples of data-based multiscale cardiovascular and respiratory models and applications ", 1h, M2, MEC 550 - Biofluid Mechanics and Mass Transport, Ecole Polytechnique (engineering school), France

- Master: I. Vignon-Clementel, "Modélisation numérique des écoulements biofluides", 1,5 h, UE Initiation à la bio-ingéniérie, Master de Sciences, technologies et Santé Mention Biologie Integrative, Sorbonne U., France.

- Master: I. Vignon-Clementel, "Modélisation hémodynamique and simulation numérique comme outil pour la chirurgie", 1h, M2 Sciences Chirurgicales de l'Université Paris Sud, France

- Bachelor: I. Vignon-Clementel, "Simulations numériques pour des applications cliniques" (2h), Ecole de l'Inserm Liliane Bettencourt EdILB (mix MD/Pharma students who want to do a PhD in science), Winter school Feb 2022

- Bachelor: I. Vignon-Clementel, "Modélisation numérique des écoulements biofluides", continuum mechanics class at AgroParisTech (engineering school), France

### 10.2.2 Supervision

- Modeling project with Polytechnique students (X-PSC): "Modeling and simulation of bacteria colonies and biofilms", Sept. 2022 - April 2023, supervisors: J. Pesek, J. Dichamp, P Van Liedekerke (UGent), D. Drasdo.

- Master Internship: W. Liu, "3D blood flow simulations for understanding vasculopathy in sickle cell disease across ages", March-Sept. 2022, supervisors: I. Vignon-Clementel and L. Papamanolis

- Master Internship: P. Kottman, "Modelling of advection-diffusion processes in liver tissue", Sept.-Dec. 2022, supervisors: I. Vignon-Clementel and D. Drasdo

- Master Internship: J. Kowalski, "Whole body vascular transport model and applications to human liver diseases", May.-Nov. 2022, supervisors: I. Vignon-Clementel and L. Sala.

- Master Research year in Medicine: A. Facque (MD), "Understanding portal thrombosis after extended right partial hepatectomy through 3D simulations.", Nov 22 - present, supervisors: N. Golse (MD), L. Sala, I. Vignon-Clementel, in collaboration with Weiqiang Liu.

- PhD in progress: J. Kowalski, "Whole-body vascular transport and pharmacokinetics models: application to imaging, in particular of liver ", Dec. 2022 - present , supervisors: I. Vignon-Clementel, D. Drasdo and L. Sala.

- 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 - present, supervisors: G. Soulez (CR-CHUM, Montreal, Canada), I. Vignon-Clementel

### 10.2.3 Juries

Irene Vignon-Clementel:

- PhD committee: Arif Badrou, INSA Lyon, Sept 2022 (member)

- Young researcher award committee, 17th International symposium on Biomechanics in Vascular Biology and Cardiovascular Disease, April 21rst-22nd 2022

- External member for promotion to associate professor (U. of Cyprus), 2022

- Hiring committee for assistant professor (Ecole CentraleSupelec), 2022

- mid-thesis jury of Alexandra Haugel (MD), Christian Kassasseya (MD), and end thesis for Mocia Abgbalessi

## 10.3 Popularization

### 10.3.1 Articles and contents

Article in RT Flash Science and Technologie, R Tregouet, rapporteur de la Recherche et président du groupe de prospective du Senat

### 10.3.2 Education

- Simbiotx group: Hosted at Inria a group of junior high school students (February 2022) and 2 high school students (June 2022)

- Irene Vignon-Clementel: Junior high school intervention 'women in engineering', May 2022, Ville d'Avray

### 10.3.3   Interventions

- Jules Dichamp, Oral presentation, AFNet Standard Days, *Multi-scale digital twins of liver and multicellular-systems.* Paris, May 2022.

- Irene Vignon-Clementel: Webinaire Bernoulli Lab (INRIA-APHP), with E. Vibert, PU-PH, May 19th 2022

- Irene Vignon-Clementel: Round table at SantExpo on modeling for future of surgery, May 18th 2022

- Irene Vignon-Clementel: Presentation at WiMLDS meet-up at Paris Women in Machine Learning and Data Science, Paris, April 5th 2022

## 11   Scientific production

## 11.1   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.

[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.

