RESEARCH CENTRE
Saclay - Île-de-France

2021
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

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Project-Team SIMBIOTX

Creation of the Project-Team: 2021 March 01

Keywords

Computer sciences and digital sciences

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

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B2.4.3. – Surgery

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1 Team members, visitors, external collaborators

Research Scientists

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- Jules Dichamp [Inria, until May 2021]

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- Jules Dichamp [Inria, Engineer, from Jun 2021]

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Interns and Apprentices

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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. One important challenge is the systems behavior at the microscale and at the macroscale scale. In medicine, clinical decisions are still largely guided by clinical experience, as completely standardized workflows and protocols are hampered the complexity of the human body and the variety of patient responses on therapeutic approaches. Medicine permits acquisition of an increasing amount of data on the individual patient at all levels, which requires correct interpretation and processing to ensure the optimal decisions for each patient are taken. SIMBIOTX aims at better understanding by in-silico modeling how non-invasive imaging reflects the underlying organ architecture, perfusion and function. In synergy with the first aim, SIMBIOTX aims at guiding clinical decisions by mathematical models integrating the data to inform clinicians and build predictions of possible therapy consequences. Both, models and software generated in that process will pertain to standardization. Systems toxicology aims at grasping the complexity of a substance-system interaction, ideally by direct extrapolation from in vitro toxicological experiments to human toxicity, thereby reducing animal experiments. SIMBIOTX aims at building models explaining the outcome of in vitro experiments and guiding in vivo toxicity predictions from in vitro toxicity data, eventually by building spatial-temporal in silico abstractions of the in vitro and in vivo systems. Biotechnology increasingly develops sophisticated experimental set ups that more and more resemble in vivo systems to permit realistic experiments with human material in vitro that otherwise cannot be performed, and to generate replacement tissue to long-term replace donor organs in transplantations. SIMBIOTX aims at calibrating models with this data, to explain the underlying processes, which may contribute to a better control of experiments, and to guide their designs by mimicking bioengineering process scenarios. Particular emphasis of SIMBIOTX is on liver and liver cells.

3   Research program

SIMBIOTX's research addresses research topics in three main related subject areas, on systems medicine, systems toxicology and systems biotechnology, and in addition a complementary subject image analysis as one major interface between modeling and data. The choice and the development of a method or model (the "theoretical technology" or "methodology") are in most cases driven by a specific application. Most of the methods and models address within a specific application specific sub-components of the system (e.g. cells, flow, transport), that may occur also in other applications. Accordingly, the development of methods and models that was originally driven by one guiding application can later often be adapted to another application.

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

3.1 Methodology 1: Agent-based models

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

3.1.1 Cells

Several of our applications in systems medicine and systems biotechnology address questions at the tissue micro-architecture at cell-and sub-cellular spatial scale. In these applications we present each cell as individual unit ("agents") in continuum space using mainly two modeling technologies, which we have co-developed: center-based models (CBMs) and deformable cell models (DCMs) [7].

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. [5]).

An in-between model, typically to take into account the effect of a varying vessel cross-sectional area in space and time, is the 1D (Euler) equations of flow. It is solved here in small networks of vessels [27]. For networks of thousands of small conduits, resistance (0D) models are typically solved, where a finer rheology can be incorporated [9]. 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 [37] [28]. In such models, we usually apply ordinary differential equations (ODEs) for the compartment concentration as a function of time. The second type emerges if concentrations can vary in space (e.g. along a blood vessel) in which case usually partial differential equations (PDEs) for the local concentrations depending on space and time are considered [9], [8]. 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. [1]). 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 [2].

3.4 Complementing methodologies

3.4.1 Image analysis

Many parameters used to calibrate the models have to be inferred from images [33]. For this purpose, the team has been repeatedly performing image analysis. As free tools are usually not suited for the images used, tools to analyze images of multiple modalities (e.g. light sheet microscopy, confocal laser scanning microscopy, MRI) to extract information from images are developed. This partially includes new and refined algorithms to better bridge the gap between experimental images and computational models (e.g. [31]).

For patients, model parameterization needs to occur from non-invasive or moderately invasive modalities, e.g. from biomarkers or non-invasive imaging. While non-invasive functional imaging has been a very active field of research, its translation to the clinics is impeded by a good understanding of how the extracted parameters relate to the underlying tissue characteristics. A first approach consists in constructing in-silico models of such tissue images and study how model parameter changes relate to these in-silico images. A second approach is to perform quantitative image analysis and correlation of different image modalities [38]. 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.

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

Biophysical models can also be complemented by machine-learning approaches [4, 36].

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 model of a digital liver (e.g. [30]). Prospectively the models should be implemented within a single or within linked software tools permitting systematic hypothesis testing with small extra effort. Applications in liver concern liver tissue architecture and function in the healthy liver serving as a reference state, as well as acute liver damage, disease development and its functional consequences, as well as treatment of aberrant states, for which a prominent example is liver surgery. The computational models integrate information from in vitro experiments, animal models and human data. At the methodology level, liver modeling requires all elements introduced in the previous section, integrating agent-based modeling approaches for cells and molecules, ODE/PDE models of molecular transport, flow, as well as inter-cellular and intra-cellular reactions (which can for example be signaling cascades, metabolic reaction networks or detoxification reactions) by ODE models or, if required, stochastic modeling methods.

