ERA PerMed

JTC2019: HeartMed, An ICT platform combining pre-clinical and clinical information for patient-specific modelling in cardiovascular medicine to improve diagnosis and help clinical decision-making

ERA PerMed Mid-Term Seminar - October 25-26, 2022

Dr. Irina Balaur, Luxembourg Centre for Systems Biomedicine, University of Luxembourg, on behalf of the HeartMed Consortium

Content

- Consortium composition
- Objectives and innovations
- Scientific Work Packages
- Scientific Outcomes and Collaboration within the Consortium
- Expected impact and Sustainability
- Communication and Dissemination
- Unforeseen Issues and Corrective Measures
- Patient Involvement
- Future plans
- Other

Consortium Composition

PARTNERS	NAME	ENTITY	COUNTRY
Coordinator	Titus Kühne	Charité – Universitätsmedizin Berlin	Germany
P2	Dominik N. Müller	Max Delbrück Center for Molecular Medicine in the Helmholtz Association	Germany
P3	Reinhard Schneider	University of Luxembourg	Luxembourg
P4	Constantin Suciu	Siemens SRL	Romania

https://heartmed.pages.uni.lu/

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN MDC MAX DELBRÜCK CENTER FOR MOLECULAR MEDICINE IN THE HELMHOLTZ ASSOCIATION LCSB uni.lu UNIVERSITÉ DU LUXEMBOURG SIEMENS

Objectives and innovations

Main objective: to enable patient-specific modelling for improved diagnosis and clinical decision-making in cardiovascular medicine

Pre-clinical research: to identify biomarkers at the molecular level (myocardial metabolism) based on the clinical (patient) and pre-clinical (animal) data characterization

Clinical Research: to improve patient-specific modelling and classification following combination of heterogeneous multidimensional data (omics, sensor, imaging), mechanistic modelling and ML tools

Data and ICT: to provide a secure and GDPR data and computing platform to facilitate harmonization, integration, analysis and modelling of multidimensional data

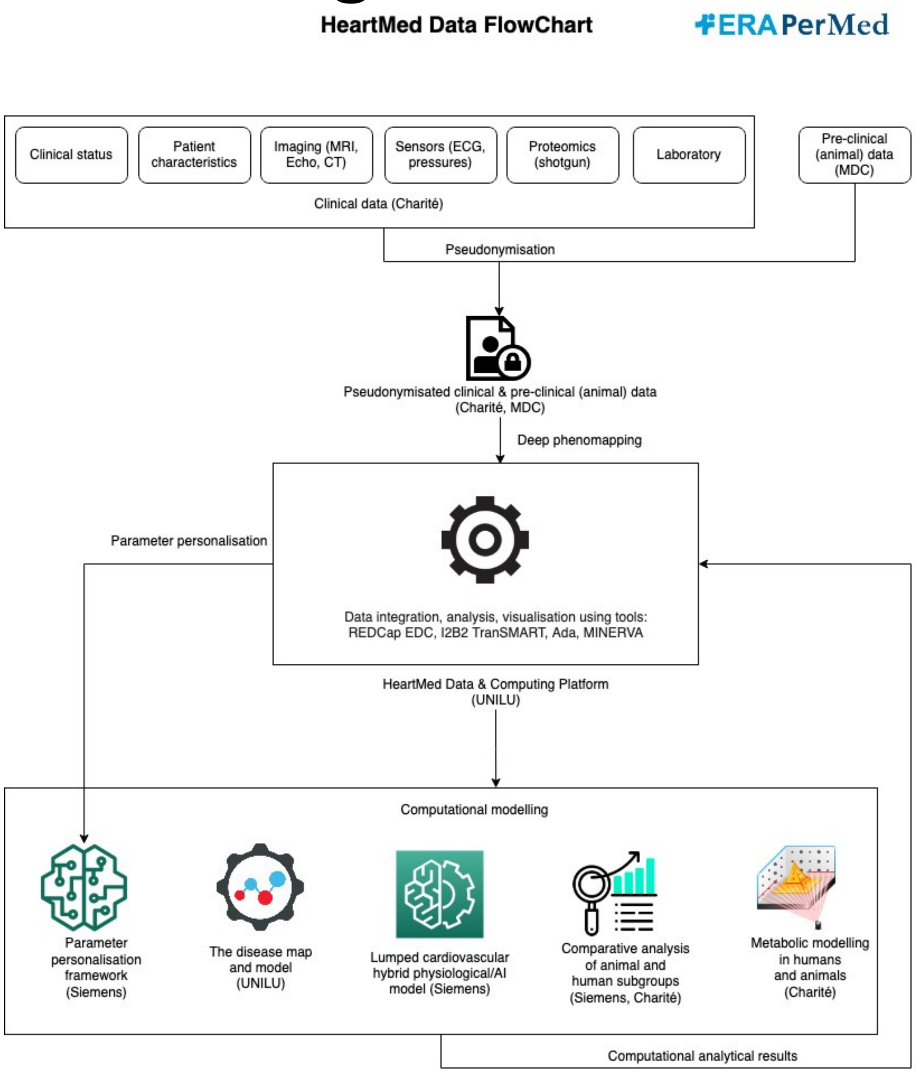
Optimising Health Care System: to evaluate which patient subgroups benefit from the tools developed in HeartMed and how these tools influence costs towards enabling personalized medicine in patients with heart failure

