RESEARCH CENTRE

Inria Saclay Centre

2023 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

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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

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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 data from multiple sources to inform clinicians and build predictions of possible therapy consequences. Both, models and software generated in that process will pertain to standardization. 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], [33], [34].

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 [21]. For networks of thousands of small conduits, resistance (0D) models are typically solved, where a finer rheology can be incorporated [23]. 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 [32] [22]. 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 [23], [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 [27]. 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. [26, 25]).

For patients, model parameterization needs to occur from non-invasive or moderately invasive modalities, e.g. from biomarkers or non-invasive imaging. While non-invasive functional imaging has been a very active field of research, its translation to the clinics is impeded by a good understanding of how the extracted parameters relate to the underlying tissue characteristics. A first approach consists in constructing in-silico models of such tissue images and study how model parameter changes relate to these in-silico images [10]. A second approach is to perform quantitative image analysis and correlation of

different image modalities [35]. One can then study how non-invasive imaging, a macroscale information, relates to organ microscale architecture, perfusion or function.

3.4.2 Integrative, Multiscale, multilevel and multicomponent models

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

So far the mostly chosen method is a systematic simulated parameter sensitivity analysis by variation of each model parameter within its physiological range and studying how this modifies the agreement between model simulation result and data from experiments for patients. A sensitivity analysis performed on such models would be crucial in order to (i) identify the most significant parameters to influence the desired output, (ii) test the robustness of a model in the presence of uncertainties, (iii) determine the interactions among parameters, and (iv) unveil the optimal regions within the parameters space for optimization studies. An example is the Saltelli algorithm to compute the Sobol' indices, a variance-based sensitivity analysis that exploits the variance decomposition (ANOVA) also in non-linear and non-monotonic cases. An example of such sensitivity analysis applied to our virtual human twins is [13].

Biophysical models have also been complemented by machine-learning approaches [5, 31].

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

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

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

4.1.2 Congenital heart disease

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

While great advances have been made in the last decades in their clinical treatment (mainly through surgery), these patients still suffer from significant mortality and morbidity, due in part to interactions between heart, systemic circulation, pulmonary circulation and other components such as implanted graft or devices. The goal here is to perform patient-specific modeling to better understand such interactions (e.g. [29]). Choosing the treatment option (surgical, interventional, drug) and optimizing it based on modeling opens up several research directions.

4.1.3 In vitro cell populations, tumors and cancer

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

4.2 Systems Biotechnology and Systems Toxicology

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

Part of our activity is to establish computational models for simulating detoxification processes in in vitro and in vivo situations and implementing them in software. These models shall mimic both, processes in digital in vitro experiments and drug effects in digital organs, eventually in time and space. An important example is drug action of paracetamol ([28], sect. 4.1.1, Dichamp et al., 2023).

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

5 Social and environmental responsibility

5.1 Impact of research results

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

6 Highlights of the year

6.1 Awards

- Trophée de l'Innovation et de la Transformation Numérique 2023 ( )
- Our group have successfully applied to an EU-call on digital patient twins by the project Artemis, that focusses on the liver-heart axis.
- Roel Meiburg, postdoc in the team was awarded 3rd place for the Young Investigator's Award at the European Heart Rhythm Association conference in Barcelona, Spain [April 2023].
- Weiqiang Liu, research assistant in the team was awarded the McGill Engineering Doctoral Award and J.W. McConnell Memorial Fellowship in Montreal, Canada [March 2023].
- Weiqiang Liu, research assistant in the team was awarded IP Paris BME Conference fellowship in Engineering for Health Annual Forum, France [July 2023].
- Mahdi Rezaei Adariani, PhD student in the team, received the Travel Award at the 28th Congress of the European Society of Biomechanics conference in Maastricht, The Netherlands [July 2023].
- Mahdi Rezaei Adariani, PhD student in the team, received the best poster prize at the Engineering for Health (E4H) conference in Paris, France [June 2023].

6.2 Patent

Tumour imaging device Authrs: I Vignon-clementel, D Drasdo, Y Yin US Patent App. 18/003,171

An imaging device includes: a memory, an upsampler, a slicer a selector and a guide. The memory is arranged to receive imaging data, biopsy data including needle data defining dimensions of a puncture carried out by means of a biopsy needle, and procedure data. The upsampler is arranged to upsample a raster image into a processing image. The slicer is arranged to partition the processing image from the upsampler into a set of regions. The selector is arranged to determine within the set of diffusion parameters a subset of diffusion parameters, and to return a subset of regions derived from the set of regions. The guide is arranged to determine, from the subset of regions, puncture parameter set data a puncture orientation and a puncture entry point and defining with the needle data a puncture zone.

7 New software, platforms, open data

A number of smaller codes than the softwares listed below have been developed in the team. For example: dynamic contrast-enhanced (DCE) perfusion imaging has shown great potential to non-invasively assess cancer development and its treatment by their characteristic tissue signatures. In [14], we proposed an in-silico approach in order to better interpret the interplay of DCE-image-(function) and histology (structure) data. We constructed a pipeline that consists in a vascular architecture with hierarchical vessel networks, the flow/transport modeling of the contrast agent in and out of the vessels, generation of dynamic in-silico images and parameter inference from tracer kinetic models. It is applied in the context of a tissue-embedded tumor. To our knowledge such pipeline, based on a spatial in-silico model, is new. We made the code opensource on the Inria gitlab . More project details can be found below.

7.1 New software

7.1.1 LumpedFlow

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

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

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

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7.1.2 TiSim

Name: Tissue Simulator

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

Functional Description: TiSim is a software that permits agent-based simulations of multicellular systems. - center-based lattice-free agent-based model - modular - C++, Qt, OpenGL, GUI, batch mode - permits multiscale simulations by integration of molecular pathways (for signaling, metabolisms, drug) into each individual cell - applications so far: monolayer growth, multicellular spheroids - Boolean networks (development time = coding time ($\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

7.1.3 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

7.1.4 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, Charles Boulitrop

Contact: Dirk Drasdo

7.2 Open data

In [13], we developed an innovative approach to reduce the computational cost of performing sensitivity analysis of models, constrained by physiological bounds. The computed results give new insights on how to improve the calibration of some model parameters from patient data. Moreover the final parameter distributions enable the creation of a virtual population available opensource for future works (openAire,).

8 New results

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

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

The paragraphs summarize results from 2023, 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.