The first step is to provide biologists, pharmacologists, toxicologists, and clinicians with a better understanding of the interplay of the many components pertaining to liver function, injury, and the disease progression in a systems approach. In a further step, modeling is increasingly used to guide the design of experiments and data acquisition. While a number of aims and concepts can be developed based on animal models, where mechanisms may be validated, a key challenge will be to develop strategies and concepts for model and parameter identification in human. The long-term aim is to support clinicians in diagnosis by informing about disease progression, possible disease origin, disease reversal, and predict the possible consequences of therapy options. An important example for a therapy studied in SIMBIOTX is liver surgery [3].

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

4.1.2 Congenital heart disease

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

While great advances have been made in the last decades in their clinical treatment (mainly through surgery), these patients still suffer from significant mortality and morbidity, due in part to interactions between heart, systemic circulation, pulmonary circulation and other components such as implanted

graft or devices. The goal here is to perform patient-specific modeling to better understand such interactions (e.g. [35]). 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 [6], which makes them prone to be implemented first in models of the in vitro setting before integrating them into in vivo tumor growth models.

4.2   Systems Biotechnology and Systems Toxicology

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

Part of our activity is to establish computational models for simulating detoxification processes in in vitro and in vivo situations and implementing them in software. These models shall mimic both, processes in digital in vitro experiments and drug effects in digital organs, eventually in time and space. An important example is drug action of paracetamol ([34], sect. 4.1.1).

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

5   Highlights of the year

5.1   Awards

- Lorenzo Sala, postdoc in the team received an invitation to the research program SQuaREs (1 week) at the American Institute of Mathematics in San Jose, California (USA)

- Mathieu de Langlard, postdoc in the team received the award of the best PhD thesis competition organized by the International Society for Stereology and Image Analysis (ISSIA). Mathieu de Langlard was then invited to present his work at the *10th International Symposium on Signal, Image, Video and Communications* (ISIVC) in April 2021.

- Omar Ali, PhD student in the team received (as part of the Guerbet Dev AI Team) an award for winning the AI for Heath Challenge 2020 organized with APHP.

- Nicolas Golse (liver surgeon at Hop. Paul Brousse, Inserm U1193) and PhD student in SIMBIOTX, was awarded the 'Prix de l'Innovation Technologique Chirurgicale' 2021 from the national Surgery Academy for his Virtual Reality work with S. Cotin.

5.2 Events

[This event is reported this year as I. Vignon-Clementel and coworkers could not report their activity last year] I. Vignon-Clementel was co-chair of the Virtual Physiological Human international conference (VPH2020), Paris (switched to online), Aug 24th-28th 2020 (around 600 participants). Lazaros Papamanolis and Omar Ali helped to run it online. VPH2020 was organized by Inria, in collaboration with Ecole Polytechnique, INSA-Lyon and APHP, in partnership with the VPH Institute and EIT Health France.

6 New software and platforms

6.1 Lumpedflow

Participants: Lorenzo Sala, Luca Thiebaud, Irene Vignon-Clementel.

The code LumpedFlow 6.4.1 that contains a collection of forward and inverse mathematical models (ODEs) for biomedical applications (lumped parameter models of the entire blood circulation and pharmacokinetic models) has been migrated from GForge to Gitlab[1]. This year new contributions have been made to the human liver virtual hepatectomy model adapted from [12], in particular: 1) dynamic implementation of peroperative events, 2) upgrade of libraries, 3) automatization and speed up of the simulation pipeline to run on a database.

6.2 TiSim

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

While part of the TiSim framework entered its maintenance phase in the middle of last year, some development still continues, extending the code's functionality and improving its applicability. In the last year we extended the current capabilities of our TiSim framework by: coupling the APAP model inside liver lobule to external compartments, adding an ammonia detoxification to fibrotic simulations, improving deformable cell model (DCM) with addition of apical constrictions, osmosis model and tight junctions for [26],8.1.2, and further by providing a support for interaction between a fixed triangulated boundary and DCM. Additionally, we further achieved a combined speed-up by factor two in the DCM by improving implementation of sweep-and-prune, deformable cell division and conjugate gradient algorithms. Moreover, new functionality was integrated by adding new model elements for cell types participating in liver regeneration, which are hepatic stellate cells, macrophages, neutrophils, and for collagen fibres, and their contact force with existing elements. **Collaborators: Tim Johann (IfADo, Dortmund), Stefan Hoehme (Univ. Leipzig)**

6.3 New generation Tissue Simulator

Participants: Jiri Pesek, Jules Dichamp, Paul Van Liedekerke, Dirk Drasdo.

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[1]lumpedflow code

TiSim has a huge functionality. However, due to the high effort now required to extend TiSim further, mainly due to *tight coupling* between individual components impeding the further development of the current platform, a prototype for a new platform has been designed to avoid the shortcomings of the current platform. In the prototype the extensibility, test driven and data oriented designs are put forward with the aim to develop flexible, testable and maintainable platform for simulating cell and agent based systems, or in more broader terms, any discrete element method system.

Contact: Jiri Pesek

6.4 New software

6.4.1 LumpedFlow

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

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

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

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

Contact: Irene Vignon Clementel

6.4.2 TiSim

Name: Tissue Simulator

Keywords: Systems Biology, Bioinformatics, Biology, Physiology

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

Functional Description: TiSim is a software that permits agent-based simulations of multicellular systems. - center-based lattice-free agent-based model - modular - C++, Qt, OpenGL, GUI, batch mode - permits multiscale simulations by integration of molecular pathways (for signaling, metabolisms, drug) into each individual cell - applications so far: monolayer growth, multicellular spheroids - Boolean networks (development time = coding time ($\tilde{6}0$ MMs) + model development time ($\tilde{2}64$ MMs)) - in follow-up version 1: - liver lobule regeneration - SBML interface - in follow-up version 2: - deformable cell model (by triangulation of cell surface) - deformable rod models - extracellular matrix - vascular flow and transport TiSim can be directly fed by processed image data from TiQuant.