Scientific Work Packages

Work Package	Title	Lead	Cooperation
WP1	Clinical data management and processing	Charité	MDC, LCSB
WP2	Deep phenomapping	LCSB	Charité, Siemens
WP3	Personalized modelling in animal and human subgroups	Siemens	Charité
WP4	HeartMed: A software platform for combining biomedical data and mechanistic models for patient specific modelling and classification	Charité	Siemens, LCSB
WP5	Research towards Responsible Implementation in Health Care	Charité	Siemens

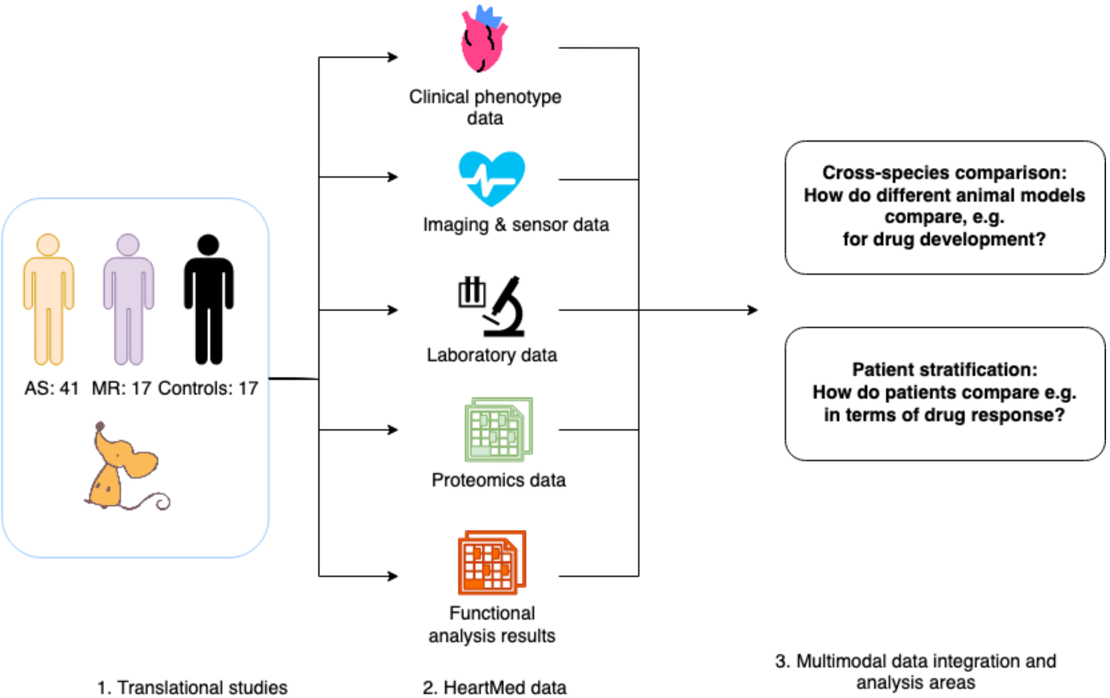
Scientific Outcomes

