Building the European Virtual Human Twin

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Minutes of the Ecosystem Meeting Paris, January 18th – 19th 2024

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Executive summary

On January 18th and 19th 2024, the EDITH consortium organised the first Ecosystem Meeting on the Virtual Human Twin in Paris. This document contains the agenda and the notes from this meeting. It is complemented by the slides of the different plenary and break-out sessions.

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Acronyms

Acronym	Full name
AI	Artificial Intelligence
AR	Augmented reality
ASME	American Society of Mechanical Engineers
CellML	Markup language for mathematical models
CoU	Context of Use
CSA	Coordination and Support Action
CWL	Common workflow language
DLT	Distributed Ledger Technology
DT	Digital Twin
DTH	Digital Twin in Healthcare
DTM	Deep Thinkers Meeting
EC	European Commission
EHDS	European Health Data Space
EHR	Electronic healthcare record
ELIXIR	European life sciences infrastructure
EM	Ecosystem Meeting
EMA	European Medicine Agency
EOSC	European Open Science Cloud
EU	European Union
FAIR	Findable, Accessible, Interoperable, Reproducible
FEM	Finite Element Modeling
GDPR	General Data Protection Regulation
GUI	Graphical User Interface
HPC	High performance Computing
ID	Identity
ISW_CoP	In Silico World Community of Practice
IT	Information Technology
LLM	Large Language Model
ML	Machine learning
MRI	Magnetic Resonance Imaging
nD	n-dimensional
OoC	Organ-on-Chip
PDE	Partial Differential Equations
QoI	Question of Interest
SaMD	Software as a Medical Device
TRL	Technology Readiness Level
UQ	Uncertainty quantification
US	United States of America
VHT	Virtual Human Twin
VR	Virtual reality
VV-40	Verification and Validation 40
WP	Work Package

1 Purpose of the meeting

1.1 Meeting objective

The EDITH coordination & support action is working on facilitating an ecosystem-driven creation of the roadmap for the Virtual Human Twin (VHT). The Virtual Human Twin (VHT) is envisioned as a systematic, ever-growing digital and quantitative representation of the actionable knowledge available on human pathophysiology. The European VHT platform will enable the pooling of resources and assets to develop digital twins in healthcare and assess their credibility. It entails the development of a federated public infrastructure and the collection of appropriate resources (data, models, algorithms, computing power, storage *etc*.), driven by the engagement of a collaborative ecosystem. With the help of the consortium, advisory boards, experts and the wider ecosystem (though public meetings and a public feedback phase), a first draft of the VHT roadmap was created. The purpose of this first draft is to indicate the different elements that need to be elaborated and supported in the scope of the VHT and provide a tangible handle to facilitate further discussion with all actors in the ecosystem.

The purpose of the Paris Ecosystem Meeting was to further the work on the VHT roadmap, ensuring that in its final form it will be comprehensive in its inclusion of all necessary building blocks and considerations for realizing the VHT. Hence, the meeting consisted of a mix of plenary sessions and break-outs. Topics included (amongst others) clinical uptake, commercialization, real-world data, AI, ethics, integration of resources, European platforms, incentivization and new use cases. The work of the 14 break-out sessions was briefly presented to the entire audience to provide all participants with a full view on the different topics. Finally, testimonies from clinicians and representatives of other large scale simulation platforms or public infrastructures provided clear purpose and bench marks for the VHT infrastructure.

Over 175 people registered for the meeting, representing all aspects of the ecosystem: academia, industry, research institutes, hospitals, HPC centers, HTA agencies, legal offices, ethics societies, as well as social sciences, civil and patient organisations. The meeting was hosted by EDITH partner INRIA at the Palaiseau Campus of the Institut Polytechnique de Paris.

1.2 Agenda

Day 1: January 18th

12:00 - 13:00 Welcome buffet lunch, networking

13:00 - 13:40 Welcome addresses by the Host (Irene Vignon-Clementel, Marie-Hélène Pautrat and Abdul Barakat (Inria), Jean Colombel (Dassault Systèmes))

13:40 - 14:00 Introduction & organisation of the meeting (Liesbet Geris (VPHi))

14.00 - 16.00 Breakout sessions

- Integration of resources (Alfons Hoekstra (UvA))
- Ethics (Ine Van Hoyweghen, Elisabetta Biasin, and Elisa Leila Elhadj (KU Leuven))
- Generation of data (OoC, sensing, …) (Adrian Ionescu (EPFL))
- Business models (Enzo Fabiani (Pi School))
- Envisioned platform processes and services (Amaryllis Raouzaiou (ATHENA), Sabato Mellone (UNIBO))
- User roles/identities (Gökhan Ertaylan, Elfi Goesaert, Frederic Jung (VITO))

