ARTEMIS

The Power of Virtual Twins to Fight MASLD

D5.1 – DESCRIPTION OF SUBMODEL DEVELOPMENTS BY EACH MODEL EXPERT

Project Full Title: *AcceleRating the Translation of virtual twins towards a pErsonalised Management of steatotic liver patients*
Project acronym: *ARTEMIs*
Project type: Horizon Europe | RIA (Topic HORIZON-HLTH-2023-TOOL-05-03)
Grant agreement no: 101136299

Document information:

Deliverable no.	**D5.1**
Title	Development of submodels
Work Package	5
Dissemination level	SEN
Nature	R – Document, report
Responsible partner	DKFZ
Main Contact person	Prof. Dr. Ursula Klingmüller
Deliverable due submission date	31/12/2024
Deliverable actual submission date	23/12/2024

Document validation:

Validated by	Name	Organisation short name	Visa
Responsible	Prof. Dr. Ursula Klingmüller	DKFZ	OK
Reviewer 1	Irene Vignon-Clementel	INRIA	OK
Reviewer 2	Jens Timmer	ALU-FR	OK

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History of changes:

Change explanation	Pages affected	Change made by (Name & surname)	Date

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INTRODUCTION

The main objective of this deliverable is to evaluate and exploit different modelling approaches to develop submodels at different scales and functional levels around the liver-heart axis for application in the four use cases in ARTEMIS. Within the past six months, based on publicly available large data sets, strategies for the development of machine learning submodels for disease course prediction have been tested and deep learning approaches were evaluated to improve model performance and calibration. To formalize hypothesis on mechanisms on progression of fibrosis in MASLD and the interaction with the heart, relevant intracellular models of key regulatory mechanisms in liver cells are selected that could impact the interaction with the heart, strategies for patient-specific parametrization of the models were tested and likewise approaches to assess the impact of therapeutic drugs were evaluated. To explore consequences in the complex interplay of functional units at different levels, up to blood biomarker and imaging signatures of patients, decisions on procedures for the establishment of spatio-temporal submodels of liver and heart tissue through extending the existing liver virtual twin by components that are used as clinical biomarkers for disease progression towards and beyond fibrosis were taken. Furthermore, an approach for setting up a core of virtual twin of the heart myocardium at microarchitectural level with view on fibrosis was proposed. Finally, the developments of submodels for hemodynamics and transport at the tissue level and hemodynamics and transport at the organ level as well as at the whole-body level coupling of the liver-heart axis was planned, and some components implemented. Jointly, these developments provide the basis to test the consequence of different mechanisms, as well as of therapeutic interventions and thus for the development of virtual twins, towards clinical decision support systems.

1. Machine learning submodels for disease course prediction (MUV, BU)

The goal of image processing is to facilitate the establishment of submodels to study processes leading from MAFLD to HCC. This includes the prediction of HCC by the detection of potentially malignant regions as well as the characterization of stages of the liver parenchyma during disease progression, including but not limited to: inflammation, fibrosis, cirrhosis, HCC. This will be performed utilizing methods based on machine learning and deep learning.

The work performed by **MUV** over the past months focussed on a preexisting local cohort. The data consists of a time series for each involved patient of MRI scans, and some associated demographic data. When working with time series, images should be registered to consistently study the same regions of the organ of interest. Registration can be performed intra-patient or inter-patientwise. **MUV** evaluated an intra-patient approach and

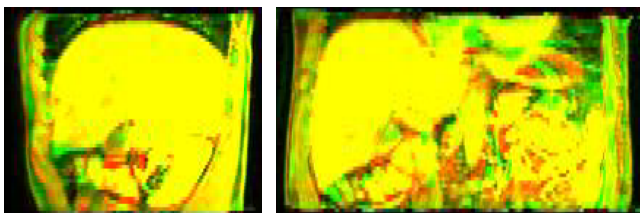

Figure 1: Result of ANTs registration on sagittal and coronal slices of liver MRI. Original and registered images overlapped. Yellow areas show coincidence of image, green and red indicate difference.

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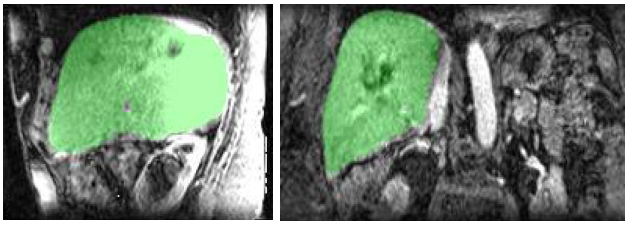

Figure 2: Sagittal and coronal slice of liver MRI with the TotalSegmentator prediction (green) overlapped.

utilized VoxelMorph [1] and ANTs [2] registration, but had suboptimal results (Fig. 1). It was tried to use segmentation to support the registration, but the major morphological and parenchymal variability present in the liver, often due to the progression of chronic liver disease, renders the registration task challenging and arguably incoherent. As an alternative approach registration of the main hepatic vessels was exploited to facilitate the identification of regions, even in cases where there is a significant deformation of the organ. Currently, **MUV** is developing a model that is able to reliably segment the liver, which is challenging due to the size of the cohort, the different scanners in use and the the high heterogeneity of liver morphology, both at the inter and intra-patient level. The current approach relies on 3D-Unet [3] and/or nnU-net [4] architectures, which is trained with annotated (segmented) local images. Automatic pre-trained tools like TotalSegmentator [5] have been tested but the results were suboptimal (Fig. 2) and reduced the performance of the registration.

In parallel to developing the image analysis methods, we started to explore means of connecting the deep learning models for extracting features and time series of features from patients with simulation models that capture biological mechanisms in the data in initial conversations between **MUV** and **ULEI**. The imaging data is anticipated to serve as evidence to generate and to verify hypotheses regarding disease progression. Current work is focussing on identifying disease characteristics that can be mapped to dynamics of MRI time series. Details on these developments are also reported in deliverable 3.1.