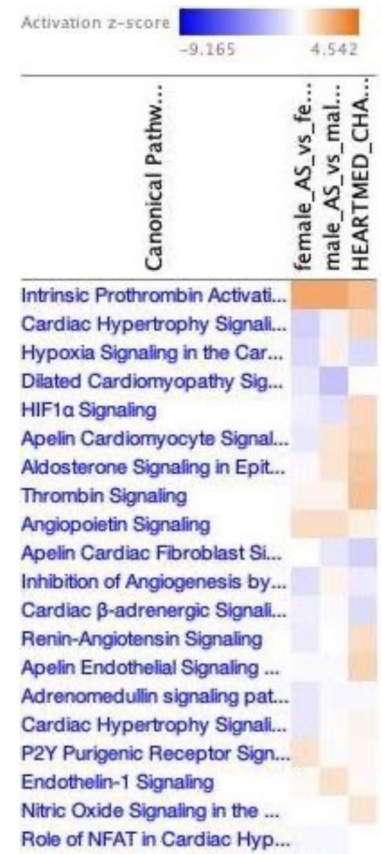
WP1: Data flow diagram



- Secured data transfer
- GDPR-compliant data and computing platform

WP2: Patient stratification and cross-species comparison

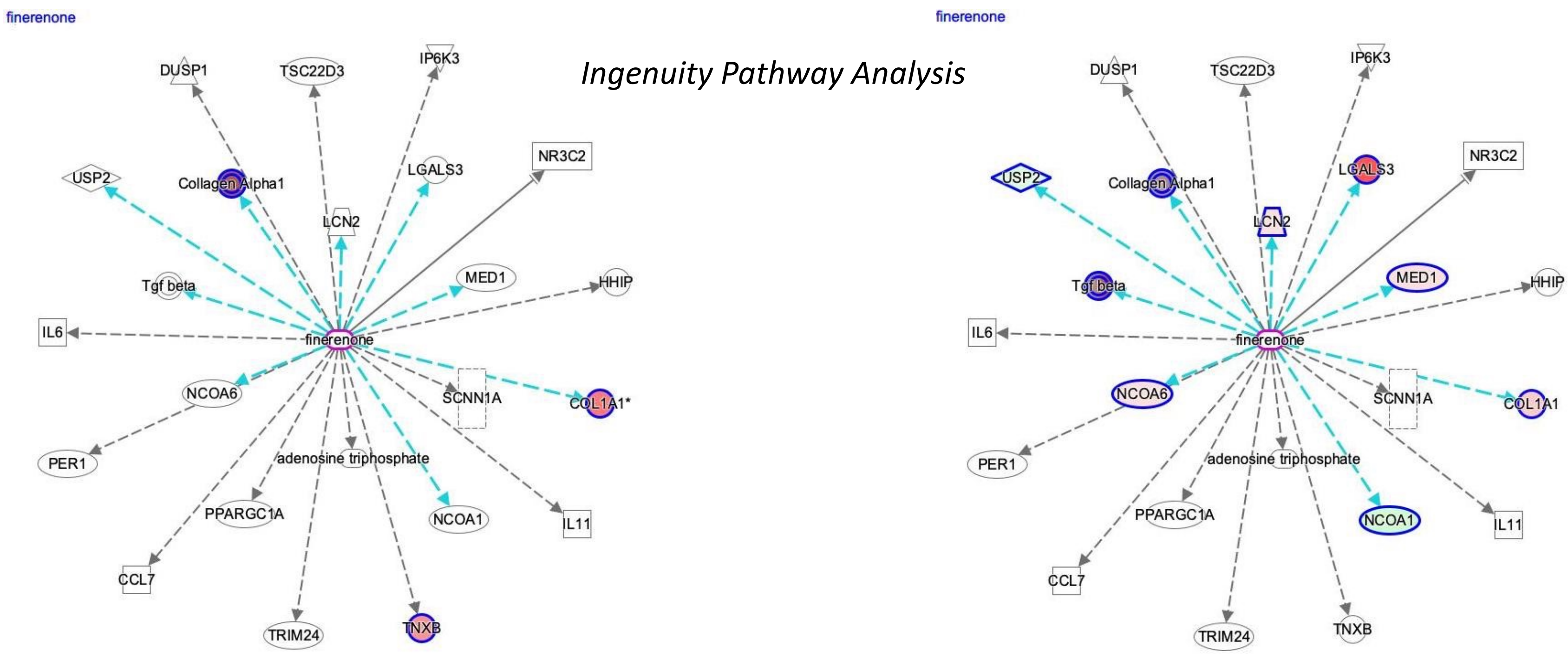




Ingenuity Pathway Analysis

- Legend: AS (aortic stenosis), MR (mitral valve regurgitation)
- Set of **cardio-related pathways** predicted to be **Activated** or **Inhibited** based on HeartMed proteomics: Female AS patients (1st row), Male AS patients (middle), Male rat (3rd row)