- Standards for digital twins and their implementability (Martin Golebiewski and Gerhard Mayer (HITS))

16:00 - 16:30 Coffee break
16:30 - 18:00 Breakout session reports by breakout session chairs
18.00 - 18.20 Plenary address by Kyriacos Hatzaras (European Commission, DG CNECT)
18:30 - 21:00 Dinner, drinks & networking

Day 2: January 19th

08:00 - 08:30 Arrival, coffee
08:30 - 09:00 The clinical perspective (Eric Vibert (Greater Hospital in Paris AP-HP))
09.00 – 11.00 Breakout sessions

- Clinical engagement (Caroline Roney, Elisa Rauseo, Laura Bevis (QMUL))
- Large infrastructures & networks (Amaryllis Raouzaiou (ATHENA))
- Contributing to the VHT resources with new use cases: how to? (Sabato Mellone (UNIBO))
- The role of AI in the VHT (Gökhan Ertaylan (VITO))
- Incentivization (Irene Vignon-Clementel, Roel Meiburg, Anna Niarakis (Inria))
- Economic preconditions for a thriving ecosystem (Edwin Morley-Fl*etc*her (Lynkeus))
- Social acceptance and trust (Ine Van Hoyweghen, Elisa Lievevrouw (KU Leuven) and Zita Van Horenbeeck (VPHi))

11.00 - 11:30 Coffee Break
11.30 - 13:00 Breakout session reports by breakout session chairs
13.00 - 14:00 Buffet lunch
14.30 - 15:30 Plenary presentations of existing platforms and initiatives + plenary discussion

- BBMRI-ERIC: Konrad Lang (BBMRI)
- EBRAINS: Victor Jirsa (Inserm)
- 12 Labours: Thiranja Prasad Babarenda Gamage (AIB)

15:30 - 16.00 Next steps, timeline & prioritization, wrapping up (Liesbet Geris (VPHi))

2 Overview EDITH activities and results

Slides: EDITH_EM_Paris_ master file

The presentation discussed the realisations of the EDITH consortium

- Ecosystem building: mapping, advisory boards, stakeholder meetings and development of tools (LLM Web App for Knowlegde Discovery[1]) and collections (FAIRsharing standards collection[2], standardization landscape[3] and implementation guide[4]).
- VHT roadmap development: vision[5], first draft[6], approach, various stakeholder involvement activities
- Repository & Platform: pre-selected use cases, call for new use cases, governance principles, requirements, architecture and user interface/training
- Sustainability: VHT Value proposition developed with Industry Advisory Board (IAB), Evolutionary Ecosystem Approach, Business model development, VHT market place, research infrastructure benchmarks, Incentivization
- VHT Manifesto[7]

The aim of the meeting was explained (as explained in Section 1), along with the goals of the breakout sessions.

[1] https://www.edith-csa.eu/edith-knowledge-base/
[2] https://fairsharing.org/4787
[3] https://zenodo.org/records/10492796
[4] https://zenodo.org/records/10524795
[5] Viceconti M, De Vos M, Mellone S, Geris L. Position paper From the digital twins in healthcare to the Virtual Human Twin: a moon-shot project for digital health research. IEEE J Biomed Health Inform. 2023 Oct 11;PP. https://www.doi.org/10.1109/JBHI.2023.3323688.
[6] https://zenodo.org/records/8200955
[7] http://www.virtualhumantwins.eu

3 Breakout sessions

3.1 Integration of resources

Slides: EDITH_EM_Paris_Breakout_Integration
Breakout chair: Alfons Hoekstra (UvA))
Breakout notes: Janaki Raman Rangarajan (VPHi)

The discussion was a continuation of the work developed in the roadmap after discussions during internal meetings and the Rome Deep Thinkers meeting. It focused on the integration of different resources and more specifically aimed to dive deeper into questions related to workflows, accessibility and standardization.

- **Resources** include: data objects, annotation services, model objects, workflow objects and execution, storage and networking services
- Integration of resources is considerd at 2 levels
    - **Inside** the models/data/compute/storage spaces
        - For *models*, *e.g.* integration of single scale models into multi-something models
        - For *data*, *e.g.*g pooling of raw, synthetic, transformed, simulated data, including data transformation services, for (stratified populations fr individuals.
        - For *compute and storage*, *e.g.* federating some local and remote resources
    - **Between** models, data, compute, storage
        - This is actulally needed to create a full blowns DTH and execute it
- **Communication** between different resourcees for a specific digital twin, can be achieved through the use of workflows, providing access to or communication between resources.