8.1 Liver: micro-architecture

At the microarchitectural level important bricks towards a digital liver twin model prototype for the entire drug induced liver injury (DILI) circle that includes the drug action on the liver, the regeneration process, and the effect of DILI on the liver metabolic function have been significantly advanced in 2022.

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

Participants: Jieling Zhao, Dirk Drasdo.

Hepatocellular carcinoma (HCC) is the most common liver cancer in adults and ranked 3rd in cancer-caused death. To understand the disease mechanism behind HCC is important to identify patents at risk and develop possible therapeutical strategies. However, due to the complexity of the disease progression process, the limited number of quantities that can be simultaneously measured in animal models, and the even more limited access to patient data, a holistic view on the disease progression mechanisms is missing. As a consequence classification of patients with regards to disease progression prognosis, which is important to design a patient-specific surveilance strategy is mainly based on experience and crude indicators, many of them varying from clinics to clinics. The mechanistic relationship between these indicators is largely unknown and largely emphirical, while a holistic mechanistic view could provide a much more systematic approach to disease progression prognosis, and moreover help to identify patient-specific therapeutic strategies and targets. We extended our computational virtual twin model of liver regeneration and fibrosis towards a chronic liver disease (CLD) progression model that permits to mimic disease progression from healthy liver to HCC. This model currently includes many cell types, the communication among them, and a wide range of signaling molecules, some that may be detected in the blood serum and hence qualify as signatures of the stage of the disease. The focus is currently on the transitions to cirrhosis and HCC, and our preliminary results permitted to identify possible interaction networks that do recapitulate observed or hypothesized disease progression scenarios.

Main collaborators currently: S. Hammad, S. Dooley (Heidelberg University), S. Wolf, J. Bode, A (Dusseldorf University Hospital), Friebel, S. Hoehme (Leipzig University), Bantel, H (Univ. Clinics of Hannover)

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

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

Chronic liver disease (CLD) displays an increasing incidence. While much focus is on CLDs with Hepatocellular carcinoma as a possible endpoint (see above), cholestatic diseases, where the flow of bile from the liver to the duodenum is impaired, can be equally devastating: e.g. primary biliary cholangitis or primary sclerosing cholangitis are both irreversibly progressing diseases with cholagiocarcinoma, the 2nd type of primary liver cancer, as possible endpoint. Effective treatment of CLD requires a deep understanding of liver function in healthy liver, as well as its changes during disease progression and in response to therapeutic interventions. The high complexity of the underlying disease processes, over many time and length scales favors a systems medicine approach.

The liver guarantees its function as main detoxifying organ by a complex microarchitecture that permits a perfect exchange of metabolites between blood and hepatocytes, whereby some molecular species are secreted into the biliary system. While blood microcirculation became the subject of intensive research in past years and has been addressed by experimental and modeling methodologies, the biliary system has yet to receive the same attention. For example, the driving mechanisms of bile salt transport have recently moved back into the research focus, partially giving rise to controversial discussions on whether bile salt transport inside liver microarchitecture is dominated by flow or diffusion[9].

We implemented as a first approach a 1D model of bile salt transport towards, inside, and out of the liver lobule. This captures the transport of bile salts with the blood into the liver lobule over the portal vein and hepatic artery, inside the basic functional liver units (lobules) through the sinusoids, the capillaries of the liver tissue, and from the sinusoids into the hepatocyte as well as from the hepatocytes into the biliary canaliculi system, from which the bile salts are carried to the gallbladder. We compare different kinds of transport on this path ([KottmanMasterThesis]).

Collaborators: E. Rohan, UWB Pilsen, Czech Republic

8.1.3 Temporal diffusion spectroscopy for the characterization of NASH

Participants: Charles Boulitrop, Jiří Pešek, Dirk Drasdo, Irene Vignon-Clementel.

The gold standard in the staging of many liver diseaes is the evaluation of a histological sample of the patient. Optaining tissue material for histolopathological evaluation requires invasive interventions such as taking biopsies, which underlies strict criteria due to the possible adverse effects. The objective is hence to gather knowledge on histopathological characteristics non-invasively, as this not only minimizes size effects but also permits longitudinal follow-ups. A typical usecase is the classification of nonalcoholic steatohepatitis (NASH), which includes hepatocyte ballooning. Ballooning is characterized by accumulation of lysis vesicles in the cytoplasmic space, hepatocyte swelling and alterations of the intermediate filament cytoskeleton. Temporal diffusion spectroscopy (TDS), a development of Diffusion-Weighted-Magnetic Resonance Imaging, has recently enabled identification of appearant diffusion coefficients that may permit to probe balooning non-invasively. The short-coming of the methodology so far is that the interpretation of the obtained signals is difficult. We developed first model prototypes to simulate the movement of magnetic moments inside tissue microarchitectures represented within the framework of agent-based models using the team's novel simulation software CompuTiX, and to subsequently mimic the measurements of MRI-signals within a modeling approach, to study, how the MRI-signals relate to the tissue microarchitecture. The conceptual approach is reminiscent of comparing direct and inverse methodologies in tissue perfusion [14].

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

8.1.4 Microvascular modeling for medical imaging and toxicity assessment

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

Dynamic-contrast-enhanced medical imaging can be used to detect non-invasively tissue abnormalities like tumors, to evaluate organ function, or to assess drug efficacy. Tracers injected into the body may reflect tissue perfusion and function, depending on whether they are taken up and/or metabolized by the cells or not. Distinguishing spatial and functional contributions to the signal obtained from *in-vivo* analyses is challenging, which is why we develop *in-silico* models for better image interpretation, again following a conceptual strategy as in ref. [14].
In organs such as the liver, cells are nourished by networks of capillaries, small fenestrated vessels called sinusoids. Remodeling of liver microarchitecture during chronic liver disease may modify the fenestration of the network resulting in an impaired liver function, such as the modification of detoxification of the blood from potentially hepatotoxic drugs. On the other hand, hepatotoxicity of most drugs is dose-dependent, which requires to determine the critical concentration of no-observed-adverse-effect levels (NOAEL) at the location of the hepatocytes. Recent findings indicate that the tissue microarchitecture and the spatial-temporal distribution of the drug may play an important role in the determination of the NOAEL [11]. *In-vitro* experiments permit to determine the concentration at which a substance a cell is exposed to is hepatotoxic (the pharmadynamics), but to know the concentration distribution, information on the microarchitecture of the liver, the drug kinetics, and the distribution of a drug in the liver needs to be known. This seems feasible with the help of mathematical models addressing flow and transport in liver tissue microarchitecture.
We assessed three *in-silico* models that, based on a common mathematical framework, simulate blood flow and drug transport in and out of a diseased micro-vascular network, and their effect on cells [18] . To that end, the main pillars of multi-phase multi-species flow and transport models are first derived from primary principles and then transcribed for a vascularized tissue. The chapter provides overall a methodology to link changes in vascular network architectures, microcirculation consequences and some macroscale biomarkers relevant for dynamic medical imaging or toxicity predictions.