Contact: Dirk Drasdo

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

Partner: IZBI, Université de Leipzig

6.4.3   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   New results

Participants include former members of the team (at the time in teams REO or MAMBA). N. Golse has 15 papers not reported in the results below as they are focussed on clinical research.

7.1   Liver: Hemodynamics and pharmacokinetics modeling

7.1.1   Hemodynamics modeling for liver surgery: digital twins

> **Participants:**   Chloe Audebert, Prisca Combari, Nicolas Golse, Florian Joly,
> Quentin Nicolas, Irene Vignon-Clementel.

Despite improvements in medical and surgical techniques, post-hepatectomy liver failure (PHLF) remains the leading cause of postoperative death. High postoperative portal vein pressure (PPV) and portocaval gradient (PCG), which cannot be predicted by current tools, are the most important determinants of PHLF. Therefore in [11], we assessed a digital twin to predict the risk of postoperative portal hypertension (PHT). A lumped parameter model of the entire blood circulation was developed with a zoom on the liver, to simulate partial hepatectomy. Patient-specific simulations were run after model parameterization for a major hepatectomy patient cohort. Simulated PPV and PCG were favorably compared to intraoperative measurements, especially when taking into account peroperative events. Future work is warranted in this direction to go beyond the proof a concept. This innovative approach in liver surgery has prompted a discussion, see [12]. **Collaborators: E. Vibert and coworkers at APHP-hop Paul Brousse.**

In [32] [not reported last year], the same hemodynamics model was adapted to simulate different steps of an innovative surgery, the RAPID. This procedure includes total hepatectomy in 2 steps with small graft transplantation at the first stage. To avoid graft portal hyperperfusion, portal vein pressure monitoring is required after revascularization and right portal vein clamping. The model could successfully predict pressures at this critical step on a few patients, demonstrating its potential to help clinical decision making. **Collaborators: E. Vibert (APHP-hopital Paul Brousse) and P Dal-Line (Oslo University Hospital)**.

7.1.2   Pharmacokinetics quantification for liver surgery

Participants: Nicolas Golse, Quentin Nicolas, Irene Vignon-Clementel.

The incidence of primary nonfunction (PNF) after liver transplantation (LT) remains a major concern with the increasing use of marginal grafts. Because few early predictors are available, in [29] [not reported last year] we quantified the time-intensity curve of the indocyanine green (ICG) fluorescence of grafts during LT to predict 3-month survival. A parameter extracted from these curves was found significantly higher in the re-LT group and was the only independent predictive factor of graft survival at 3 months. This promising quantitative parameter needs to be further evaluated for its clinical impact. **Collaborators: D. Dousse, E. Vibert and coworkers at APHP-hop Paul Brousse.**

7.1.3   Flow and transport in the liver lobule: modeling and numerical schemes

Participants: Noemie Boissier, Dirk Drasdo, Irene Vignon-Clementel.

When modeling a detoxifying organ function, an important component is the impact of flow on the metabolism of a compound of interest carried by the blood. In [9], we studied the effects of red blood cells (such as the Fahraeus-Lindqvist effect and plasma skimming) on blood flow in typical microcirculatory components such as tubes, bifurcations and entire networks, with particular emphasis on the liver as important representative of detoxifying organs. Under certain conditions, oscillations between states were found and analyzed. A convection-reaction equation was studied to simulate the transport of a compound in these microcirculatory networks and its uptake by the surrounding cells. Different types of signal sharpness have to be handled depending on the application, which can be numerically challenging. We here extended existing numerical transport schemes to handle converging bifurcations, and more generally multi-furcations. We studied the accuracy of different numerical schemes as well as the effect of reactions and of the network itself on the bolus shape. The proposed methodology can readily be applied to other capillary network geometries besides the liver lobule, such as bioengineered network designs.

7.2   Liver: Paracetamol toxicity *in vitro* to *in vivo* extrapolation

Participants: Jules Dichamps, Dirk Drasdo.

Paracetamol is a drug widely used to reduce pain, however, at high doses it is hepatotoxic. As it is widely spread the hepatotoxic mechanisms have been and are still subject of intense research. Moreover, it has become a model drug to understand in vitro - in vivo toxicity extrapolation, which has become a major aim to prospectively replace animal experiments. We established a pipeline of *in vitro* and *in vivo* digital twin models to test in how far mechanistic models based upon well-characterized toxicity pathways are able to quantitatively predict *in vivo* toxicity. For this purpose, the model parameters of the *in vitro* digital twin have been pre-calibrated by comparision with *in vitro* experimental data. The *In vivo* digital twin encapsulates a model of blood flow, transport of paracetamol in the vascular network, uptake by the cells and intracellular metabolism of paracetamol elimination in order to take into account the liver tissue architecture and physiology. For a number of parameter sets, the *in-vivo* toxicity can be well predicted by the model, but this is not the case for all parameter sets. This finding leads to recommendations with regard to which parameters need or do not need to be experimentally identified with high accuracy. **Collaborators: Noemie Boissier (previously INRIA), Geraldine Celliere (previously INRIA), Ahmed Ghallab, Jan G. Hengstler, both IfADo, Dortmund.**

7.3 Liver: Regeneration and degeneration at the tissue scale

7.3.1 In silico model of liver regeneration: a virtual liver twin to test different perturbation or mechanism behind recovery of liver injury

Participants: Jieling Zhao, Dirk Drasdo.