The questions discussed during the breakouts were the following

- Do you agree that we **define a workflow** as the combination of models and input / output data, dynamically requesting access to compute / storage / networking resources?
- Will we **support a single workflow system**, *e.g.* CWL and build on that, or support requested system?
- Should we strive for a **VHT-workflow standard**, leveraging existing standards?
- Are there **prototypical DTH workflows**, or standard components for DTH workflows?
    - Generic DTH
    - Population specific DTH: *e.g.* having standard components that automatically check the CoU/QoI for which the DTH is validated and issue warnings when DTH is used outside that context?
    - Subject specific DTH: As above, and maybe other functionalities that kick in when moving from population to subject specific?
    - Or for UQ campaigns: *e.g.*, maybe each DTH workflow could/should be equipped with automatic non-intrusive UQ (relying *e.g.* on easyVVUQ developed in the EU-funded VECMA project)?
    - Validation workflows according to V&V40? following ASME workflow
- **Composing DTH workflows**
    - Using advanced user interfaces, manoeuvring atlases of human anatomy? Of the quality of *e.g.* Elsevier's complete anatomy, https://www.elsevier.com/solutions/complete-anatomy
    - Leveraging the 6D framework as backbone?
    - Exploiting advanced knowledge graphs on human (patho)physiology? *E.g.* Elsevier's Healthcare Knowledge Graph or Biology Knowledge Graph (see https://www.elsevier.com/solutions/biology-knowledge-graph) or comparable efforts.
    - Re-using existing workflows, maybe even automating that?
    - Advanced AI to help, *e.g.* a ChatGPT like interface, advanced search engines in all available data/models/literature, to propose templates of workflows to be further tailored by DTH developers?
- **Executing DTH workflows**
    - Completely automated, hiding all complexity from the DTH user?

- Automatically sending jobs to most suitable compute resources, pulling data from the right locations, moving data around, invoking dedicated networking infra, *etc*?
- For HPC jobs, advanced reservation, collocation of pooled resources, *etc*?
- What are VHT specific demands in this respect, if any? Security of data? Other?

Additional discussions evolved around a variety of tech stack related topics

- **Credibility** and **tracking** it: definitions of credibility – including credibility of data, models and workflows, as well as tracking it when doing greedy computations
- **VHT standard**, with constructs on credibility framed within a workflow?
  - EDITH cannot enforce a standard (excludes), but we need to facilitate its realization
- **Community** effort:
  - whole range of CoUs, put them into workflow one by one
- Protype of WORKFLOWS - Workflow comes with UQ, by default
  - Every DTH for personalized level need to have UQ is pre-requisite
- **Automate** existing workflows
- Workflow **translation** services

3.2 Ethical Manifesto

Slides: EDITH_EM_Paris_Breakout_Ethics
Breakout chair: Ine Van Hoyweghen, Elisabetta Biasin, and Elisa Leila Elhadj (KU Leuven)
Breakout notes: Zita Van Horenbeeck (VPHi)

Previous activities related to Responsible Research and Innovation (RRI) in EC funded projects brought up a range of discussion topics related to the ethics around the use of computer modelling and simulation. This crystallized into the need for an Ethical Manifesto on ethical and social responsibilities related to model development and use, which can serve as a sort of compass for in silico modelers and the in silico community as a whole.

After a general introduction, the session continued with moderated Group Conversations (5 participants per group), following the card-based method inspired by the IMAGINE RRI tool developed by Felt et al., (2018)[8]. This brought on the following discussion points.

- **Responsibility and Model Usage**
  - Shared models require ethical considerations on usage.
  - New projects demand awareness of potential negative (ethical & social) impacts; modelers responsible for integration and modifications.
  - Multiscale models necessitate collective vigilance; and alert modelers to potential misuses.
  - Researchers with private companies face challenges; ethical considerations should be a collaborative effort.
- **Licensing and Regulation**
  - Use disclaimers for restrictions; institutional responsibility to track use.
  - Open research/data repository encouraged for reproducibility.
  - Clinical applications require strong regulations to prevent misuse.
  - Modelers' role: alert institutions and international organizations to potential misuse.
- **Ethical Screening in EC Projects**
  - Consider legal aspects (GDPR, AI Act) in projects.
  - Address potential uses in the general public and the medical field.
  - Suggest the division of model interpretation for public use and expert use.
  - 1 x a year session on ethics, not only ethics committees
- **Inclusion**
  - Acknowledge potential biases; collaboration is essential.
  - Highlight the need for interdisciplinary collaboration and ethical committees.
  - Emphasize responsibility, accountability, and mutual support among scientists.