8.1.5 Physics informed tissue architecture reconstruction

Participants: Jiří Pešek, Mathieu de Langlard, Dirk Drasdo.

Microscopic architecture of tissue influences the outcome of many cell processes from signalling, proliferation and, ultimately, the cell fate. In order to study these processes, it is imperative to obtain a realistic and detailed microarchitecture of the tissue. Despite recent advances in imaging and image analysis techniques, they are still insufficient to provide all necessary data for a successful detailed tissue microarchitecture reconstruction directly from the experimental data. This issue is even more pronounced in complex tissues like liver, with many different structures that have to be taken into account. We offer an alternative method where the traditional image analysis is augmented with a model driven tissue reconstruction. In this method, the physical and mechanical cell properties are used to complement the information obtained from a classical image analysis in order to recover cell shapes and consequently the overall tissue microarchitecture. We demonstrate[1] that such method offers a higher accuracy of reconstructed cell shapes and tissue organization when compared to traditional methods like morphological watershed.

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

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

Hyperammonemia i.e., a critically elevated ammonia blood concentration, can lead to encephalopathy and patients' death and constitutes the major reason for acute liver failure. Recent works guided by compartment models led to the identification of a previously unrecognized ammonia sink mechanism that could be used as a treatment option in hyperammonemia. However, compartment models are not well suited to mimic hyperammonemia in chronic liver diseases such as fibrosis or cirrhosis, as they lack architectural representation. We thus introduce a digital liver twin that reflects the remodeling of architecture and all key processes relevant in ammonia detoxification during fibrosis development. We demonstrate, that the architectural changes alone can explain most of the experimentally observed changes in ammonia detoxification during fibrosis. Our findings suggest a novel modeling strategy in toxicology modeling in tissues during acute liver tissue damage or disease development, by first studying the effect of tissue remodeling of a toxic substance, and subsequently adapt intracellular processes to capture the observed concentrations of toxic substances. A manuscript is in preparation.

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

8.2 Liver: From the micro- to the mesoscale 3D

8.2.1 3D digital histopathology: a new methodology for morphological characterization of the human liver

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

2D histopathology is a common technique 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. It would enable better understanding and earlier diagnosis of liver diseases. We developed an automatic pipeline of 3D histology reconstruction based on image registration and segmentation to analyze large and consistent liver sample volumes from the micro- to the mesoscale. Morphological quantifications emerging from such an analysis can furthermore inform computational models permitting to probe the possible functional consequences of architectural alterations. Within our pipeline, micro- and mesoscale vascular systems and bile ducts were visualized in 3D, with topology described using the diameter-defined Strahler system. Morphological analysis included computing mean diameter and length, showing an exponential law for vessel segments.

[1] Manuscript in preparation.

This work achieved the first-time 3D reconstruction and quantification of a large human liver tissue volume reconstructed from 2D histological images. The method, evaluated on healthy tissue, can be applied to pathological cases, offering consistent three-dimensional analysis for detailed morphological alterations across liver disease stages .

Collaborators: Olivier Trassard, Anne Dubart-Kupperschmitt, Jean-Charles Duclos-Vallée, Catherine Guettier-Bouttier, APHP (hopital Paul Brousse, Le Kremlin-Bicetre), INSERM U1193.

8.3 Liver: Organ-scale

In this section, we present a number of computational modeling results of flow and transport of particles or injected substances. Such biophysical approach is complemented by AI approaches. The common goal is to create digital twins to help design or assess the risk of liver cancer treatment.

8.3.1 Automatic Generation of Liver Digital Twins with Artificial Intelligence: Application to Liver Resection Complexity Prediction

Participants: Omar Ali, Amaury Facque, Irene Vignon-Clementel.

Liver resection (LR) is the most prevalent curative treatment for primary liver cancer, yet overall mortality/morbidity rates remain remains elevated, particularly for complex/difficult liver resections in non-specialized centers. The conventional evaluation of the liver resection complexity occurs at the preoperative stage, continues to require significant medical expertise and/or extended clinical tests. The conventional definition and classification of LR complexity (LRC) considers the number of liver segments to be removed, while lacking the analysis of the tumor's position with respect to the major liver vessels. These major vessels are defined to be up to the 2nd bifurcation in the portal vein, and the emergence of the three hepatic veins. Therefore, we propose an automatic digital tool to predict the LRC at the intraoperative stage, solely from the portal phase of preoperative CT scans, after: (1) transforming the liver region into a quantifiable space, (2) identifying the tumors and major liver vessels, and (3) generating a reference frame based on a new concept, the hepatic central zone. This tool can help orient patients towards appropriate medical centers depending on the predicted level of surgery complexity. The 3D reconstructions of the liver, tumors, and hepatic venous vessels from preoperative CT scans are generated with in-house trained deep learning models. A topological analysis of the reconstructed vessels is performed on the generated vessel segmentations to identify the major liver vessels and generate the hepatic central zone (HCZ). Imaging biomarkers such as the depth and proximity of the tumor to the HCZ are leveraged to predict the LRC. The LRC predictions obtained with the proposed automatic digital tool accurately predict intraoperative LRC (AUC = 0.85) and outperform the predictions of five trained liver surgeons (3 experts, 1 junior, and 1 resident). This tool gives a basis for liver surgery planning and patient orientation towards centers adequate to treat their pathology.

Collaborators: A. Bône and M-M Rohe at Guerbet, C. Accardo, B. Acidi, P. Valleur, C. Salloum and E. Vibert at APHP-hopital Paul Brousse.

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

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

Extended liver resection is the only curative treatment of cholangiocarcinoma which is a liver tumor that develops from the biliary tract, and it is a surgery that is associated with high morbidity and mortality. A relatively common but very serious complication is the portal vein thrombosis, which is the development of a blood clot in the portal vein leading to liver failure and potentially to the death of the patient. Thrombosis formation is likely influenced by vessel geometry, nevertheless there is poor literature regarding the analysis the correlation between portal vein geometry and formation of thrombosis.