BU explored a variety of ML techniques to develop submodels and to address two specific research questions about disease progression. These techniques can be categorised into supervised and unsupervised ones. Moreover, such techniques are not all distributed to enable federated learning (FL) because the investigated data is publicly available not requiring any privacy-preservation mechanisms like FL. Once the consortium data is made available in ARTEMIS to apply and/or develop distributed algorithms, the privacy requirements through FL will be addressed. In particular, in a first stage, **BU** will investigate the application of existing federated ML models to be built around Flower [7], such as Federated XGBoost [8], Flex-trees [9], Federated-clustering [10], and Bi-clustering (FIST) [13] although these techniques are not adapted to longitudinal data as required in ARTEMIS. In a nutshell, **BU** will be looking at distributed ML techniques that can operate on multi-modal and longitudinal data (radiomics, clinical, and genomic data) to uncover deeper insights into fibrosis progression and applications in the other three use cases.

To employ Supervised Learning techniques for understanding progression of liver steatosis and fibrosis **BU** carried out experiments on use case 1 regarding fibrosis progression in MAFLD patients using a publicly available dataset named "Advanced Non-alcoholic fatty liver dataset with clinical metadata and ultrasound images for Deep learning Models (BEHSOF)" [11]. It comprises 113 samples belonging to patients from Taleghani Hospital (TAL) and Behbood Clinic (BEH) labelled on steatosis (12 with stage 0, 57 with stage 1, 36 with stage 2, and 8 with stage 3) and fibrosis stages (24 with F0, 78 with F1, and 11 with F2). Considering that ultrasound images are not yet publicly available, **BU** solely worked on clinical data including patients' demographic features, blood test results, and Fibroscan outcomes.

Using the abovementioned dataset, **BU** aimed to perceive which clinical features have the highest impact on the progression of liver steatosis and fibrosis to assess the development of the disease.

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To this end, **BU** started by evaluating various ML classification techniques (Random Forest, Decision Tree, Gradient Boosting, XGBoost, and KNN) to classify steatosis and fibrosis stages. Random Forest classifier (RF) achieved the best results with an accuracy of 69.56% and a ROC-AUC score of 82.66%. According to the results presented in Table 1, steatosis stages 0 and 1 had the best classification performance with a precision score of 80% and 71%, and a recall score of 80% and 91%, respectively, while stages 2 and 3 had very low precision and recall scores, very likely due to the small size of the data related to such stages".

Considering explainability of the algorithms, **BU** interpreted the classification results using the Local Interpretable Model-Agnostic Explanations (LIME) method [12] to highlight the most important features for each stage. Applying RF, the preliminary results showed that the stiffness level of the liver measured using FibroScan, CAP-Score measures, and the triglyceride level had the highest influence in predicting the steatosis stage. For a clearer insight about the key features triggering steatosis progression, **BU** applied both hierarchical clustering using Ward as a linkage method and bi-clustering techniques using the Frequent Itemset mining using Suffix-Trees (FIST) Bi-Clustering approach [13].

Table 1: Performance results of various ML models on steatosis classification

Models **Metrics**	**Random Forest**	**Decision Tree**	**Gradient Boosting**	**XGBoost**	**KNN**
Accuracy	**69.56%**	47.82%	52%	60.86%	34.78%
Avg Precision	**62%**	36%	49%	58%	35%
Avg Recall	**70%**	48%	52%	61%	35%
Avg F1-Score	**65%**	40%	50%	59%	34%
ROC-AUC	**82.66%**	54.11%	71.93%	76.11%	52.39

To employ unsupervised learning techniques for understanding fibrosis progression and related comorbidities in NASH (MASH) patients, preliminary experiments and tests were carried out by **BU** based on use case 1. Publicly available data from a study mirroring use case 1 was used. The study [14] was aimed at performing multivariate analysis to find risk factors associated with liver fibrosis progression. It is a multicentre retrospective cross-sectional study of 215 NASH (MASH) patients from Mexico, including demographic information (age, gender), key metabolic parameters (cholesterol, triglycerides, fasting glucose, AST, ALT), and histological assessments using the Kleiner scoring system for fibrosis (F0–F4) and NAFLD Activity Score (NAS). This enabled grouping patients by fibrosis severity (non-significant F0–F2 vs. significant F3–F4) and examining comorbidities (T2DM, hypertension, cardiovascular disease, metabolic syndrome).

BU conducted experiments to address key research questions, identifying the clinical variables most influential in fibrosis progression and evaluating the extent to which the identified clusters correlate with fibrosis stages and related comorbidities. These experiments also explored methodological considerations, such as the impact of different classes of clustering algorithms and the effects of employing distributed, privacy-preserving federated adaptations for clustering medical data, including processes like aggregation, alignment, and optimisation for non-IID data distributions.

The federated clustering experiments were performed using distributed hard K-means within the Flower framework. After PCA-based dimensionality reduction, the data was split among three clients (simulation) that performed local K-means clustering. A central server aligned clusters

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using the Hungarian algorithm and aggregated local cluster centres weighted by client sample size over five federated rounds. Five final global clusters mapped back to original clinical variables, highlighting distinct NASH (MASH) patient subgroups, particularly in platelet counts, liver enzymes, and cholesterol levels, revealing patterns related to fibrosis progression. Five clusters were chosen based on the Kleiner scoring system of F0-F4. The cluster centres, mapped back to the original clinical variable space, revealed distinct subpopulations of the NASH (MASH) patients based on key medical parameters. Cluster 1 exhibited high platelet count, triglycerides, and cholesterol levels, indicating active metabolic dysregulation. Cluster 2 also showed elevated platelet count and lipid abnormalities but with comparatively lower blood glucose levels, suggesting a subgroup with significant but less severe metabolic disturbances. Cluster 3 had moderately high platelet count and cholesterol, representing patients with milder metabolic issues. Cluster 4 was characterised by elevated alkaline phosphatase and cholesterol, along with high blood glucose, likely corresponding to individuals at greater risk of liver dysfunction and glycaemic irregularities. Cluster 5 displayed extremely high liver enzyme levels (AST and ALT) and lower cholesterol, indicating advanced liver damage and unique clinical patterns. These profiles provide valuable insights into the heterogeneity of fibrosis progression in NASH (MASH) patients.