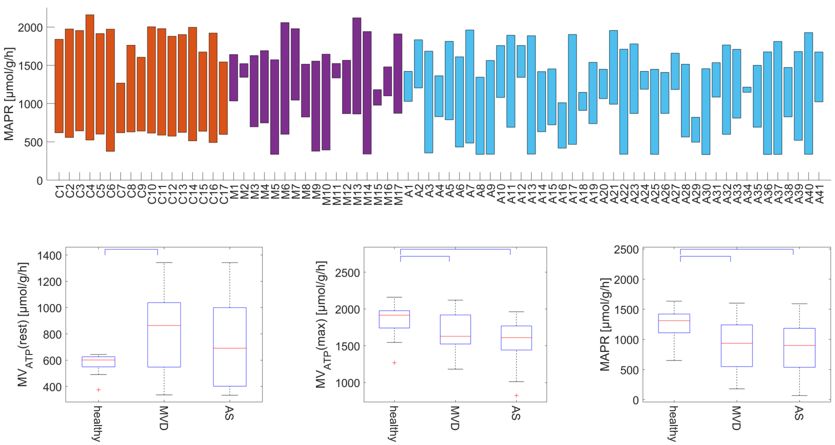
WP2: Explore interaction network of known drugs (e.g. Finerenone) with the HeartMed proteomics

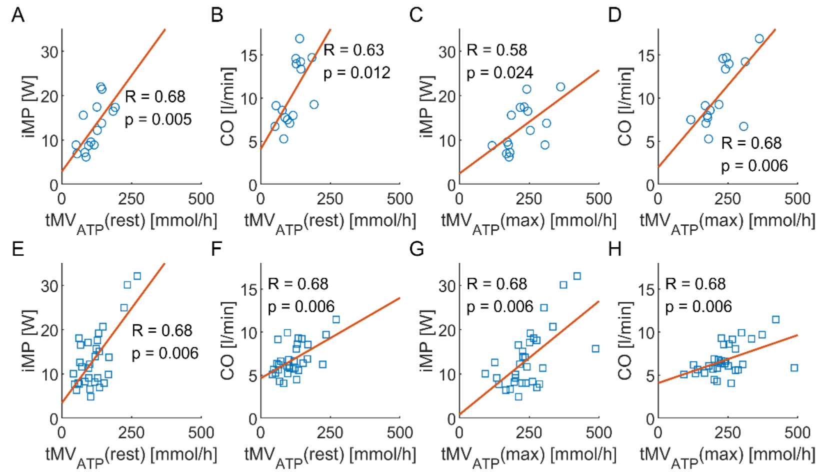


a) Human proteomics   b) Animal proteomics

- Finerenone - reported for use in cardio diseases: failure of heart, fibrosis of heart, hypertrophy of heart, intestitial fibrosis of left ventricle etc.
- Finerenone interaction network with the HeartMed a) human and b) animal proteomics

WP3: Personalized Metabolic capacities of patients with mitral valve disease and aortic stenosis



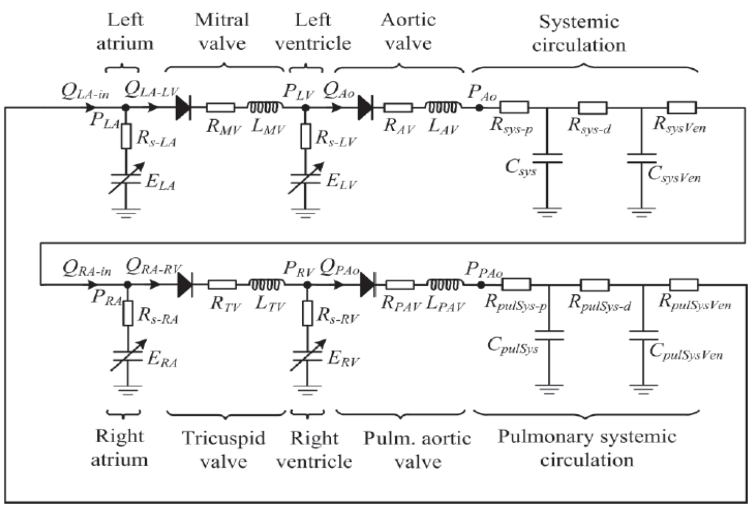


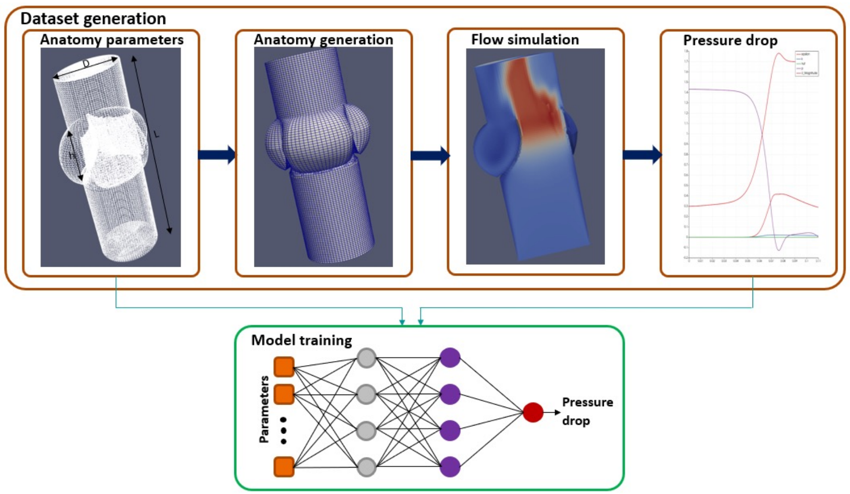
Simulate metabolic capability in dependence of substrate availability and energetic demand.