Our project aims to study real patient models of the portal vein in order to simulate the blood flow in the portal vessels and analyse the impact of geometry on post-operative thrombosis of the portal vein. The study was conducted using a clinical database as a support for combined 3D-Modeling and Computational Fluid Dynamics (CFD) analysis. The preliminary results of the study have shown a correlation between vessel diameter discrepancy and thrombosis occurrence. We could also observe a link between the angle formed by the branches of the portal vein and the thrombosis and the onset of thrombosis. We are now confirming these hypotheses that could change the way the surgery is performed in order to lower the risk of thrombosis after partial hepatectomy.

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

8.3.3 Hemodynamics modeling for liver surgery: digital twins

Participants: Roel Meiburg, Kevin Hakkakian, Ramdane Bessaïd, Clémence Finotto, 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 [13, 17], 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 (openAire,). A further identifiability analysis revealed that certain importaint cardiac parameters were unidentifiable with the current workflow. The protocol was therefore amended to included additional cardiac measurements, namely ejection fraction via ultrasound. These measurements are part of clinical routine and therefore do not pose an additional burden.

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

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

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

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

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

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

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

8.4 Digital twins for a better understanding and leveraging of medical dynamic imaging data

8.4.1 A proof-of-concept pipeline to guide evaluation of tumor tissue perfusion by dynamic contrast-agent imaging: Direct simulation and inverse tracer-kinetic procedures

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

Dynamic contrast-enhanced (DCE) perfusion imaging has shown great potential to non-invasively assess cancer development and its treatment by their characteristic tissue signatures. Different tracer kinetics models are being applied to estimate tissue and tumor perfusion parameters from DCE perfusion imaging. The work published in [14] provides an in silico model-based pipeline to evaluate how these DCE imaging parameters may relate to the true tissue parameters. As histology data provides detailed microstructural but not functional parameters, the presented work can also help to better interpret such data. To this aim in silico vasculatures are constructed and the spread of contrast agent in the tissue is simulated. As a proof of principle we show the evaluation procedure of two tracer kinetic models from in silico contrast-agent perfusion data after a bolus injection. Representative microvascular arterial and venous trees are constructed in silico. Blood flow is computed in the different vessels. Contrast-agent input in the feeding artery, intra-vascular transport, intra-extravascular exchange and diffusion within the interstitial space are modeled. From this spatiotemporal model, intensity maps are computed leading to in silico dynamic perfusion images. Various tumor vascularizations (architecture and function) are studied and show spatiotemporal contrast imaging dynamics characteristic of in vivo tumor morphotypes. The Brix II also called 2CXM, and extended Tofts tracer-kinetics models common in DCE imaging are then applied to recover perfusion parameters that are compared with the ground truth parameters of the in silico spatiotemporal models. The results show that tumor features can be well identified for a certain permeability range. The simulation results in this work indicate that taking into account space explicitly to estimate perfusion parameters may lead to significant improvements in the perfusion interpretation of the current tracer-kinetics models.

Collaborators: N. Jagiella, W. Lederle (RWTH Aachen, Germany), H. Laue (Fraunhofer MEVIS, Institute for Digital Medicine, Bremen, Germany), F. Kiessling (RWTH Aachen, Germany), O. Sedlaczek (DFKZ Heidelberg, Germany)

8.4.2 Whole-body vascular transport and pharmacokinetics models: application to imaging

Participants: Jérôme Kowalski, Ihsane Hadeg, Dirk Drasdo, Irene Vignon-Clementel.

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

Work has been conducted towards the understanding of the transport of a chemical species through a vascular tree [15]. Building on top of the *insilico* model developed last year, a framework for analyzing real vasculatures has been introduced along with precise metrics which aim at quantitatively interpreting the relation between a change in the geometry (*e.g.* following a major surgery or the development of a disease) and the hemodynamic and transport behaviors. A collaboration has started with Gent University

(Belgium) to analyze the development of a hepatic cirrhosis and relate architectural modifications of the rat liver vascular trees with blood flow and transport of chemical species in it.

As a first clinical application, a focus was given on the estimation of the blood perfusion in the legs following a revascularization surgery, using Indoycianine-Green (ICG) signals ; in collaboration with vascular surgeons form Leiden University Medical Center (LUMC, the Netherlands). A simple model for the closed-loop blood circulation and transport of ICG has been developed and later refined to help the interpretability by the surgeons. A preliminary validation of the model was performed based on clinical data.

Collaborators: L. Sala (Inrae), Jan R. van der Vorst (LUMC, The Netherlands), C. Debbaut (UGent, Belgium)

8.5 Digital twins of blood flow for disease or treatment assessment

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

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

Participants: Raoul Sallé de Chou, Mohamed Ali Srir, 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.

A previous model was developed for myocardial perfusion simulation for coronary artery disease in [30] to replace the actual exam with a numerical twin and conduct it via simulations. The model aims at reproducing [15O]H2O PET imaging exam using only CT scans as input. The simulation is based on : 1. Detection, segmentation and simulation of blood flow through the coronary vessels visible on the injected CT scan; 2. A patient-specific method for generating small 3D vessels consistent with the vessels detected. The rules for the growth of these vessels are based on physiology and simulated blood flows; 3. a perfusion simulation model that considers the myocardium as a porous medium. A Darcy model is used to simulate blood flow through the porous medium. However, in addition to a high computational cost, the simulation fails to accurately reproduce some diseases, particularly those that affect medium-size coronary branches.

The main goal of this project is to combine Machine Learning (ML) methods with physical simulations in order to improve the current simulation pipeline. ML algorithms are used to learn from PET imaging exams while being guided by simulation hypothesis, thereby diminishing the dependency on patient data. To achieve this, each part of the simulation is to be replaced by an ML model. Following successful replication of simulation outcomes, the model will undergoes refinement using patient data.

A finite volume informed graph neural network was developed to solve the Darcy equations on irregular shapes serving as a substitute for the myocardium component in perfusion simulation. Preliminary results indicate superior performance of this model in terms of accuracy and generalization compared to classical ML approaches. In [16], we introduced a novel optimization framework for the generation of the synthetic small vessels utilizing the constructed constrained optimization (CCO) method. Our new approach simulated similar 2D vascular trees as the original CCO method in terms of morphometry

while producing better optimal solutions at lower computational cost. This new approach is expected to be more readily reproducible using ML methods compared to the original CCO technique. Additionally, work has been conducted towards the determination of the myocardium perfusion regions. Determining these regions, and their associated vessel is a crucial step in current simulation pipeline. However, the current calculation method is inaccurate and highly sensitive to the resolution of segmented vessels. A more robust and accurate model, employing graph neural networks (GNNs), has been developed for the determination of these regions.