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2. Deep learning for performance improvement and model calibration (ULEI, BU)

ULEI has evaluated numerous deep-learning-based approaches for the approximation of the analytical solution of complex mathematical equations that are the building blocks of many established multiscale mechanistic tissue models developed by **ULEI** in close collaboration with **INRIA** and **DKFZ**. Compared to traditional analytical and heuristic modelling methods, the deep-learning-based approach investigated by **ULEI** is fundamentally different, allowing for the learning and construction of reduced-order models which are faithful representations of the full, high-dimensional complex dynamics [1]. First, **ULEI** evaluated the conversion of the problem of solving differential equations using ANNs into an optimization problem by using a method for solving both ordinary differential equations (ODEs) and partial differential equations (PDEs) relying on the function approximation capabilities of feedforward neural networks [2]. In the last years, this has evolved into two types of approaches, respectively named data-constrained approaches [1] that use label data to predict the model and physics-constrained approaches [3] that do not include any label information, only utilizing initial and boundary physical conditions for constraints [4]. Moreover, physics-informed methods have been published that consider both types of constrained methods [5]. **ULEI** used Pytorch and TensorFlow to evaluate the suitability of data-constrained methods like multilayer NNs that can be regarded as approximation of higher-order functions [6]. Additionally, recent research shows that data constraints can be combined with prior additional restrictions (physics constraints) to feed the training of the model as a part of the loss function [6]. One of the most influential works are Physics-Informed Neural Networks (PINNs) proposed in 2019 [4, 7]. For specific PDEs, **ULEI** utilized the DeepXDE library that implements the newly proposed residual- based adaptive refinement (RAR) method as an improvement of PINNs in terms of training efficiency [8]. In additional ongoing work, **ULEI** experimentally evaluated the Fourier Neural Operator (FNO) approach [9] and verified accuracy of FNO by error bounds approximation.

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3. Intra cellular model of liver cells in interaction with the heart (DKFZ, ALU-FR, INRIA, ULEI, UKHD)

3.1 Patient subgroup specific parameterization of models

Together with our clinical partners in the ARTEMIS network, we selected as patient subgroups for our mathematical modelling approaches, patients that showed rapid or slow progression of fibrosis and with or without a cardiac phenotype. To identify features that are informative for disease progression in patient subgroups, **ULEI** provided fresh-frozen liver tissue samples of 62 patients with chronic liver disease (22 with steatosis, 18 with F1/F2 fibrosis, 22 with F3/F4 fibrosis). For the identification of changes in the protein abundance in liver tissue correlating with disease progression and thus constitute disease progression features, **DKFZ** employed a global proteomics approach using data independent acquisition (DIA) and identified 7932 proteins in the liver tissue of the 62 patients. The comparison of the global proteome of patients with steatosis and F1/F2 fibrosis yielded 106 proteins, which were significantly changed in their abundance. Likewise, the abundance of 96 proteins was changed in the comparison of the proteome of liver tissue from patients with steatosis and F3/F4 fibrosis. However, the overlap between both comparisons was small, suggesting that different mechanisms are responsible for the transition to more advance fibrotic states. To prepare for the assessment of dynamic processes, **DKFZ** shared existing proteome data on longitudinal liver tissue samples from a mouse model fed with a Western Diet (high sugar, rich fat) with **ULEI.** Using a machine learning algorithm that selects features with a strong relationship to steatosis, but a weak relationship to each other (MRMR – maximum relevance minimum redundancy), a panel of 8 proteins was identified that correlates with steatosis progression. This approach will be further developed exploring other AI-tools (i) to identify other features correlating with disease progression and additional mechanisms that contribute besides known mechanism to fibrosis progression, (ii) to elucidate the connection to alterations in the heart and (iii) to stratify patient subgroups.

For the mathematical representation of known mechanisms that contribute to liver fibrosis, **DKFZ** and **ALU-FR** selected established intracellular dynamic models relevant for ARTEMIS (Fig. 3):