Correlation of metabolic capacity with mechanical work and cardiac output

Berndt et al. (2021) Circulation

WP3: Personalized modelling in animal and human subgroups

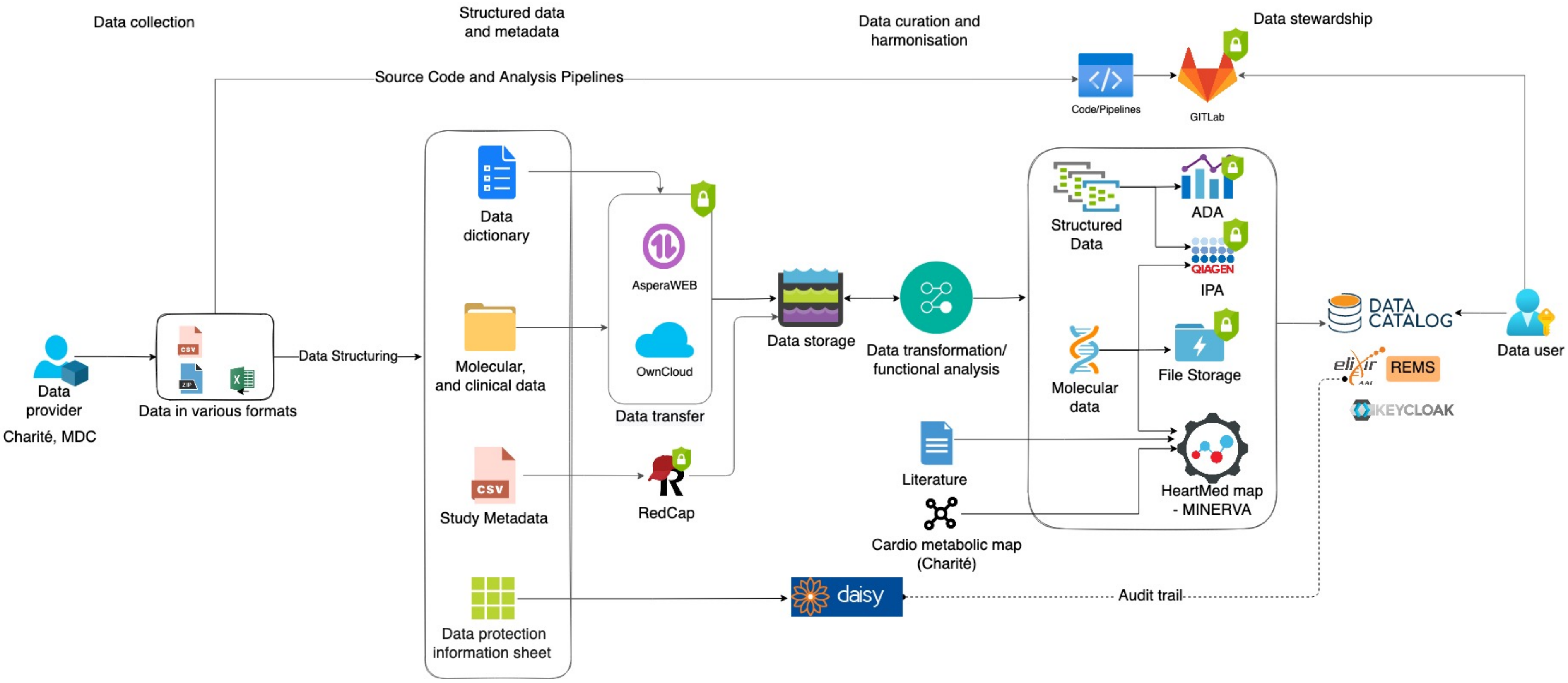




- Adapted parameter personalization methods for animal data
- Extended parameter personalization procedure for better matching time-varying quantities (volume, pressure)

Extend lumped parameter model to better capture cardiovascular pathological hemodynamics
→ Develop AI based aortic valve pressure drop model for aortic stenosis patients

WP4: The HeartMed Platform - overview



Data protection; GDPR compliance; FAIR principles (Findable, Accessible, Interoperable, Reusable)

Collaboration within the Consortium

- General assembly regular meetings (~every 3 months) and dedicated task meetings
- IP requirements detailed in Consortium Agreement
- Data management plan – details on data protection and security, data sharing and access etc.
  - Secure data transfer into the HeartMed Data & Computing platform
  - Authorisation and authentication system etc.