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

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

Participants: Pavlos Varsos, Irene Vignon-Clementel.

The Potts shunt emerges as a palliative treatment option for pediatric patients, facing unsuccessful drug treatments for suprasystemic Pulmonary Arterial Hypertension, and for whom lung transplantation is not yet feasible. Despite its intent, a considerable number of surgeries prove unsuccessful, leading eventually to mortality, with the failure mechanism still eluding comprehension. This study aims to investigate the underlying factors that influence the success or failure of the procedure, while exploring various shunt designs, ranging from anastomoses to conduits, and with or without the integration of a unidirectional valve. A multiscale model (0D-3D) was initially developed, for which, an extensive sensitivity analysis was conducted. Preliminary findings suggest that pre-operative selection of shunt geometry is crucial for surgery success. Patient-specific factors, including hemodynamic conditions as well as cardiac chamber structural characteristics, may prove to be prohibitive for shunt placement. Results show that different shunt designs maintain oxygen saturation in the upper body, but larger shunt diameters lead to decreased oxygenation in the lower body. Post-operative hemodynamics indicate increased right ventricular workload due to higher stroke volume, although ejection fraction improves to normal levels across all cases.

Collaborators: S. Pant, Necker-Enfants Malades Hospital

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

Participants: Weiqiang Liu, Irene Vignon-Clementel.

Sickle cell disease (SCD) is the most prevalent inherited blood disorder in the world, caused by a single mutation leading to pathological hemoglobin (HbS). HbS polymerization during deoxygenated states attributes to the characteristic sickled shape of red blood cells (RBCs). The deformability and rigidity changes of RBCs lead to impaired oxygen delivery and vaso-occlusion, resulting in anemia, multisystem damage and long-term inflammation. The incidence of cerebral vasculopathy (CV) during the first decade of life in pediatric patients with sickle cell disease establishes SCD as the first cause of stroke in children worldwide. The main known risk factor for CV is a pathologically elevated intracranial arterial velocity. However, the causes of these elevated velocities and their relationship with CV are not well understood.

In this study, we simulated in-silico blood flow in the internal carotid arteries of SCD patients from different age groups. Results revealed that pathological velocities can only be reached in children, even for moderate levels of blood flow. The occurrence of such elevated velocities was most frequent in the distal part of the internal carotid, aligning with the positions where stenosis typically manifests. The Dean number, a fluid mechanics concept combining both flow and geometry, revealed that high flow rate, small diameter and large curvature contribute together to extreme blood velocities. Given that the high oxygen requirement for cerebral growth in children combined with anemia lead to elevated cardiac output, we hypothesize the following underlying mechanism: high cardiac output, together with

geometrical characteristics, lead to elevated blood velocities in SCD. The resulting complex flow would subsequently injure the endothelium and activate platelets, leading to CV. One journal paper is under submission.

Collaborators: Suzanne Verlhac(MD, Hôpital Robert Debré AP-HP), Pablo Bartolucci and team (MD, Univ Paris Est Créteil/Hôpitaux Universitaires Henri Mondor AP-HP, Créteil), Lazaros Papamanolis (Stanford university, USA, California)

8.5.4 Multiscale modeling of feto-placental hemodynamics

Participants: Pascalle Wijntjes, Jérôme Kowalski, Irene Vignon-Clementel.

Pregnancy induced hypertension (PIH) is one the most prevalent pregnancy complication. It often leads to more complex pregnancy complications as fetal growth restriction, pre-eclampsia, HELLP. Later in life, these women have a 5 to 10 times higher chance of cardiovascular diseases. Therefore, early diagnosis and treatment would reduce the morbidity of worse outcomes.

This study focused on modelling hemodynamical behaviour of the feto-placental vasculature to gain insights into the cause of complications. To tackle this, numerical problems and stability issues for hemodynamic modelling of the multiscale placental vasculature were encountered and solved within the research visit of six months. At the end of the visit, the hemodynamics model is capable of dealing with both the bigger and smaller vessels in the placental system.

Collaborators: F.N. van de Vosse, W. Huberts (TU/e, The Netherlands), M.B. van der Hout-van der Jagt (TU/e & MMC, The Netherlands)

8.5.5 Methodology on blood flow model parameter estimation

In [19], we published an overview in a bookchapter for the French speaking community on how to set up blood flow simulations boundary conditions (3D models) or parameters (0D models) depending on the available clinical data and the resistance to flow in the 3D domain. It is also explained how this enables predictive simulations, i.e. for intervention planning.

9 Bilateral contracts and grants with industry

9.1 Bilateral contracts with industry

9.1.1 Guerbet

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

This project in collaboration with E. Vibert (APHP-Hop Paul Brousse, France) and the company Guerbet is on AI as a decision support tool for the curative treatment of primary liver cancer. See the PhD thesis of Omar Ali for more information ().

9.1.2 Heartflow

Participants: Mohamed Ali Srir, Raoul Sallé de Chou, Irene Vignon-Clementel *(correspondant)*.

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

10 Partnerships and cooperations

10.1 International research visitors

10.1.1 Visits of international scientists

Prof. Eduard Rohan

Status Professor

Institution of origin West Bohemia University

Country Czech Republic

Dates 3 days (May 2023) and 3 days (November 2023)

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

Dr. Yi Yin

Status Postdoctoral research associate

Institution of origin University of Oxford

Country United Kingdom

Dates 3 days (May 2023)

Context of the visit Simbiotx weekly seminar, ERC MoDeLLiver

10.1.2 Visits to international teams

Research stays abroad Jérôme Kowalski visited the group of C. Debbaut, BIOMMEDA, U. of Ghent (1 week, September 2023) in the context of the ERC MoDeLLiver.

10.2 European initiatives

10.2.1 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: Jules Dichamp, Dirk Drasdo, Amaury Facque, Kevin Hakkakian, Peter Kottman, Jerome Kowalski, Mathieu De Langlard, Weiqiang Liu, Roel Meiburg, Ramdane Bessaid, Jiri Pesek, Mahdi Rezaei Adariani, Pavlos Varsos, Ana Vlasceanu, Irene Vignon-Clementel *(correspondant; grant holder)*
  .