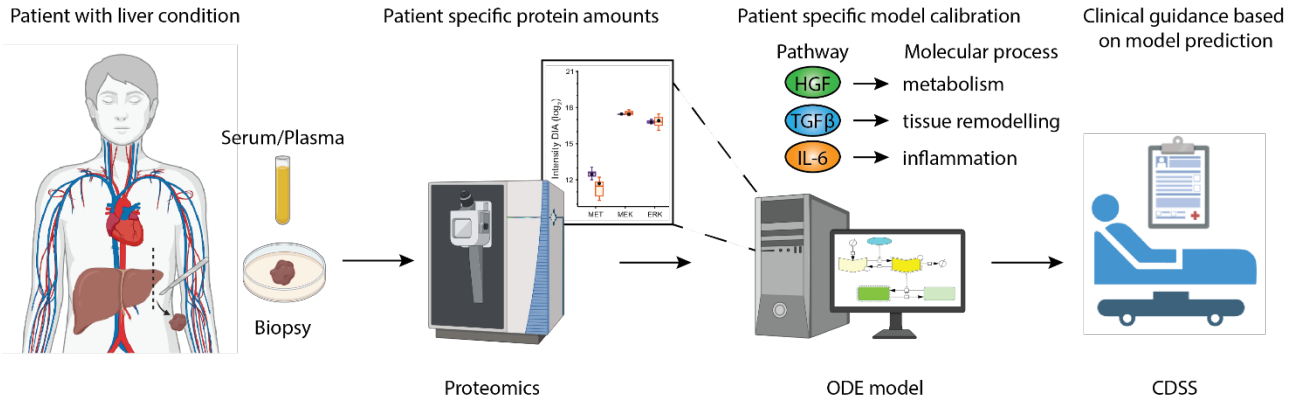

Figure 3: Established workflow for patient-specific parameterization of mechanistic ordinary differential equation (ODE) models and selection of hepatocyte growth factor (HGF), transforming growth factor beta (TGF□) and interleukin 6 (IL-6) signal transduction models to assess the link of proliferation and metabolism, the impact of tissue remodelling and of inflammation on MASLD progression to fibrosis, cirrhosis and HCC as well as the communication with the heart as a basis for virtual twin models as clinical decision support systems (CDSS).

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A critical factor for liver regeneration is hepatocyte growth factor (HGF) that induces hepatocyte proliferation and has protective functions [1]. Both processes could be altered during the progression of fibrosis and might have a major role for slow or fast fibrosis progression play a major role in regulating the speed of fibrosis progression. Therefore, **DKFZ** and **ALU-FR** selected a dynamic pathway model consisting of coupled ordinary differential equations (ODE) of HGF signal transduction in hepatocytes. The dynamic pathway model was developed using time- and dose-resolved data obtained for primary mouse hepatocytes that were either healthy or showed a steatotic phenotype. Quantitative proteomics analysis allowed the quantification of all relevant pathway components and thereby facilitated model calibration and parameter identifiability. The careful interrogation of the HGF signal transduction model revealed that the parameter of basal phosphorylation of the HGF receptor MET was key to explain the difference in phosphatidyl inositol (PI)3 kinase signal transduction observed in steatotic hepatocytes and thus help to identify a novel mechanism correlating with increasingly deregulated proliferation of hepatocytes. To transfer the mechanistic model to the human situation and to evaluate strategies for patient-specific model parametrization, **DKFZ** acquired time resolved data on HGF signal transduction in primary human hepatocytes (PHH) obtained from surgical resections and information on the abundance of pathway components in the PHH from individual patients by quantitative proteomics. Based on these data **ALU-FR** calibrated the mechanistic HGF-signal transduction model for PHH and established the basal MET phosphorylation rate as the key patient-specific model parameter that correlated with patient recovery after liver surgery. Taken together these studies suggested that basal phosphorylation of MET can be used as an indicator for liver fitness [2] and established a general strategy for the patient-specific parameterization of ODE-based mathematical models of signal transduction pathways. Furthermore, **DKFZ** and **VHIR** are investigating the impact of high glucose and fructose on disease progression and are sharing the data with **ALU-FR** to parameterize the ODE-based model of HGF signal transduction including regulation of the energy metabolism to integrate alterations in metabolism and to assess this aspect on the progression of liver fibrosis.

Transforming growth factor beta (TGFbeta) is a main driver of the secretion of extracellular matrix (ECM) proteins such as collagens and thus has a key role in liver fibrosis [3]. In the liver TGFbeta is primarily produced by activated hepatic stellate cells and acts in an autocrine manner on hepatic stellate cells but also on hepatocytes to foster ECM remodelling. To resolve mechanisms that regulate TGFbeta-induced production of ECM proteins by hepatic stellate cells and thereby potentially drive fibrosis progression, **DKFZ** and **ALU-FR** built on their ODE-based TGFbeta signal transduction model in hepatocytes that established the three most relevant phosphoSMAD2, phosphoSMAD3 and SMAD4 trimeric complexes [4]. Based on time- and dose-resolved quantitative immunoblotting data and quantitative proteomics data obtained for the immortalized hepatic stellate cell line LX2 the model has been parametrized for TGFbeta-induced signal transduction including the induction of collagens in the hepatic stellate cell line. Preliminary results show that key features of the dynamic behaviour of TGFbeta signal transduction captured by the mechanistic model can be reproduced in primary hepatic stellate cells derived from patients.

For the communication of alterations in the liver driving slow or fast fibrosis inflammatory processes could be critical [5]. A key inflammatory cytokine is interleukin 6 as it triggers acute phase responses and thus has broad effects. To interrogate the impact of IL-6 on hepatocytes and potential modulation through therapeutic drugs such as painkillers, **ALU-FR** and **DKFZ** used their previously published ODE-based IL-6 signal transduction model that revealed the importance of drug reapplication to improve responses to the JAK inhibitor Ruxolitinib [6] and focussed on early

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inflammatory responses to IL-6 in hepatoma derived cells as well as in PHH. The mathematical modelling approach revealed that the common painkillers diclofenac and paracetamol dim the induction of acute phase response proteins but amplify expression of the iron metabolism regulator hepcidin. These results demonstrated the potential of the approach to provide a systems-wide view on complex interrelations and resolve mechanisms of action of therapeutically used drugs, which could provide means to establish promising intervention strategies to e.g. slow down fibrosis progression or prevent cardiac complications.