[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.

[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.

[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.

[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.

[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.

[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.

[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.

## 11.2   Publications of the year

**International journals**

[10]   P. Degond, A. Manhart, S. Merino-Aceituno, D. Peurichard and L. Sala. 'How environment affects active particle swarms: a case study'. In: *Royal Society Open Science* 9 (2022), p. 220791. URL: https://hal.archives-ouvertes.fr/hal-03684115.

[11]   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.

[12]   M. Dong, A. Azarine, F. Haddad, M. Amsallem, Y.-W. Kim, W. Yang, E. Fadel, L. Aubrege, M. Loecher, D. Ennis, J. L. Pavec, I. Vignon-Clementel, J. Feinstein, O. Mercier and A. Marsden. '4D flow cardiovascular magnetic resonance recovery profiles following pulmonary endarterectomy in chronic thromboembolic pulmonary hypertension'. In: *Journal of Cardiovascular Magnetic Resonance* 24.1 (Dec. 2022), p. 59. DOI: 10.1186/s12968-022-00893-x. URL: https://hal.science/hal-03949822.

[13]   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://hal.inria.fr/hal-03702928.

[14]   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://hal.inria.fr/hal-03690837.

[15]   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* (4th Nov. 2022). DOI: 10.1007/s10439-022-03098-6. URL: https://hal.archives-ouvertes.fr/hal-03839072.

[16]   I. Vignon-Clémentel, D. Chapelle, P. Moireau, A. I. Barakat, A. Bel-Brunon and E. Vibert. 'Special Issue of the VPH2020 Conference: "Virtual Physiological Human: When Models, Methods and Experiments Meet the Clinic"'. In: *Annals of Biomedical Engineering* 50.5 (2022), pp. 483–484. DOI: 10.1007/s10439-022-02943-y. URL: https://hal.archives-ouvertes.fr/hal-03659783.

[17]   M. Zaid, L. Sala, J. Ivey, D. Tharp, C. Mueller, P. Thorne, S. Kelly, K. A. S. Silva, A. Amin, P. Ruiz-Lozano, M. Kapiloff, L. Despins, M. Popescu, J. Keller, M. Skubic, S. Ahmad, C. Emter and G. Guidoboni. 'Mechanism-Driven Modeling to Aid Non-invasive Monitoring of Cardiac Function via Ballistocardiography'. In: *Frontiers in Medical Technology* 4 (16th Feb. 2022). DOI: 10.3389/fmedt.2022.788264. URL: https://hal.science/hal-03919153.

**International peer-reviewed conferences**

[18] 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: *CoRe: An Automated Pipeline for the Prediction of Liver Resection Complexity from Preoperative CT Scans*. Medical Image Computing and Computer Assisted Intervention – MICCAI 2022. Vol. 13602. Lecture Notes in Computer Science. Sentosa, Singapore, Singapore: Springer Nature Switzerland, 20th Nov. 2022, pp. 125–133. DOI: 10.1007/978-3-031-19660-7_12. URL: https://hal.science/hal-03919572.

**Conferences without proceedings**

[19] O. Ali, A. Bone, M.-M. Rohe, E. Vibert and I. Vignon-Clementel. 'Learning to Jointly Segment the Liver, Lesions and Vessels from Partially Annotated Datasets'. In: 2022 IEEE International Conference on Image Processing (ICIP). Bordeaux, France: IEEE, 16th Oct. 2022, pp. 3626–3630. DOI: 10.1109/ICIP46576.2022.9897470. URL: https://hal.archives-ouvertes.fr/hal-03919568.

[20] K.-A. Nguyen-Peyre, W. Liu, L. Papamanolis, C. Kassasseya, N. Belkeziz, V. Amar, G. Nahas, S. Eckert, P. Vedel, L. Lenoir, K. Drémont, S. Cleophax, F. Pirenne, F. Segonds, S. Verlhac, I. Vignon-Clémentel and P. Bartolucci. 'Impact of Carotid Geometry on Sickle Cell Diseases-Related Cerebral Vasculopthy Development'. In: *Blood*. 64th ASH American Society of Hematology Annual Meeting. Vol. 140. Supplement 1. New Orleans, United States, 15th Nov. 2022, pp. 7820–7821. DOI: 10.1182/blood-2022-156410. URL: https://hal.science/hal-03931644.