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), C. Debbaut (U. Ghent, Belgium), J.r. Van der Vorst (LUMC, The Netherland).

10.2.2 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 in chronic liver disease towards Hepatocellular cancer. The project is a large network project linking many partners all over Germany.

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

10.3 National initiatives

- **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. 04/2020 - 12/2023.

- **ANR STEDI-NASH**

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

  The project led by Philippe Garteiser (Inserm, Hopital Beaujon) aims at a Temporal diffusion spectroscopy (TDS) approach, a development of Diffusion-Weighted-Magnetic Resonance Imaging, to extract histological information in NASH (non-alcoholic steatohepatitis) non-invasively. 10/2020 - 03/2024.

11 Dissemination

11.1 Promoting scientific activities

- I. Vignon-Clementel represented Inria at the inauguration of a new pre-exascale EuroHPC supercomputer in the Barcelona Supercomputer center, Dec 2023

- I. Vignon-Clementel represented Inria at the European Virtual Human Twins Initiative launch event on Thursday 21st Dec 2023. She represented Academia at the Round Table on why do we need a European Virtual Human Twins Initiative?

11.1.1 Scientific events: organisation

A. Facque and I. Vignon-Clementel organized with D. Garcia (INSERM) a day of courses for clinicians , 28th Nov 2023: L'Art de Soigner, la Science de Comprendre. Cours de Biomécanique Médicale

General chair, scientific chair

- L. Sala and I. Vignon-Clementel: chair of the session "C-02: Clinical Biomechanics & translational research II", CMBBE 2023 Symposium, Paris, May 2023
- L. Sala, I. Vignon-Clementel, D. Drasdo: Organization of the session "D-07: Digital twin of different scales and biological processes: the example of liver", CMBBE 2023 Symposium, Paris, May 2023

Member of the organizing committees I. Vignon-Clementel, Member of the organizing committee of the French working group GDR mecabio santé

11.1.2 Scientific events: selection

Member of the conference program committees

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

Reviewer

- I. Vignon-Clementel, reviewer for ESB, SBM conferences.

11.1.3 Journal

Member of the editorial boards

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

Reviewer - reviewing activities

- The most senior team members have reviewed articles for a number of journals.
- I. Vignon-Clementel, Review Committee for the European Society of Biomechanics Huiskes Medal

11.1.4 Conferences and Talks

- Omar Ali, Poster presentation, CMBBE 2023 Symposium, Paris, May 2023
- Mathieu de Langlard, Poster presentation, EASL Congress 2023, in session *Hepatocyte Biology*, Vienna, June 2023.
- Jules Dichamp, Oral presentation, CMBBE 2023 Symposium, in session *Structures and systems biomechanics*, Paris, May 2023
- Dirk Drasdo, invited presentation, "Towards a digital liver", santé globale et bio-ingénierie, INSA Lyon 25/04/2023

- Dirk Drasdo, invited presentation, "Towards a digital liver twin - and where the immune system matters", Building Immune Digital Twins", Saclay campus, Paris area, France, June, 2023
- Dirk Drasdo, invited presentation (keynote), "Towards a full digital liver twin: injury, regeneration and disease progression", EMBO workshop, Girona, November 2023
- Ihsane Hadeg, Oral presentation, GDR Mécabio Santé 2023, in session *Hémodynamique*, Lyon, December 2023.
- Peter Kottman, Oral presentation, ICCB 2023, in session *Multiscale modelling of flows and transport in tissues*, TU Wien, September 2023.
- Peter Kottman, Oral presentation, GDR Mécabio Santé 2023, in session *Hémodynamique*, Lyon, December 2023.
- Jérôme Kowalski, Oral presentation, CMBBE 2023 Symposium, in session *Structures and systems biomechanics*, Paris, May 2023
- Jérôme Kowalski, Poster presentation, 7th VPHi Summer School, Barcelona, June 2023.
- Jérôme Kowalski, Poster presentation, Engineering 4 Health Annual Forum, Palaiseau, July 2023.
- Jérôme Kowalski, Oral presentation, Complex Networks 2023, in session *Biological networks*, Menton, November 2023
- Jérôme Kowalski, Poster presentation, Journée de l'école doctorale IP-Paris, in session *Ingénierie, Mécanique, Énergétique*, Palaiseau, December 2023.
- Weiqiang Liu, Oral presentation, CMBBE 2023 Symposium, in session *Clinical Biomechanics and Translational Research VI*, Paris, May 2023.
- Yassine Machta, Oral presentation, GDR Mécabio Santé 2023, in session *Vasculaire*, Lyon, December 2023.
- Roel Meiburg, Oral presentation, EHRA 2023, in session *Young Investigator Award - Basic and Translational Science*, Barcelona, April 2023.
- Roel Meiburg, Poster presentation, Engineering 4 Health Annual Forum, Palaiseau, July 2023
- Roel Meiburg, Poster presentation, Digital Twins 4 Health, Leuven, September 2023.
- Roel Meiburg, Oral presentation, GDR Mécabio Santé 2023, in session *Hémodynamique*, Lyon, December 2023.
- Jiří Pešek, Oral presentation, CMBBE 2023 Symposium, in session *Mechanobiology III*, Paris, May 2023.
- Mahdi Rezaei Adariani, Poster presentation, Engineering 4 Health Annual Forum, Palaiseau, July 2023.
- Mahdi Rezaei Adariani, Oral presentation, EuroMech 2023, in session *Effect of particle shape*, Nice, June 2023.
- Mahdi Rezaei Adariani, Oral presentation, ESB 2023, in session *Biofluids and transport*, Maastricht, July 2023.
- Mahdi Rezaei Adariani, Oral presentation, APS 2023, in session *Particle-Laden Flow: Non-Spherical Particles*, Washington, Nov 2023.
- Lorenzo Sala: Oral presentation, CMBBE 2023 Symposium, in session *Clinical biomechanics and translational research.* Paris, May 2023.