A spatial-temporal model was established studying the interplay of cell types that are believed to be relevant in drug-induced liver injury (DILI). It implements alternative hypotheses on their mechanistic interplay towards a construction of a digital liver twin [39]. In a first step, the consequence of alternative hypotheses discussed in the biological community about the interplay of different cell types on regeneration have been studied. It was found that three out of six alternative sets of hypotheses failed to explain functioning liver regeneration i.e., three sets of hypotheses are either false or incomplete. In a second step, to demonstrate how this model can be used to guide experimental design, the outcome of perturbation experiments suppressing certain interaction in a model that was able to explain regeneration was studied. For three out of four simulated perturbation experiments the regeneration then failed. The work presents a modeling-based strategy of guiding experimental design to efficiently identify mechanisms at work. **Main collaborators: groups Ahmed Ghallab, Jan G. Hengstler (IfADo, Dortmund).**

7.3.2 Simulation of the pattern formation of liver fibrosis: focus on the interplay between cell mechanics and cell kinetics

Participants: Jieling Zhao, Mathieu de Langlard, Dirk Drasdo.

So far the mechanisms that may be responsible for the characteristic fibrotic walls in liver fibrosis are unrecognized. We present a spatial-temporal computational liver model of fibrotic wall formation, which can be viewed as a sub-model of a digital liver twin. The model extends an earlier introduced model ([30] and refs. therein) by those cell types that are believed to be key in the disease process, as well as of the formation and degradation of those extracellular matrix that are forming the fibrotic walls. The model is able to provide a functioning scenario of fibrotic wall formation as a conseqence of mechanical and cell-kinetic processes orchestrated by the interplay of several cell types. The determination of the pattern-characterizing parameters in this study were obtained through analysis of 2D and 3D images from mouse experiments [39]. **Main collaborator: group S. Dooley (University Hospital Mannheim).**

Participants: Dirk Drasdo.

7.4 Regeneration after partial hepatectomy

Partial hepatectomy (PHx) is a surgical intervention where a part of liver is removed. We established a computational model of the regeneration of the remnant liver of a mouse by a model representing each hepatocyte individually [25]. Our model simulates an entire liver lobe (a liver consists of four lobules in mouse) that can consists of hundreds of liver lobules. The model accounts for a biomechanical control of cell cycle progression (Biomechanical Growth Control; BGC). The model reproduced the available experimental observations only if BGC was taken into account. The model predicted different cell proliferation patterns in pigs and mice that corresponded to data obtained from regenerating tissue of the two species. In conclusion, the here established model suggests that biomechanical control mechanisms may play a significant role in liver regeneration after PHx. **Stefan Hoehme, Univ. Leipzig, Jan G. Hengstler, IfADO, Dortmund, Rolf Gebhardt, Univ. Leipzig, Germany.**

7.5 Liver: Development and function of the biliary system

7.5.1 Influence of cell mechanics in embryonic bile duct lumen formation: insight from quantitative modeling

Participants: Paul Van Liedekerke, Dirk Drasdo.

This work, mentioned in the last year report of MAMBA [26] has now been accepted for PLOS Comput. Biol. in its final version. Multiple hypotheses have been discussed in the biological community, which mechanism may drive the formation of a bile duct lumen in embryonic development, which is observed to occur out of a double layer of cells. In its final form, the work identifies osmosis as the key process in the stable and reproducible initiation of bile duct formation during which salt is expelled into the extracellular space between the two cell layers, providing the osmotic force for water to generate a lumen. Differential cell division in only one layer of a double cell layer, or apical constriction, where cells forming a double layer actively deform into a wedge-like shape to generate a lumen are not sufficient to form a stable lumen within a tissue a growing tissue. **Main collaborator: Frederic Lemaigre and coworkers at Université catholique de Louvain, Bruxelles.**

7.5.2 Bile salt transport

Participants: Dirk Drasdo, Irene Vignon-Clementel.

Since decades there is a consensus assuming bile salts to be transported with osmotically-driven fluid flow inside the bile canaliculi (the bile conduits inside a liver lobule) as in the bile ducts, carrying the bile salts to the gal bladder. A recent finding obtained within a systems biology approach, in which a computational model simulating bile salt transport within a 3D murine liver micro-architecture was able to reproduce the concentration profiles experimentally observed in intra-vital experiments in a mouse model by diffusion alone [21]. The results hence challenge the hypothesis of osmotically-driven bile salt transport. The arguments in favor and dis-favor of bile salt transport dominated by flow or by diffusion was thoroughly discussed together with its possible clinical consequence in ref. [20]. **Main collaborators: groups Natiket Vartak, Jan G. Hengstler (IfADo, Dortmund).**

7.5.3 Cholestatic liver injury

Participants: Dirk Drasdo.