**Scientific book chapters**

[21] W. Yang, J. Feinstein and I. Vignon-Clementel. 'Modeling the Pulmonary Circulation in CHD: Clinical Concepts, Engineering Applications, and an Integrated Medico-Engineering Approach'. In: *Modelling Congenital Heart Disease*. Modelling Congenital Heart Disease. Springer International Publishing, 20th Apr. 2022, pp. 157–167. DOI: 10.1007/978-3-030-88892-3_14. URL: https://hal.inria.fr/hal-03949834.

**Reports & preprints**

[22] Y. Yin, K. Breuhahn, H.-U. Kauczor, O. Sedlaczek, I. Vignon-Clementel and D. Drasdo. *Diffusion-weighted MRI -guided needle biopsies permit quantitative tumor heterogeneity assessment and cell load estimation*. 23rd June 2022. URL: https://hal.inria.fr/hal-03702898.

[23] J. Zhao, A. Ghallab, R. Hassan, S. Dooley, J. G. Hengstler and D. Drasdo. *A digital twin of liver predicts regeneration after drug-induced damage at the level of cell type orchestration*. 25th July 2022. URL: https://hal.inria.fr/hal-03738207.

[24] J. Zhao, S. Hammad, M. de Langlard, P. Erdoesi, Y. Li, A. Buttenschön, J. G. Hengstler, M. Ebert, S. Dooley and D. Drasdo. *Integrated spatial-temporal model for the prediction of interplay between biomechanics and cell kinetics in fibrotic street formation*. 2022. URL: https://hal.inria.fr/hal-03512915.

[25] J. Zhao, H. Reham, A. Ghallab, J. G. Hengstler and D. Drasdo. *Modelling the orchestration of different types of cells and factors during liver regeneration in a virtual liver twin*. 2022. URL: https://hal.inria.fr/hal-03512744.

**Other scientific publications**

[26] M. Rezaei Adariani, J. Pešek, N. Li, C. Debbaut, G. Soulez and I. Vignon-Clementel. 'Numerical investigation of particle aggregate steering with magnetic resonance navigation for targeted embolization'. In: 75th Annual Meeting of the Division of Fluid Dynamics. Indianapolis, United States, 20th Nov. 2022. URL: https://hal.inria.fr/hal-03938250.

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[27] 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.

[28] 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.

[29] 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.

[30] 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.

[31] 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.

[32] S. Hammad, S. Hoehme, A. Friebel, I. von Recklinghausen, A. Othman, B. Begher-Tibbe, R. Reif, P. Godoy, T. Johann, A. Vartak, K. Golka, P. O. Bucur, E. Vibert, R. Marchan, B. Christ, S. Dooley, C. Meyer, I. Ilkavets, U. Dahmen, O. Dirsch, J. Böttger, R. Gebhardt, D. Drasdo and J. G. Hengstler. 'Protocols for staining of bile canalicular and sinusoidal networks of human, mouse and pig livers, three-dimensional reconstruction and quantification of tissue microarchitecture by image processing and analysis.' In: *Archives of Toxicology* 88.5 (May 2014), pp. 1161–1183. DOI: 10.1007/s00204-014-1243-5. URL: https://hal.inria.fr/hal-01110657.

[33] S. Hoehme, M. Brulport, A. Bauer, E. Bedawy, W. Schormann, M. Hermes, V. Puppe, R. Gebhardt, S. Zellmer, M. Schwarz, E. Bockamp, T. Timmel, J. Hengstler and D. Drasdo. 'Prediction and validation of cell alignment along microvessels as order principle to restore tissue architecture in liver regeneration'. In: *Proceedings of the National Academy of Sciences of the United States of America* 107.23 (June 2010), pp. 10371–10376. DOI: 10.1073/pnas.0909374107. URL: https://hal.inria.fr/hal-03954313.

[34] 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.

[35] 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.

[36] 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.

[37] 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.

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