- Mohamed Ali Srir, Oral presentation, GDR Mécabio Santé 2023, in session *Vasculaire*, Lyon, December 2023.
- Pavlos Varsos, Oral presentation, GDR Mécabio Santé 2023, in session *Hemodynamique*, Lyon, December 2023.
- Pavlos Varsos, Attended, Workshop on Scientific Machine Learning at CWI, Amsterdam, October 2023.
- Pascalle Wijntjes, Poster presentation, BME-NL 2023, Egmond aan Zee, January 2023.
- Pascalle Wijntjes, Poster presentation, CMBBE 2023 Symposium, in session *Methods in mechanics for biology and medicine*, Paris, May 2023.
- Pascalle Wijntjes, Poster presentation, Engineering 4 Health Annual Forum, Palaiseau, July 2023.
- Pascalle Wijntjes, Oral presentation, ESB 2023, in session *Cardiovascular biomechanics*, Maastricht, July 2023.
- Pascalle Wijntjes, Attended, Workshop on Scientific Machine Learning at CWI, Amsterdam, October 2023.
- Pascalle Wijntjes, Poster presentation, DUCOMS-day 2023, in session *Multiscale Modeling*, Utrecht, November 2023.
- Jieling Zhao, Oral presentation, GASL 2023, Bochum, January 2023.
- Jieling Zhao, Oral presentation, CMBBE 2023, in session *Digital twin of different scales and biological processes: the example of liver*, Paris, May 2023.
- Jieling Zhao, Oral presentation, ENUMATH 2023, in session *Mathematical and computational models of cells, cell-populations, and applications thereof*, Lisbon, September 2023.
- Irene Vignon-Clementel, presentation BOPA for the new French Agency Innovation Santé, Jan 5th 2023
- Irene Vignon-Clementel, BME faculty seminar, Jan 11th 2023, IP Paris, France
- Irene Vignon-Clementel, round table on Digital Twin, Symposium on Digital Twin, Feb 9th 2023, Ecole CentraleSupelec Saclay, France
- Irene Vignon-Clementel, Seminar, Feb 16th 2023, Ghent U., Belgium
- Irene Vignon-Clementel, Keynote speaker, CFC, April 25th-28th 2023, Cannes, France
- Irene Vignon-Clementel, invited presentation, CMBBE, May 3rd-5th 2023, Paris, France
- Irene Vignon-Clementel, invited presentation, Immune System Digital Twins workshop, May 23rd 2023, Institut Blaise Pascal, Orsay, France
- Irene Vignon-Clementel, Webinar initiative Biomeca2023 promotion M&SN pour les dispositifs médicaux, June 13th 2023, online
- Irene Vignon-Clementel, WIC (surgical innovation week-end), June 23rd-25th 2023
- Irene Vignon-Clementel, STIMULATE Colloquium, Universty of Magdeburg, June 29th 2023, Germany (online)
- Irene Vignon-Clementel, E4H forum, round table, July 5th 2023, IP Paris, France
- Irene Vignon-Clementel, invited talk, ESB 2023, July 10-12th, Maastricht, The Netherland
- Irene Vignon-Clementel, round table on numerical twin, TERATEC forum, Sept 26th 2023, Paris
- Irene Vignon-Clementel, conférence de réanimation pré hospitalière « Mardi du Val » de la BSPP (Firefighters of Paris), Oct 10th 2023, Paris
- Irene Vignon-Clementel, invited talk, GDR mecabio santé, Nov 29th-Dec 1rst 2023, Lyon

11.1.5 Leadership within the scientific community

- D. Drasdo is member of the scientific leadership team of the German LiSyM-Cancer network project.
- 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)

11.1.6 Scientific expertise

- I. Vignon-Clementel is member of the Advisory Board, EPSRC Healthcare Technologies NetworkPlus – BIOREME project (UK), since Sept 2021
- I. Vignon-Clementel for INRAE: WG to write a report on the concept of *digital twin* (metaprogramme DIGIT-BIO)

11.1.7 Research administration

- D. Drasdo is modeling coordinator of German LiSyM-Cancer network project.
- D. Drasdo is associated with IfADo Leibniz Institute, having directed a postdocs from that institute.

11.2 Teaching - Supervision - Juries

11.2.1 Teaching

Practical and lab work supervision:

- Bachelor: R. Salle de Chou, "Probability", 24h, L3, ESIEE, Universite Paris Gustave Eiffel, France.
- Bachelor: R. Salle de Chou, "Introduction to object-oriented programming", 26h, L1, ESIEE, Universite Paris Gustave Eiffel, France.

Student project supervision:

- Master: R. Salle de Chou, "NLP methods for sentiment analysis on twitter", 34h, M1, ESIEE, Universite Paris Gustave Eiffel, France.
- Master: J. Pešek, J. Dichamp, "Modélisation et simulation de colonies de bactéries et de biofilms", 5 students, 1 day per week, Sept. 2022 – April 2023, École polytechnique, Saclay, Île de France.

Focused Interventions:

- Master: D. Drasdo, "Étapes vers un foie VIRTUEL ", 1,5 h, UE Initiation à la bio-ingéniérie, Master de Sciences, technologies et Santé Mention Biologie Integrative, Sorbonne U., France.
- Master: D. Drasdo, "Integrated and spatial-temporal multiscale modeling of liver guide in vivo experiments in healthy and chronic disease states: a blue print for systems medicine", 1h, M2, MEC 550 - Biofluid Mechanics and Mass Transport, Ecole Polytechnique (engineering school), France
- Jiří Pešek, GDR Mécabio Santé 2023, *Mechanics of life - Simulations of tissues and cellular interactions*, Lyon, December 2023.
- 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, "Modélisation numérique des écoulements biofluides", continuum mechanics class at AgroParisTech (engineering school), France
- Bachelor: I. Vignon-Clementel, "Digital twins of hemodynamics modelling for clinical applications: are we there yet?", Classes European Week, 1,5h, April 6th 2023, Ecole CentraleSupelec, France
- Bachelor : I. Vignon-Clementel, Table ronde numerique Robotique Cachan, June 6th 2023, IUT Cachan, France