Expected impact and Sustainability

Long-term sustainability of HeartMed tools and data :
- under discussion during this last year of the project
- potential to use ELIXIR-Luxembourg (https://elixir-luxembourg.org/)

Communication and Dissemination

Circulation

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Home > Circulation > Vol. 144, No. 24 > CARDIOKIN1: Computational Assessment of Myocardial Metabolic Capability in Healthy Controls and Patients With Valve D…

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RESEARCH ARTICLE

PDF/EPUB

CARDIOKIN1: Computational Assessment of Myocardial Metabolic Capability in Healthy Controls and Patients With Valve Diseases

Nikolaus Berndt, Johannes Eckstein, Iwona Wallach, Sarah Nordmeyer, Marcus Kelm, Marieluise Kirchner, Leonid Goubergrits, Marie Schafstedde, Anja Hennemuth, Milena Kraus, Tilman Grune, Philipp Mertins, Titus Kuehne and Hermann-Georg Holzhütter

Originally published 11 Nov 2021 | https://doi.org/10.1161/CIRCULATIONAHA.121.055646 | Circulation. 2021;144:1926–1939

Used to assess the energy status of the left ventricle of healthy donors and patients with aortic stenosis and mitral valve insufficiency

Communication and Dissemination contd.'

Conferences > 2020 24th International Confe...

Deep learning models based on automatic labeling with application in echocardiography

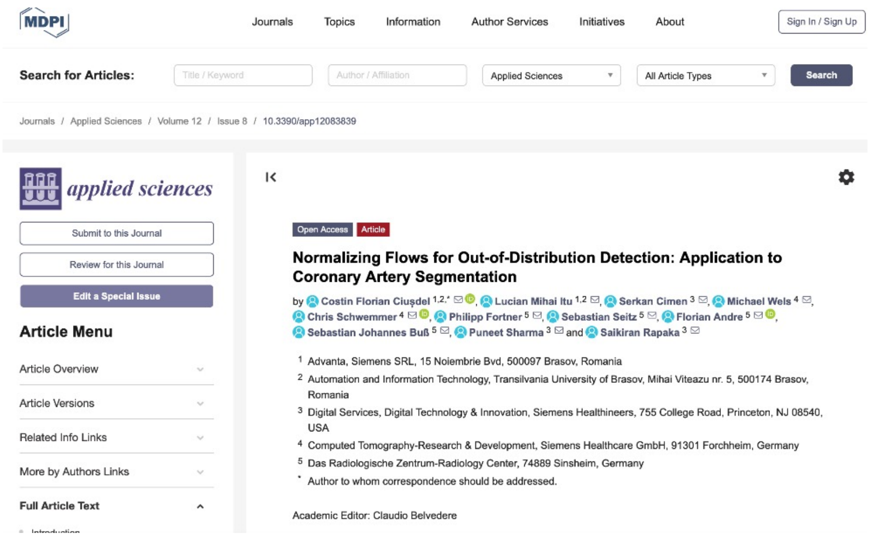
Publisher: IEEE | Cite This | PDF

Manuela Danu ; Costin Florian Ciuşdel ; Lucian Mihai Itu **All Authors**

73 Full Text Views

Abstract	**Abstract:**
Document Sections	Our goal is to apply deep learning (DL) based techniques in the context of medical imaging in order to perform automatic data labeling. Generally, training a neural network requires large amounts of (annotated) data, which is often very difficult to obtain, especially in the medical field. To alleviate this
I. Introduction	problem, we propose the use of pre-trained models. In this paper, we present two pre-training

Extension of hemodynamic model to consider time-varying quantities (volume, pressure)



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Normalizing Flows for Out-of-Distribution Detection: Application to Coronary Artery Segmentation

by Costin Florian Ciuşdel [1,2,*], Lucian Mihai Itu [1,2], Serkan Cimen [3], Michael Wels [4], Chris Schwemmer [4], Philipp Fortner [5], Sebastian Seitz [5], Florian Andre [5], Sebastian Johannes Buß [5], Puneet Sharma [3] and Saikiran Rapaka [3]

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5 Das Radiologische Zentrum-Radiology Center, 74889 Sinsheim, Germany
* Author to whom correspondence should be addressed.