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease of unknown aetiology for which there are no approved therapeutic options. Patients with PSC display changes in gut microbiota and in bile acid (BA) composition; however, the contribution of these alterations to disease pathogenesis remains controversial. In ref. [19] a role for microbiota-dependent changes in BA synthesis was identified that modulates PSC pathophysiology. In a genetic mouse model of PSC, it was shown that loss of microbiota-mediated negative feedback control of BA synthesis results in increased hepatic BA concentrations, disruption of bile duct barrier function and, consequently, fatal liver injury. The preclinical data highlight the microbiota-dependent dynamics of BA metabolism in cholestatic liver disease, which could be important for future therapies targeting BA and gut microbiome interactions, and identify a potential biomarker to functionally stratify patients with PSC and predict disease outcomes. Intravital two-photon-based imaging of bile transport using the synthetic green-fluorescent BA analogue cholyl-lysyl-fluorescein (CLF) was applied to visualize the spatial-temporal dynamics of bile salts in the liver of the mouse model, and subsequently quantified from image analysis. **Main collaborators: Groups Ahmed Ghallab, Jan G. Hengstler (IfADo, Dortmund); group Christian Trautwein (RWTH Aachen).**

7.6   Cardiovascular flow in large conduits coupled to their distal systems

7.6.1   Myocardial Perfusion Simulation for Coronary Artery Disease: A Coupled Patient-Specific Multiscale Model

Participants: Lazaros Papamanolis, Irene Vignon-Clementel.

Patient-specific models of blood flow are being used clinically to diagnose and plan treatment for coronary artery disease. A remaining challenge is bridging scales from flow in arteries to the micro-circulation supplying the myocardium. In [16], we proposed a multiscale patient-specific model enabling blood flow simulation from large coronary arteries (visible by imaging and synthetically generated downstream) to myocardial tissue. Simulated results on five patients with non-obstructive coronary artery disease compare overall well to groundtruth PET imaging data for both resting and hyperemic conditions. Results on a patient with severe obstructive disease link coronary artery narrowing with impaired myocardial blood flow, demonstrating the model's ability to predict myocardial regions with perfusion deficit. This is the first report of a computational model for simulating blood flow from the epicardial coronary arteries to the left ventricle myocardium applied to and validated on human data.   **Collaborators: C. Jaquet and L. Najman (ESIEE - U Gustave Eiffel), H. Talbot (CentraleSupelec), the group of P. Knaapen (UMC Amsterdam), and Heartflow.**

7.6.2   Assessing Early Cardiac Outflow Tract Adaptive Responses Through Combined Experimental-Computational Manipulations

Participants: Irene Vignon-Clementel.

Mechanical forces are essential for proper growth and remodeling of the primitive pharyngeal arch arteries (PAAs) into the great vessels of the heart. Despite general acknowledgement of a hemodynamic-malformation link, the direct correlation between hemodynamics and PAA morphogenesis remains poorly understood. In [13], we combined minimally invasive occlusion experiments in the avian embryo with 3D anatomical models of development and computational fluid dynamics in-silico testing of experimental phenomenon. Blood flow was simulated based on 3D-0D models and their purely 0D models derived for parameter identification and functional analysis. Morphological and hemodynamic changes were quantified along the PAAs following vessel occlusion. Small changes in flow distribution led to significant length, ellipticity, and WSS-morphology trends upon experimental IVR vessel occlusion. In-silico occlusion models captured the instantaneous effects of altered hemodynamics loading, allowing us to propose an adaptive model for PAA morphogenesis. This work was the first step in understanding the effect of varying degrees of PAA occlusion in what is programmed to be the dominant arch of the aorta. **Collaborators: S. Lindsey and J. Butcher (Cornell University).**

7.6.3   Patient-specific, noninvasive cardiovascular assessment via physiology-based modeling and ballistocardiography-based evolutionary algorithms

Participants: Lorenzo Sala.

The work proposed in [14] present a novel approach to obtain personalized estimates of cardiovascular parameters by combining (i) electrocardiography (ECG) and ballistocardiography (BCG) for noninvasive cardiovascular monitoring, (ii) a physiology-based mathematical model for predicting personalized cardiovascular variables, and (iii) an evolutionary algorithm (EA) for searching optimal model parameters. The results show that the proposed approach successfully captures amplitudes and timings of the most prominent peak and valley in the BCG curve. In particular, the blood pressure predicted by the

physiology-based model with the personalized parameter values provided by the EA search exhibits a very good agreement with the cuff-based blood pressure measurement. The combination of EA with physiology-based modeling proved capable of providing personalized estimates of cardiovascular parameters and physiological variables of great interest. This novel approach opens the possibility for developing quantitative devices for noninvasive cardiovascular monitoring based on BCG sensing. **Main collaborator: group G. Guidoboni (University of Missouri)**

7.7 Further subjects

7.7.1 Lung: A whole lung in silico model to estimate age dependent particle dosimetry

Participants: Irene Vignon-Clementel.

Anatomical and physiological changes alter airflow characteristics and aerosol distribution in the developing lung. Correlation between age and aerosol dosimetry is needed, specifically because youth are more susceptible to medication side effects. In this study [17], we estimated aerosol dosages of μm particles in an infant, a child, and an adult by performing whole lung subject-specific particle simulations throughout respiration. Flow and particles were modeled in 3D in the larger bronchi, coupled to reduced models for the distal lung. Due to their lower tidal volumes and functional residual capacities the deposited mass was smaller while the tissue concentrations were larger in the infant and child subjects, compared to the adult. Furthermore, we found that dose cannot be predicted by simply scaling by tidal volumes. These results highlight the need for additional investigation of optimizing dosage levels in order to alleviate side effects, in youth. **Collaborators: K Poorbahrami and J. Oakes (Northeastern U.), and S. Shadden (U. of California, Berkeley).**

7.7.2 Eye: ocular biomechanics and hemodynamics mathematical model to investigate entangled factors in glaucoma development

Participants: Lorenzo Sala.