3.2 Drug-specific influence on signalling dynamics and model output

As described in 3.1, the ODE-based approach of **DKFZ** and **ALU-FR** can yield mechanistic insights on the impact of therapeutic drugs on the dynamics of signal transduction in cells. Furthermore, the dynamic pathway model of HGF signal transduction is extended to capture regulation of glucose metabolism and thus provides the basis to study the impact of the inhibitor of the sodium glucose transporter 2 (SGLT2) in hepatocytes. Specifically, **DKFZ** received from **ULEI** PHHs of 10 patients with increasing degrees of steatosis. The time- and dose-resolved quantitative immunoblotting data revealed that in correlation with an increase in the degree of steatosis the extent of HGF-induced activation of AKT is diminished. AKT is a central mediator of PI3 kinase signal transduction and a key regulator impacting mTOR signal transduction linking signal transduction to the regulation of glucose metabolism. The data including proteomic quantification of the patient specific abundance of key signalling components is currently utilized by **ALU-FR** to establish an integrative mathematical model of HGF signal transduction and glucose metabolism to quantitatively assess the impact of SGLT2 and identify patient specific parameters. Furthermore, DKFZ confirmed the effect of the therapeutic drugs diclofenac and paracetamol on IL-6 signal transduction analysing PHH provided by **UKHD** and thus validated the approach to identify drug specific effects on the dynamics of signal transduction.

To address the systems-wide impact of drugs and to resolve effects on the communication between the liver and heart during the progression of fibrosis, longitudinal plasma/serum samples are a suitable source. Therefore, to gain insights into the effects of drugs approved for fibrosis treatment, **DKFZ** and **UKHD** have planned longitudinal experiments to characterize the dynamics of proteomic alterations in liver and heart tissue as well as serum from steatotic mice that have been treated with SGLT2 inhibitors or were left untreated. This will provide insights into the dynamics of the communication between the liver affected by progressive fibrosis and the heart and will identify changes induced by drug administration and their relation to the dynamics of phenotypic changes in the heart and liver.

3.3 Patient specific parametrization

Key for patient-specific parameterization of the developed mathematical models is the robust D1.3_Record of dissemination and communication actions undertaken in the previous 12 months, and updated plansemi-automated workflow for quantitative global, phospho and serum/plasma proteomics established by **DKFZ**. To optimize and standardize the quantitative proteomics workflow, one of the most advanced liquid chromatography devices, a Vanquish Neo system has been purchased through ARTEMIS, and was successfully integrated into the **DKFZ** workflow. This allowed to further improve chromatographic conditions such as gradient length for superior

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separation of human plasma/serum samples. Further, through titration experiments the ideal sample load (amount of plasma or serum) and injection volume thresholds were established. During these optimization steps, key metrices such as total protein identifications, peptide level resolution, and protein intensity reproducibility were rigorously evaluated, which together are critical steps for achieving high-resolution and reproducible quantification of patient-specific proteomes. To complement the proteome-wide studies in individual patients and to facilitate the quantification in changes in very low abundance proteins such as some inflammatory cytokines, a robust and reproducible workflow for antibody-based multiplexed arrays has been established by **DKFZ**. The aim is to determine patient-specific cytokine values, that can be used as input for the mathematical models developed in collaboration with **ALU-FR** and thereby enable patient-specific parameterization and model predictions.

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4. Spatio-temporal submodels of liver and heart tissue (INRIA-Drasdo; ULEI, ALU-FR, DKFZ, ICAN, UKHD, VHIR)

4.1 Extending the existing liver virtual twin (L-VT) by components that are used as clinical biomarkers for disease progression towards and beyond fibrosis

The virtual twin models are complex, requiring at tissue-scale the simultaneous representation of tissue microarchitecture in 3D space, flow and transport processes, deformation, regeneration and degeneration processes and coupling of cell-level processes to intracellular processes as well as of flow and transport at tissue microarchitectural level to whole organ and body scale. Moreover, the long duration of disease progression requires adequate modelling strategies.

To ensure re-usability of the models in-line with FAIR principles, **INRIA-Drasdo** first thoroughly analysed the current main software tool TiSim. Given the high interconnectedness of individual algorithms inside TiSim originally thought to improve performance, it was difficult and time-consuming to extend the code while guaranteeing its intelligibility. Therefore, instead of modifying TiSim, **INRIA-Drasdo** focussed on a novel software tool (CompuTiX) that has been designed as a community tool, so that the models can be used, modified and extended by other researchers. This required re-coding of all model elements established before in TiSim and hence significant more effort compared to previous tissue simulation tools of the group such as CellSys [1] or TiSim [2]. By common efforts CompuTiX was advanced to ~250 000 lines of code, and the center-based and deformable cell models were implemented with many functionalities such as cell growth, division, cell movement/migration, cell-cell interactions, interactions between cells and non-cellular objects etc. The deformable cell model triangulates the cell surface, and represents the cell surface and body by a system of semiflexible springs to reproduce the cells' mechanical response on mechanical deformation or compression. Moreover, it permits to simulate the adhesion between a cell and objects in its environment (cells, vessels etc.). Moreover, CompuTiX permits to run simulations out of image-based segmentations, and, to reconstruct 3D tissue microarchitectures out of stained volume data sets. Moreover, non-cellular structures such as vessels can be triangulated and interact with cells. The progress of the tool benefits from synergies of several modelling developers.

In parallel on a 2nd research strand, the liver disease model that combines many different cell types, has been further expanded to study disease progression from fatty liver disease (MASLD, MetALD) to advanced fibrosis. Given the high number of parameters, and the difficulty to access human tissue samples at this stage of the project, **INRIA-Drasdo** decided after numerous discussions with hepatologists at **ULEI**, **ICAN** and **VHIR** to focus on simulation of portal hypertension in different disease stages, and to implement flow and transport inside liver tissue microarchitectures (details see 5.1). This subject is considered promising by the clinical collaborators as it has less parameters and as the parameters have a higher chance to be determined. Moreover, model validation is easier than for the more complex disease progression models.

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4.2 Setting up a core VT of the heart myocardium (My-VT) at microarchitectural level with view on fibrosis

Attempts to extend the previous software tool TiSim to simulate myocardium could not be realized for reasons explained in the introduction to 5.4. For this reason, the implementation of heart cells had to be postponed. However, **INRIA-Drasdo** expects that the key step is to implement cell polarity within the deformable cell model (for which there is a blueprint in [3]), and couple this to a system of active springs.