Academic Editor: Claudio Belvedere

Communication and Dissemination contd.’

185 **Poster session 1** VPH2022 virtual physiological human conference

P1.12

Towards machine learning based pressure drop assessment in aortic stenosis

Andreea Bianca Popescu[1 2], *Cosmin Ioan Nita*[2], *Costin Florian Ciusdel*[1 2], *Lucian Mihai Itu*[1 2]

1 *Siemens SRL, Advanta, Brașov, Romania*
2 *Transilvania University of Brasov, Brasov, Romania*

1. Introduction

Aortic stenosis occurs when the aortic valve does not fully open during systole, which reduces or blocks blood flow to the systemic circulation. The treatment depends on the severity of the stenosis, which is assessed based on the trans-valvular peak pressure drop. Clinically, the pressure drop is routinely estimated analytically, which may lead to sub-optimal results because certain hemodynamic aspects are not fully captured (pressure recovery, turbulence) [1]. A promising solution is based on the use of a machine learning (ML) model to estimate the pressure drop based on certain patient-specific characteristics. Although an ML-based solution could provide the desired results in real-time, training an accurate model requires a large database of invasively measured pressure drops, which is difficult and costly to set up.

2. Materials and Methods

Our approach is to train the ML model with ground truth values computed using a high-fidelity computational fluid dynamics (CFD) model. The first step is to create a parameterizable anatomical model of the aortic valve. Meshes are then constructed based on this anatomy. The difference between inlet and outlet pressure is calculated after performing simulations for various aorta and valve dimensions, and inlet flow values, all set based on population level characteristics. Thus, a dataset that maps valve and blood flow characteristics to pressure drop is obtained. The open-source CFD software OpenFOAM [2] was employed for the dataset generation.

3. Results

In the following we present first experiments, using three adjustable parameters that influence the pressure drop: vessel diameter (D), percentage area reduction (Ar) and inlet flow (q).

D [cm]	Ar [%]	q [ml/s]	Δp [mmHg]
4	59.44	376.5	1.82
2	56.23	93.9	2.08
6	44.78	847.2	0.60
4	60.31	125.5	0.24

Table 1: CFD-based pressure drop estimation.

Steady-state simulations, corresponding to peak systole, were run. The turbulent flow in the proximity of the valve is visible in Fig. 1 (b), where the velocities are displayed.

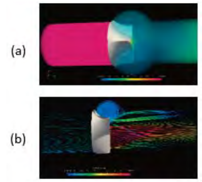


Figure 1: ParaView visualisation: (a) pressure, (b) velocity.

4. Discussion and Conclusions

The data generation process for training an ML model can be readily automated by employing Python scripts and an open-source CFD solver. The next step is to build a substantial collection of different geometries and run the flow simulations. As a result, a dataset will be constructed, enabling ML model training for pressure drop estimation in aortic stenosis.

5. References

1. *Hoeijmakers, M. et al., J Biomech Eng. 2022 Mar 1;144(3):031010. doi: 10.1115/1.4052459.*
2. *Weller, H. et al., Comp Physics, Vol. 12, Issue 6, Nov. 1998 pp. 620–631. doi: https://doi.org/10.1063/1.168744.*

Acknowledgements:
This work was supported by a grant of the Romanian National Authority for Scientific Research and Innovation, , CCCDI – UEFISCDI, project number ERANET-PERMED-HeartMed, within PNCDI III.

The ML model for predicting trans-valvular pressure drop in aortic stenosis patients