Glaucoma is a multifactorial neurodegenerative disease that involves the optic nerve head and the death of the retinal ganglion cells. The main challenge in ophthalmology is to understand the origin of this degeneration. [23] presents a virtual clinical study employing the Ocular Mathematical Virtual Simulator (OMVS), a computational and mathematical model that predicts the hemodynamics and biomechanics within the human eye. The simulation results suggest that ocular hemodynamics is strongly influenced by the interaction among intraocular pressure, intracranial pressure and arterial blood pressure. These outcomes are further investigated in [18] where a sensitivity analysis of the OMVS is proposed. The combination of a physically-based model with experiments-based stochastic input reveal a novel understanding of the physiological system in the development of this ocular neurodegeneration, accounting both for the driving mechanisms and the data variability. **Collaborators: group C. Prud'homme (Université de Strasbourg) and group M. Szopos (Université de Paris)**

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

Participants: Lorenzo Sala.

Approximately 1 out of every 7 UK couples has difficulty conceiving, and in about one quarter of these cases, the cause of infertility cannot be identified. A mathematical framework that captures the discrete interactions between swimming sperm (swimmers) and the mucin network (obstacles) within water is proposed to understand the physical mechanisms of sperm selection in the female tract through

large-scale simulation and multiscale analysis. In this study, two models that describe the interactions of swimmers and obstacles both immersed in a fluid are compared. The first one exploits a individual based description, in which the stochastic dynamics of each swimmers and each obstacle is described by separate equations. The second one is a macroscopic derivation of the previous model, which leads to a system of PDEs involving the swimmer and obstacle densities within a Stokes fluid. Interesting characteristic patterns are obtained and compared in the different regimes simulated with these two mathematical descriptions. **Main collaborators: group P. Degond (CNRS - Institut de Mathématiques de Toulouse)**

7.7.4   Distribution and propagation of mechanical stress in simulated structurally heterogeneous tissue spheroids

> **Participants:**   Jiri Pesek.

In [10] we utilized visco-elastic droplet model of cell to investigate the stress distribution and anisotropy inside spheroids. Pending the individual cell's mechanical parameters we observed and characterize a transition from the confluent liquid-like macroscopic behavior with homogeneous stress distribution to the granular pile exhibiting stress bridges characteristic for jammed granular systems. We linked the formation of stress bridges to the formation of core-periphery asymmetry. In this state cells at the periphery are under pronounced lateral stress reminiscent of mechanical state of an epithelium, while cells at the core are generally under compression. This is of importance in the context of micro-tissues, since no prior biochemical gradient is required to establish this asymmetry. **Collaborators: M. Cuvelier, B. Smeets, I. Papantoniou and H. Ramon (all KU Leuven).**

7.7.5   Estimation of 3D geometrical properties of spheroid-like particle systems using projection images

> **Participants:**   Mathieu de Langlard.

In [22] we propose a parametric method to estimate geometrical properties of a population of spheroid-like particles from 2D projection images. The method consists in, first, detecting the projection of the particles in the images, and then estimating the parameters of the supposed probability laws of the spheroids semi-axes using a Bayesian framework. Moreover, a new estimator of the Sauter mean diameter to assess the efficiency of two-phase flow processes, in the case of spheroid-like particle system, is proposed. Still in view to its practical use for the characterization of two-phase flows, the whole methodology is applied to a typical bubbly flow.**Collaborators: S. Charton and F. Lamadie (CEA/DMRC (Commissariat a l'Energie Atomique)), J. Debayle (ENS Mines St-Etienne).**

7.7.6   Packing simulation of thin flexible particles using a novel discrete element model

> **Participants:**   Jiri Pesek.

Industrial applications of discrete element method simulations often need to represent long, flat, bendable particles. We developed a novel discrete element representation of flexible, flat, thin particles, consisting of a triangulated mass-spring model of the particle's neutral plane, with the thickness of the particle incorporated in customised contact models [15]. We have shown that the model correctly predicts the resulting packing density for long, flexible, flat particles, while the dynamics of densification under vibrational compaction is characterized by the Kohlrausch–Williams–Watts stretched exponential law. Applications of the model could include the modelling of fabrics, biological material like leaves, soft

plastic, and paper. **Collaborators: M. Lehman, W. Saeys, B. Smeets (all KU Leuven), T. Leblicq (CNH Industrial).**

8 Bilateral contracts and grants with industry

8.1 Bilateral contracts with industry

8.1.1 Guerbet

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

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

8.1.2 Treefrog

Participants:	Paul Van Liedekerke, Dirk Drasdo *(correspondant)*.

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

9 Partnerships and cooperations

9.1 International research visitors

9.1.1 Visits of international scientists

Other international visits to the team   Dr. Jieling Zhao (IfADo, Dortmund) visits the team in a long stay.

9.1.2 Visits to international teams

Research stays abroad   Mahdi Rezaei Adariani visited the group of C. Debbaut, BIOMMEDA, U. of Ghent (2 weeks, Fall 2021).

9.2 European initiatives

9.2.1 FP7 & H2020 projects

H2020 ERC consolidator grant MoDeLLiver

Participants:	Nicolas Golse, Mahdi Rezaei Adariani, Luca Thiebaud, Lorenzo Sala, Irene Vignon-Clementel *(correspondant)*.

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.

Collaborators are the groups of E. Vibert (APHP-Hop. P Brousse, France), G. Soulez (CHUM, Canada) and C. Debbaut (U. Ghent, Belgium).