4.3 Setting up a My-VT of heart fibrosis

Within this task **INRIA-Drasdo** developed a model for the secretion of collagen fibres or bundles, that can subsequently diffuse, adhere to each other, and interlink to form a collagen network, or digested by macrophages. So far, the individual bundles and collagen network have been tested towards there biomechanical response on compression and stretch, and compared to published references in order to calibrate the model parameters. In that model collagen fibres/bundles are mimicked as semi-flexible chains, realized by chains of beads linked by linear springs, whereby the chains partially resist to bending. The capillaries (including sinusoids) are mimicked by hollow triangulated tubes, which response on stretch or deformation are compared to published references. Equally, the response of cells within the framework of the deformable cell models on deformation is simulated and compared to published references. All these steps serve to calibrate the biomechanical parameters necessary for later upscaling and comparison to fibroscan or elastography measurements.

4.4 Simple coupling of L-VT and My-VT

In order to link liver and myocardium, the two organs need to be linked by transport of agents (molecules, cells) with the blood. This happens in task 5.

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5. Hemodynamics & transport submodels (INRIA-Vignon, INRIA-Drasdo, ULEI, JUH, AP-HP, DKFZ)

5.1 Hemodynamics & transport at tissue level (HeTran-TL)

A key component to simulate portal hypertension as well as the communication between liver and heart is the simulation of hemodynamics and transport in tissue microarchitectures.

For the development of a hemodynamics & transport at tissue level (HeTran-TL) model, within the new modular code ComputiX (see 4. Above), blood flow in explicit blood vessel networks has been implemented by **INRIA-Drasdo** and **INRIA-Vignon** with a Poiseuille-like model. A 1D-0D (spatial compartment)-1D reduction from the 3D models has been devised for transport of molecules respectively in the blood network, hepatocytes and bile canaliculi network, which will be implemented in the same code. Transport can also be of cells (e.g. immune cells) in the vessels and extravascular space. Depending on the particular molecule considered (e.g. TGF-b, provided by **DKFZ**), cells and ECM can serve both as sources or sinks. The model is being built in order to accommodate the different tissue architectures or input/output flow and transport conditions observed during disease progression (in particular the disorganization during cirrhosis) or due to treatment (WP3, WP6). This will depend on the tissue architectures provided by WP3.4.

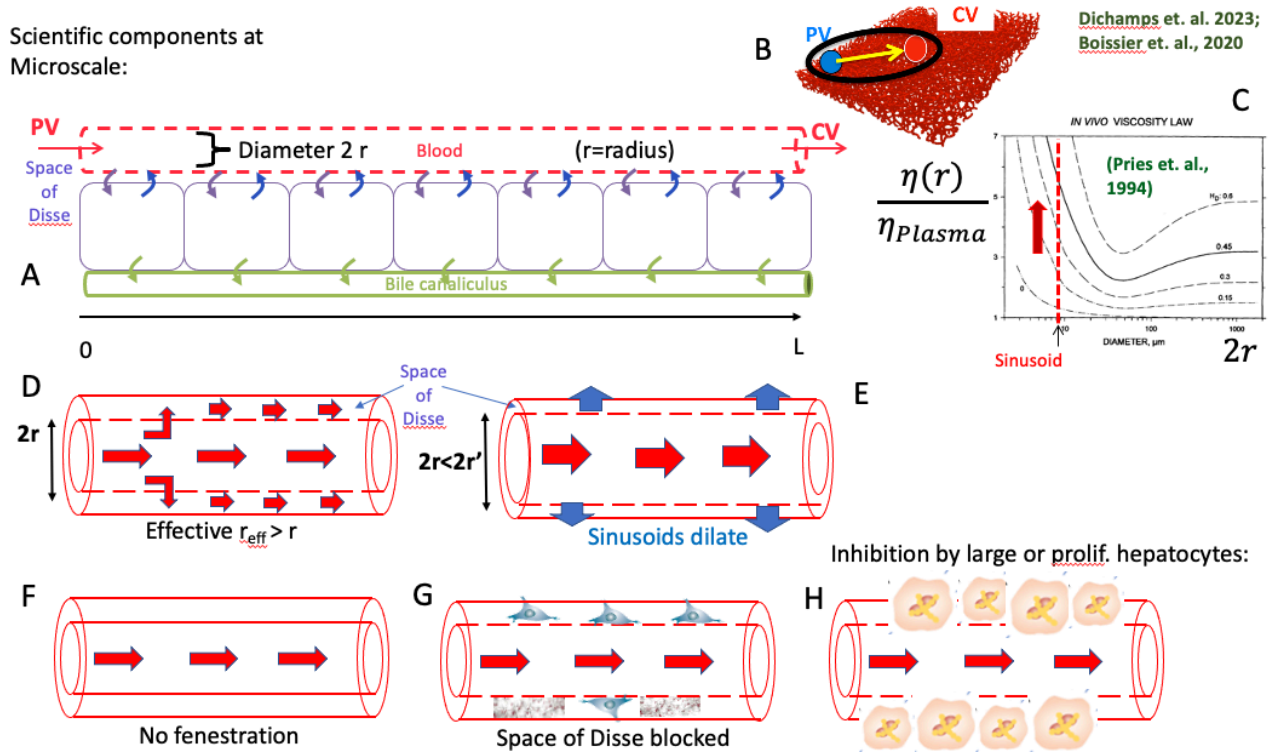

Figure 4: Elements for modeling at microscale. (A) Each sinusoid is approximated as a pipe. The sinusoidal network is a network of pipes (B). (C) The viscosity of the blood depends for small vessel radii of the radius. For very small radii, it increases. (D) It may be possible that the blood plasma partially passes through the Disse space hence increasing the effective radius, and, in case of large pressure, that the sinusoidal endothelial vessel wall may be dilated to permit a higher flow (E). In case part of the flow passes the space of Disse, an overload of the space of Disse by cells (e.g. hepatic stellate cells) or collagen (e.g. collagen I) as well as large or proliferating hepatocytes, the latter not respecting the sinusoidal alignment (Hoehme et. al., PNAS 2010) could reduce the flow able to pass a sinusoid and hence increase the flow resistance. At the level of the entire sinusoidal network any sparsening could be expected to increase the tissue flow resistance (not shown).