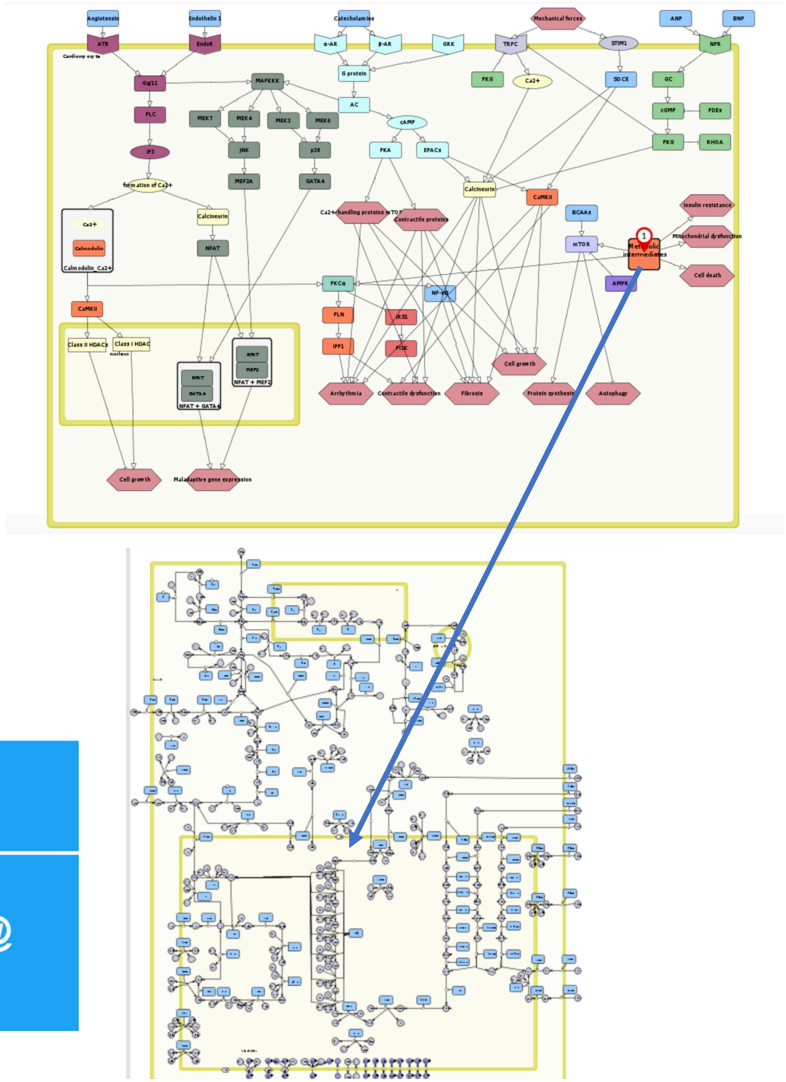
VPH 2022 CONFERENCE
VIRTUAL PHYSIOLOGICAL HUMAN

Digital twins for personalized treatment development and clinical trials
6 – 9 September 2022

Communication and Dissemination contd.’

Cardiomap (https://cardiomap.elixir-luxembourg.org):

- manually curated resource integrating multi-layer description of mechanisms of:
    - pathological/ physiological hypertrophy map;
    - cardiac energy metabolism



International Symposium on Integrative Bioinformatics 2022

16th annual meeting, 15th - 16th September 2022 @ University of Konstanz

Communication and Dissemination contd.’

The HeartMed FAIR assessment using the IMI FAIRplus indicators:

- *Findability*: **a globally unique and persistent ids for datasets**, **accompanying metadata** (study protocol, experimental parameters);
- *Accessibility*: **the Data Access model** clearly defined in the Consortium;
- *Interoperability*: **harmonised glossary** for main data types;
- *Reusability*: **Data & Computing Platform** - unified view and single point of access to the data

- Results indicated both areas with FAIR indicators achieved and areas for improvement
- Results – presented during IMI FAIRplus Fellowship meetings
- IB acknowledges the IMI FAIRplus Fellowship (no. 802750)

Unforeseen Issues and Corrective Measures

- Coped well during the COVID-19 pandemic: regular quarterly/ monthly/ bi-weekly TCs
- Due to COVID-19 pandemic, the pre-clinical data transfer had an estimated delay of 6 months, but we adjusted the project schedule - we advanced the development of the heart failure map (D2.2) - thus, no time has been lost due to the delay

Patient Involvement

- No patient involvement
- We plan to present our results to the European Society of Cardiology next year

Future plans

Remaining tasks:

- To finalise the cross-species comparison and integration of results from all partners (the pressure-volume (PV) loop with the metabolic functional analysis with the curated disease maps)

Plans for future project/ collaboration:

- To seek fundings/ new opportunities as a Consortium:
    - to have a more medical focus towards prevention
    - to combine our research approaches (e.g. artificial intelligence modelling components from Siemens, data platform from UNILU, clinical and pre-clinical data from Charité/ MDC) with publicly available UK Biobank data

Acknowledgement

Thank you!

- Colleagues from Charité, MDC, LCSB-UNILU, Siemens for contribution/ advice on:
  - data transfer: Jens (Charité), Pinar (LCSB-UNILU), Data steward team
  - data platform and website development: Jacek (LCSB-UNILU)
  - clinical aspects re. cross-species comparison, glossary, patient stratification: Sarah, Marcus (Charité)
  - the Cardiomap development: Marek, Alexander (LCSB-UNILU)
  - FAIR indicators: Danielle, Wei, Soumyabrata (LCSB-UNILU)
- Our collaborators

Questions?