9.2.2   Other european programs/initiatives

- **BMBF-LiSyM**

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

    BMBF "LiSyM" This project established liver systems medicine approaches to understand disease pathways and consequences of liver disease on liver function. The project is a large network projects linking many partners all over Germany. Further participants associated with our group in this projects were Ayham Zaza and Tim Johann (IfADo Dortmund).

- **BMBF-LiSyM-Cancer**

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

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

9.3   National initiatives

- **RHU iLite**

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

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

- **INCa/DGOS; PRT-K 2018-2021**

    Participants: Dirk Drasdo.

    The project "Mathematical modeling at micro and macroscopic level of primary central nervous system lymphomas (PCNSL)" aiming at a multilevel multimodal integrated approach of experiments, imaging and modeling is led by Khê HOANG-XUAN, Hôpital Universitaire La Pitié Salpêtrière, Paris.

- **ANR ABM-EPISPREAD**

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

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

- **ANR STEDI-NASH**

> **Participants:**   Jiri Pesek, Dirk Drasdo.

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

10   Dissemination

10.1   Promoting scientific activities

10.1.1   Scientific events: organisation

General chair, scientific chair

- N. Golse: chair of the session "Liver Transplantation Success Manual". 13th congress of the National Hepatology & Tropical Medicine Research Institute (NHTMRI), Caire – Egypte, 27 Octobre 2021

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

- I. Vignon-Clementel: co-chair of session 'Computational methods for cardiovascular applications' with F. Van de Vosse at ESB 2021, Milan (online)

10.1.2   Scientific events: selection

Member of the conference program committees

- Nicolas Golse, Scientific committee member, 17ème congrès francophone de chirurgie digestive et hépato-bilio-pancréatique (ACHBT-SFCD), Marne la Vallée, Novembre 2021

- Irene Vignon-Clementel, Programme committee member, Computational and Mathematical Biomedical Engineering Conference (postponed)

- Dirk Drasdo, Program committee for "Systems Biology of Mammalian Cells" (postponed)

Reviewer   I. Vignon-Clementel, reviewer for ESB

10.1.3   Journal

Member of the editorial boards

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

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

10.1.4   Conferences and talks

- Omar Ali, Poster, CJC-MA 2021, Congress of Young Researchers in Applied Mathematics, October 2021

- Mathieu de Langlard, Invited speaker, the 10th International Symposium on Signal, Image, Video and Communications, April 2021, St-Etienne (France).

- Dirk Drasdo, Invited talk, Fifth St. Andrews SofTMech Soft Tissue Modeling workshop, June 2021 (finally online)

- Dirk Drasdo, Invited talk, Eurotox 2021, Copenhagen, Sept. 2021 (finally online)

- Dirk Drasdo, invited talk, Cell & Tissue Hydraulics Minisymposium (#hydraulics2021), National University of Singapore, Oct 2021 (finally online)

- Dirk Drasdo, Invited talk, Symposium UCAncer: Multidisciplinary Approaches in Cancer Research, INRIA Sophia Antipolis, Oct 2021

- Dirk Drasdo, Seminar, Hepatinov, Villejuif, Dec 8th 2021

- Nicolas Golse, Invited talk, 13th congress of the National Hepatology & Tropical Medicine Research Institute (NHTMRI). Oct 2021 (Caire - Egypte, Virtual)

- Nicolas Golse, MEDICEN Round table, 'Surgery of the futur', Paris, Nov 9 2021

- Nicolas Golse, Seminar, Hepatinov, Villejuif, Dec 8th 2021

- Nicolas Golse, Invited talk, VI Curso Internacional de Cirurgia Endoscopica (société péruvienne de chirurgie laparoscopique), Oct 2021 (Lima - Perou, Virtual)

- Nicolas Golse, Invite talk, Day of research in surgery, National 'Académie de Chirurgie', 3rd Dec 2021

- Nicolas Golse, 17ème congrès francophone de chirurgie digestive et hépato-bilio-pancréatique (ACHBT-SFCD), Hotel New York, Marne la Vallée, Novembre 2021

- Nicolas Golse, Invited talk, Journée Médico-Chirurgicale Digestive de Toulouse, Radisson Blu Toulouse, 22 Octobre 2021

- Nicolas Golse, Invited talk, Congrès Français de Chirurgie (AFC), Paris Beffroi de Montrouge, Sep 2021

- Lazaros Papamanolis, Contributed talk, CMBBE 2021 Symposium, Bonn, Sept 2021 (online)

- Lorenzo Sala, Invited talk, 2021 Virtual Joint Mathematics Meetings, SIAM Minisymposium on Complex Fluids in Living Systems. Online. January 2021.

- Lorenzo Sala, Invited talk, WCCM 2021, mini-symposium Multidisciplinary Alliance in Biosciences: Modeling, Computing,Technology and Clinical Applications. Online. January 2021.