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Computing portal hypertension from non-invasive measurement has been identified by clinicians as an interesting and important contribution to the clinics. **INRIA-Drasdo** talked to experts inside and outside ARTEMIS and currently explore published references to establish the different possible causes discussed for hypertension in order to develop and implement virtual twins for this application. At microarchitectural level, changes of the sinusoidal radius, the fenestration, vessel stiffness or compression of vessels by hepatocytes containing lipid vesicles are among the discussed origins of increased flow resistance (Fig. 4).

5.2 Hemodynamics and transport at the organ level (HeTran-OL)

An upscaling of the HeTran-TL model will lead to an organ level (HeTran-OL) model, distinguishing right and left livers or inhomogeneities within segments, so that the histological scale can be related to the regional organ-level perfusion imaging performed in MRI or CT (WP2, T3.1). This part will be performed by **INRIA-Drasdo** and **INRIA-Vignon** at a later stage of development of HeTran-TL model. To model surgical interventions such as TIPS or transplantation, 3D CFD (computational fluid dynamics) hemodynamics modeling of the main entering and exiting liver vessels, and the TIPS has been started by **INRIA-Vignon** based on intensive discussions with **JUH** and **AP-HP** (Fig. 5).

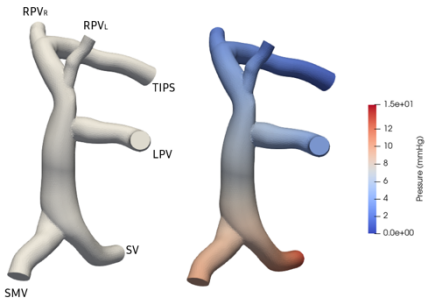

Figure 5: Preliminary results of liver vessel geometry with a TIPS and the corresponding 3D CFD simulation

It is planned that a variety of shapes, insertion locations, sizes and physiological conditions will be considered, first based on the recommendations of the use case 3 clinical partners **JUH** and **AP-HP La Pitié and Paul Brousse**. This is essential to then build corresponding reduced models of hemodynamics. The reduced model will be constructed such that parametric studies and optimization can be performed (T6.1.3).

Regarding transplantation, an important clinical question is whether to ligate natural shunts or not. This necessitates to perform 3D and reduction model steps as for the TIPS, with the difficulty of being able to segment them from imaging data.

Finally, 3D transport of molecules from the different liver inlets will be modelled later as passive tracers, to know their proportion going into the right vs left liver, or shunted by the TIPS: this will assess the importance of taking 3D geometry into account versus staying with a reduced model for distribution questions.

5.3 Hemodynamics & transport/signalling at whole body level for liver-heart coupling (HeTran-BL)

The baseline whole-body hemodynamics and transport model, which includes the liver and the heart, is currently being established by **INRIA-Vignon** in the ERC project MoDeLLiver [1]. A priori, only dynamic models (coupled ODEs) are necessary in ARTEMIs. Regarding the heart chambers, based on discussions with the clinical partners (**JUH, AP-HP** La Pitié, **AP-HP** Paul-Brousse), the one-fibre model [2, 3], the one-fibre model has been selected in order to model cardiomyopathy due to cirrhosis development or occurring after TIPS/transplantation.

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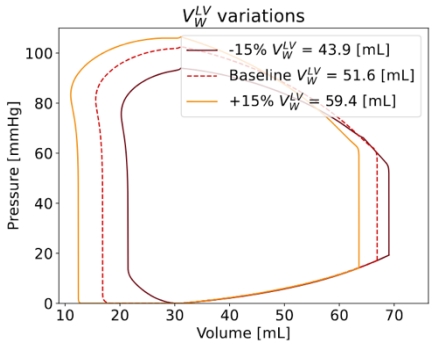

Figure 6: Example of pressure-volume loops of the left ventricle from the one-fiber model, with varying wall thickness to be able to model cardiomyopathy [4]

Regarding the liver, it is planned that the baseline model will be modified to consider the HeTran-OL model. First, the overall model will be adapted to reproduce hemodynamics at different stages of cirrhosis development. Then the TIPS and transplantation procedures will be modelled, and parameters varied to see if we can represent the typically encountered behaviours short term after the procedure. For longer term behaviours, other effects (e.g. remodelling of the organ) might have to be added to the model. Transport of soluble factors from cells or drugs (T5.3) will be included as they act on the vascular system of different organs or tissue heart structure, or as indicated as a priori important to model by the clinical partners (e.g. shunting of DAMPs, PAMPs from the liver).