11.2.2 Supervision

- CentraleSupélec Parcours Recherche project in progress: C. Finotto: "Improved personalization of a 0D hemodynamic model for liver surgery outcome", Oct. 2023 - present, supervisors: R. Meiburg, I. Vignon-Clementel
- Master Internship: M. Srir, "Graph Neural Network for perfusion regions prediction from uncomplete vesssels", July 2023 - Jan. 2024, supervisors: I. Vignon-Clementel & H. Talbot & R. Sallé de Chou
- Master Internship: I. Hadeg, "Numerical modeling for stenosis characterization", June - Oct. 2023, supervisors: I. Vignon-Clementel & J. Kowalski.
- Master Internship: Y. Machta, "Enhancing liver vessel connectivity and properties in 3D segmentation models", June - Nov. 2023, supervisors: I. Vignon-Clementel & O. Ali
- PhD in progress: P. Kottman, "Multilevel modeling of flow and transport in liver lobules in health and disease", Sep. 2023 - present, supervisors: I. Vignon-Clementel, D. Drasdo & E. Rohan (UWB Pilsen, Czech Republic).
- PhD in progress: P. Varsos, "Multi-fidelity modelling of vascular shunts and clinical applications", Jul. 2023 - present, supervisors: I. Vignon-Clementel, S. Pant, N. Golse.
- PhD in progress: J. Kowalski, "Whole-body vascular transport and pharmaco-kinetics models: application to imaging, in particular of liver ", Dec. 2022 - present , supervisors: I. Vignon-Clementel, D. Drasdo & L. Sala (INRAE).
- PhD in progress: R. Sallé de Chou, "Machine Learning based prediction of heart perfusion maps", Oct. 2021 - present, supervisors: H. Talbot (CentraleSupelec and INRIA Opis team), I. Vignon-Clementel, L. Najman (ESIEE Paris)
- PhD in progress: M. Rezaei Adariani, "Flow Dynamic Modelling to Assess the Accurate Forces Scheme of Magnetic Drug Eluting Beads Navigated by Magnetic Resonance Imaging", Sep. 2021 - present, supervisors: G. Soulez (CR-CHUM, Montreal, Canada), I. Vignon-Clementel

11.2.3 Juries

- Irene Vignon-Clementel, PhD defense committee:
  - Mahdi Daei-Daei, IP Paris, Jan 11th 2023 (president)
  - Charles Jabour, INSA Lyon, Feb 10th 2023 (reviewer)
  - Luc Bakker, TU Eindhoven, The Netherland,April 14th 2023 (reviewer)
  - Megane Decroocq, INSA Lyon, May 31rst (president)
  - Omar Ali, Université Paris Saclay, June 26th 2023 (advisor)
- Irene Vignon-Clementel, PhD monitoring committee:

  - Quentin Vanderbecq, Sorbonne Université, July 20th 2023
  - Alice Peyraut, IP Paris, Sept 18th 2023
  - Alexandra Hauguel, IP Paris, Oct 5th 2023
  - Littisha Lawrance, Université Paris Saclay, Oct 11th 2023

- Irene Vignon-Clementel, hiring committee:
  - Handicap CRCN (Junior permanent research position) for Inria, July 3rd 2023, Rocquencourt, France

- Dirk Drasdo, PhD defense committee:
  - Zheyi Yang, ENSTA / Ecole Polytechnique, 19/12/2023 (member)

11.3 Popularization

11.3.1 Internal or external Inria responsibilities

I. Vignon-Clementel, in charge of public outreach for the Inria Saclay IDF research center (since Oct. 2023)

11.3.2 Articles and contents

I. Vignon-Clementel: Interview with the French journal Capital: A Glimpse into Healthcare's Future, "Santé - Les cinq révolutions qui vont tout changer" (Health - The Five Revolutions That Will Change Everything), Aug 2023

11.3.3 Education

- SIMBIOTX group: Hosted at Inria a group of junior high school students (December 2023)
- J Kowalski and I Vignon-Clementel: helped at the Fête de la Science events (6-14th October 2023)

11.3.4 Interventions

- I. Vignon-Clementel: RJMI girls high school speed meeting, Feb 21rst 2023, Inria Saclay
- Jérôme Kowalski: CHICHE !, meeting and presentation to highschool female students for "la semaine du numérique et des sciences informatiques". At Inria Rocquencourt, Dec. 8th 2023
- I. Vignon-Clementel: CHICHE !, meeting and presentation to highschool students. At Inria Rocquencourt, June 2nd 2023
- O. Ali and I. Vignon-Clementel: Predicting Liver Surgery Complexity With AI-Based Digital Twins presented on Twin+, 9th Feb 2023
- I. Vignon-Clementel: Artificial intelligence and digital twins on FranceInter live interview (a major French national radio). 12th April 2023, Podcast
- I. Vignon-Clementel, Sept 16th, National Open Day Journée du Patrimoine, presentation on numerical twins for health, Inria Rocquencourt
- I. Vignon-Clementel, roundtable on career in research after a PhD, Université Paris Saclay, CentraleSupelec, Sept 27th 2023

12 Scientific production

12.1 Major publications

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

[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.

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

12.2 Publications of the year

International journals

[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* 11 (2023). DOI: 10.3389/fbioe.2023.1049564. URL: https://hal.science/hal-03941544.

[12] D. Drasdo and J. Zhao. 'An integrative experimental and computational twin modeling approach to understand clonal dynamics in the normal liver'. In: *Journal of Hepatology* 79.2 (Aug. 2023), pp. 273–276. DOI: 10.1016/j.jhep.2023.05.016. URL: https://inria.hal.science/hal-03512915.

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

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

International peer-reviewed conferences

[15] J. Kowalski, L. Sala, D. Drasdo and I. Vignon-Clementel. 'Understanding Organ Vascular Behavior Through their Architecture'. In: The 12th International Conference on Complex Networks and their Applications. Menton, France, 2023. URL: https://hal.inrae.fr/hal-04275318.

[16] R. Sallé de Chou, M. A. Srir, L. Najman, N. Passat, H. Talbot and I. Vignon-Clementel. 'Convex optimization for binary tree-based transport networks'. In: International Conference on Discrete Geometry and Mathematical Morphology (DGMM). Florence, Italy, 2024. URL: https://inria.hal.science/hal-04359833.

Conferences without proceedings

[17] 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: CMBBE 2023 - 18th International Symposium on Computer Methods in Biomechanics and Biomedical Engineering. Vol. 51. Paris, France, 3rd Nov. 2022, pp. 270–289. URL: https://hal.inrae.fr/hal-04075698.

Scientific book chapters

[18] J. Kowalski, D. Drasdo, P. Kottman, J. Dichamp and I. Vignon-Clementel. 'Microvascular modeling for medical imaging and toxicity assessment'. In: *Quantitative approaches to microcirculation: mathematical models, computational methods, measurements and data analysis*. SEMA SIMAI Springer Series. Springer, 2023. URL: https://hal.science/hal-04465901.

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Reports & preprints

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