- Paul Van Liedekerke, Talk on TECH DAY Online Meeting: 3D Cell Culture & Organoids, October 2021

- Irene Vignon-Clementel, Seminar, Hepatinov, Villejuif, Dec 8th 2021

- Irene Vignon-Clementel, MEDICEN Round table, 'Surgery of the futur', Paris, Nov 9 2021

- Irene Vignon-Clementel, Minisymposium keynote, CMBBE Sept 2021 (online)

- Irene Vignon-Clementel, Contributed talk, ESB July 12th 2021 (online)

- Irene Vignon-Clementel, Invited talk, Chaire Innovation BOPA workshop, Paul Brousse Hosp, June 4th 2021

- Irene Vignon-Clementel, Invited talk, IGR-UPS-Inria workshop, May 31rst 2021

- Irene Vignon-Clementel, Seminar to the French 'Academie des Technologies', March 24th 2021, online

- Irene Vignon-Clementel, Seminar to MOX Colloquium, Politecnico di Milano, Jan 21rst 2021, online

- Irene Vignon-Clementel, Contributed talk, WCCM 2021, January 2021 (online)

10.1.5   Leadership within the scientific community

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

- Dirk Drasdo leads a workpackage in the network grant ANR-iLite.

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

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

10.1.6   Scientific expertise

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

10.1.7   Research administration

- Dirk Drasdo was member of the scientific leadership board of the German flagship project LiSyM (Liver Systems Medicine) financed by BMBF (Germany) until 6/2021; and is modeling coordinator of a project within the program LiSyM-Cancer that started 7/2022.

10.2   Teaching - Supervision - Juries

Full course:

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

Focused Interventions:

- Medical 'diplôme universitaire DU': N. Golse, around 10h, in different DUs for hepatobioliary and pancreatic surgery, digestive interventional endoscopy and liver intensive care.

- Master: N. Golse, "Chirurgie des cancers", 1h, M1 Biologie Santé, UE Différenciation et Prolifération Cellulaires.

- Master: N. Golse, "Réalité augmentée en chirurgie du foie", 1h, M2 Sciences Chirurgicales de l'Université Paris Sud, France

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

- Master: I. Vignon-Clementel, "Examples of data-based multiscale cardiovascular and respiratory models & 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 & simulation numérique comme outil pour la chirurgie", 1h, M2 Sciences Chirurgicales de l'Université Paris Sud, France

- Graduate level: I. Vignon-Clementel, VPHi Summer School, June 10th 2021, online (UPF Barcelona, Spain)

- Bachelor: L. Sala, "Maths: interactive teaching", 4h, L2, Double cursus médecine/science, École de l'Inserm Liliane Bettencourt, France

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

10.2.1 Supervision

- First year internship: E. Raducanu, "Development of conversion tools between TiSim legacy and new data formats.", June-Aug. 2021, supervisors: J. Pešek, D. Drasdo

- Master 1: W. Liu, "3D blood flow simulations for the understanding of sickle cell disease across ages", April-Sept. 2020, supervisor: I. Vignon-Clementel.

- Master 2: L. Thiebaud, "Mathematical modeling of the human liver hemodynamics", April-Sept. 2020, supervisors: I. Vignon-Clementel, L. Sala.

- Master 2: M. Bourdim, "Modeling of the covid-19 epidemic with a spatio-temporal stochastic model", Mai-Sept. 2021, supervisors: J. Dichamp, D. Drasdo.

- Master 2: R. Hadjeres, "Characterization of mouse liver micro-structures from 3D confocal images", Apr-Sept. 2021, supervisors: M. de Langlard, D. Drasdo

- PhD defended in Sept 2021 (see [24]): N. Golse (liver surgeon at Hop. Paul Brousse, Inserm U1193), "Anatomical, Hemodynamic and Physiological Modeling in Liver Surgery", supervisors: E. Vibert (APHP-Hop P Brousse, U. Paris Saclay), I. Vignon-Clementel and S. Cotin (Mimesis, Inria).

- PhD in progress: O. Ali, "AI as a decision support tool for the curative treatment of primary liver cancer", Jan. 2020 - present, supervisors: E. Vibert (Paul Brousse Hospital, APHP), I. Vignon-Clementel, M.M. Rohe (Guerbet)

- PhD in progress: M. Rezaei Adariani, "Computational 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 (Montreal University- Canada), I. Vignon-Clementel, C. Debbaut (U. Ghent)

- 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)

10.2.2 Juries

- I. Vignon-Clementel, hiring committee: Inria Bordeaux Surd-Ouest (BSO) CRCN & ISFP

- I. Vignon-Clementel, PhD committee: Thibaut Alleau, UTC, Dec 16th 2021 (president)

- I. Vignon-Clementel, PhD committee: Alain Berod, U Montpellier, May 19th 2021 (president)

- I. Vignon-Clementel, PhD committee: Amel Karoui, U. of Bordeaux, April 23rd 2021 (member)

- I. Vignon-Clementel, PhD committee: Nicolas Barnafi, Politecnico di Milano, Italy, Feb 5th 2021 (member)

- I. Vignon-Clementel, PhD committee: Simone Di Gregorio, Politecnico di Milano, Italy, Feb 5th 2021 (referee)

10.3 Popularization

10.3.1 Articles and contents

- I. Vignon-Clementel, Science et Avenir La Recherche journal, num Jan 2021, interviewed, 'Les jumeaux numériques, nouveaux auxiliaires de la Santé' by Hugo Jalinière

- Article LiSyM: Mathematics as a Bridge from the Laboratory to the Clinic - Importance for Advancing Medicine.

10.3.2 Interventions

- Irene Vignon-Clementel: Women in Business become a Leader, presentation on numerical twins for liver surgery & experience discussion. Organized by U. Paris Saclay, at Hop Paul Brousse, Villejuif, Sept 9th 2021

- Irene Vignon-Clementel & Lorenzo Sala: video for Fondation Inria, 'Le numérique, appui au contrôle du risque en chirurgie', Jan 2021 (youtube video)

11 Scientific production

11.1 Major publications

[1] 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.

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