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3. CONCLUSION

In this past six months, the components to be first implemented in the different models have been identified based on first exchanges between modelers and clinical partners. Preliminary results for the first steps have been obtained. Work in the area of image analysis focussed on robust segmentation of the liver in MRI data of severely disease patients, addressing extensive variability in texture and shape of anatomical structures and several deep learning approaches were evaluated to improve the performance. Furthermore, a pipeline for quantitative global proteomics was successfully employed to analyse differentially expressed proteins in early and advanced liver fibrosis, and strategies were implemented to identify with AI-based approaches features correlating with disease progression, which will provide a systems-wide view on disease promoting mechanisms. For the in-depth characterization of known mechanisms contributing to liver steatosis, fibrosis and cancer, established mechanistic models for HGF (a key regulator of hepatocyte proliferation and protection), IL-6 (a central inflammatory cytokine), and TGFbeta (a main mediator of fibrosis) signal transduction were selected and adapted to the human situation or specific cell types. Strategies were established that allowed personalized parameterization of these mechanistic models and to evaluated the impact of therapeutic drugs. To establish spatio-temporal models to assess impacts at the tissue scale the decision was taken to utilize the novel software tool (CompuTiX) that has been designed as a community tool and to initially focus computing portal hypertension from non-invasive measurement for submodel development. To address the organ level interactions, 3D CFD (computational fluid dynamics) hemodynamics

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modelling of the main entering and exiting liver vessels, and the TIPS is proposed, with the aim to model surgical interventions such as TIPS or transplantation. With these submodel developments an important basis has been laid to address the progression of MASLD to fibrosis and HCC and the communication with the heart and advance the establishment of virtual twins towards clinical decision support systems.

Risks and challenges:

At this early stage of the network patient data from the clinical partners could not yet be shared with the modelling partners and therefore in this establishment phase, publicly available data has been extensively used. However, it is evident that there is a need for more representative datasets, ideally stage balanced to gain better insight into the performance of ML algorithms.

Another risk is that the actual patient data acquired during the project will differ more significantly than expected from the preliminary and test data used to prepare data analysis and modelling efforts thus leading to unexpected additional challenges and development requirements.

Following several exchanges between modelers and clinicians to define the retrospective data collection for each use case, it is challenging to obtain the relevant (type and quality) data to construct virtual human twins (WP6) and identify the different liver-heart cross-talk mechanisms. Additional model components or extra data analysis might be need to relate the measured data to the models, and prospective studies are of importance.

For the personalized parameterization of the mechanistic models, high-quality quantitative data is essential. Previously established proteome data, if available, could be helpful for initial orientation, but it will be essential that patient samples generated according to SOPs can be analysed with the proteomics workflows established by DKFZ. Furthermore, since disease progression in the liver and communication to the heart are dynamic processes, it is of importance to perform measurements with longitudinally collected high-quality serum or plasma samples. A challenge for plasma/serum proteomics is hemolysis. For a reliable proteomics analysis only serum/plasma samples that were processed within two hours after blood draw are suitable, which frequently is not the case for retrospectively collected samples available through biobanks. To ensure the generation of high-quality proteomics data from tissue and plasma/serum samples for the mathematical modelling approaches in ARTEMIS, prospective collections of samples according to SOPs would be of great benefit. These challenges are currently addressed in discussion rounds with the modelling partners and clinical partners and SOPs are shared. For the hemodynamics and transport models, retrospective data will likely not be enough to perform and validate patient-specific simulations: prospective studies might be necessary.

4. FUTURE WORK

The goal of the segmentation from **MUV** is to be able to isolate the liver from the image. This would facilitate future models (such as encoders) to learn relevant features that might later be linked to mechanistic models. On the other hand, segmentation of the region of interest is a crucial step for the application of certain machine learning techniques, such as radiomics (that has shown to provide relevant results related tasks [6]). Further, the associated demographic and clinical information could be used in combination with the imaging data to provide a better prediction on outcomes or analysis of the images. Ultimately, the goal is to link demographic, clinical and imagenological information as input for a more accurate prediction on disease

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development. The models would be tested on cohorts from different sites across Europe, providing a more robust and reliable model due to the diversity in patients.

Regarding the mechanistic modelling, tissue and plasma samples provided of longitudinal experiments performed by **UKHD** and **VIHR** with animal models will be analyzed by **DKFZ** utilizing global and phosphoproteomics workflows. The dynamics of changes in phosphorylation sites, alterations in the abundance of proteins and the link to changes of factors in the serum will be established by ULEI and shared with **ALU-FR** to further calibrate the selected mechanistic models, to facilitate the integration of the models to e.g. explain fast versus slow fibrosis progression, to consider in vivo relevant input concentrations and to potentially select further mechanistic models a relevant to gain insights into the communication of the liver-heart axis during MASLD progression. In collaboration with WP6 the multimodal data will be integrated by **ULEI** and AI-based approaches will be used to determine mechanisms correlating with disease progression in the liver and to identify factors essential for the communication with the heart and vice versa how disease of the heart might impact the liver.

Regarding the hemodynamics & transport models, in the next phase **INRIA-Vignon** will implement the different submodel components as described above. To prepare the inclusion of outputs from WP3 and the beginning of WP6, regular discussions will be put in place between the image analysis, data analysis and modelling partners, as well as between these and clinical partners for each use case.

Tissue microarchitecture: still a major bottle neck is the availability of tissue reconstructions from human tissue material, which requires a safe, legal framework as well as a functioning workflow from taking the samples, conserving them, transporting them to the localisation where labelling and imaging is being done, transferring the images to the person doing the image reconstruction/analysis **ULEI** and finally transfer of the results to the modelling lab (**INRIA-Drasdo**). As establishment of such a workflow is time-consuming we are currently thinking of generating artificial tissue samples by developing a liver lobule generator that permits to reflect the pathologies relevant to this project. Moreover, we are aiming at mappings from non-invasive measurement modalities to histological parameters that determine tissue flow resistance.

Disease progression modelling: The models of disease progression need to reflect the parameters that are identified as patient specific by mechanistic modelling by **DKFZ** and **ALU-FR,** and that are important in clinics to calculate scores that are used to characterize the state of patients' livers. An example for a clinical parameter is the Fib4-score. For this, the transaminases concentrations and platelet counts need to be represented in the model generated by **INRIA-Drasdo**. One key step underway now is to integrate these components, which, for the Fib4-score should be done by expanding the ammonia detoxification model from ref. (Ghallab et. al., J. Hepat. 2016).

Collaborations

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