[8] Felt, Ulrike ; Schumann, Simone & Schwarz-Plaschg, Claudia G. (2019). IMAGINE: A Card-Based Discussion Method. In Pranee Liamputtong (ed.), Handbook of Research Methods in Health Social Sciences. Springer Singapore. pp. 1167-1182.

- **Beneficence**
  - Researchers should aim for greater societal benefit, but challenges exist.
  - Collaboration is key for shared responsibility, open access, and global cooperation.
- **Non-Maleficence and training**
  - Address moral challenges in research.
  - Emphasize the importance of training on ethical, legal, and social aspects!!
- **Promises, Uncertainties**
  - Recognize benefits and risks; include both in applications & publications
  - Funding programs should encourage realistic expectations.
  - Awareness of laws and ethical reflections are necessary.
- **Justice and Time Pressure**
  - Debate on the responsibility of modelers in addressing global inequalities.
  - Acknowledge time **pressure** and frictions due to limitations.
- **Conclusion**
  - Ethics = shared responsibility; institutions should support the infrastructures.
  - Continuous training on ethical reflections is crucial for all involved parties.

3.3 Generation of data (OoC, sensing,…)

Slides: EDITH_EM_Paris_Breakout_Data
Breakout chair: Adrian Ionescu (EPFL)
Breakout notes: Sanjay Pant (Lynkeus)

This breakout session aimed to investigate information currently still missing in the roadmap, related to the production, transfer and use of data. This data could pertain to experimental human-based data (*e.g.* from organ on chip), clinical data from typical clinical tests and modalities (imaging, blood work), and patient-generated data (wearables *etc*.).

The following points and suggestions have been mentioned by participants for consideration and to be included in our roadmap of digital twins, in relation with Data Generator technologies.

- Data **measurement modalities** needed by:
  - Scale (from molecular to macro)
  - Required parameters needed for model development
- Development of new data generation technologies
  - Identification of **gaps in technologies** needed to parametrize models and/or to respond to data needed in clinical studies
  - Which **experimental data generation modalities** are needed in animal models and how these differ to the one used in humans from technical, ethical and economic points of view. The value of
  - Organs on Chip (OoC) was clearly recognized for DTs addressing adverse drug effects, drug repurposing and better mimicking the architecture of organs for modelling.
- Prioritization of new data generation technologies
  - It was suggested to **prioritize** data generator technologies that can be integrated and/or can support workflows in hospital settings, with focus on the ones with higher existing maturity (higher TRL). Also, data generators for which larger populations can benefit.
  - It is also recognized that **long term research on new technologies** in discovery studies, new sensors and new biomarkers are needed.
  - Another aspect mentioned was about priorities on classical platforms that should define for data generators precision versus time granularity (needs and specifications) and related trade-offs, pointing out to the added value that they can bring.
- Reimbursement – cost
  - We need to well justify the **economic cost** (sometimes too high) of development of data generation technologies in clinical settings; the goal is to achieve lower costs for a wider adoption and democratization of technologies

  - The involvement if **insurance companies** from early stage of developments and investments appear to be important, to select use cases, hardware, software and DT building that can be reimbursed. The example of the Boston preoperative planning, with a **reimbursement** strategy motivated by cost reduction in healthcare, was proposed. Other similar examples exist in Europe, *e.g.* in the Netherlands.
- Involvement of clinicians
  - Clinicians should be **involved early on** (co-creation) and DTs better known in the medical community. The goal is to have even early versions of DTs in the hands of clinicians for feedback. This can start with imaging and modeling. The example of better imaging, which is explainable was stressed out: an MRI with more precise parametrization (quality).
  - The **access to data** (imaging) and data value in digital twins is not well established yet.
  - A possible focus of interest for DTs is **avoidance of medical errors**: the question is what data sets are needed for such purpose? What is the role of data automatization, including entering data and HR aspects in this context?
  - Suggestion about **creating incentives** for measurements and generating data in clinical settings, otherwise the clinicians are not motivated enough. For instance, offer time to clinicians for such measurements on top of medical duties.
- Synthetic data & existing data bases
  - A discussion was dedicated to **synthetic data** and standards for well representing real data. Such data can be used for sharing and training but not yet in medical practice where there is reluctance to base medical decisions on DTs developed on synthetic data.
  - Some example of **data bases** focused on cancer and rare diseases, existing in UK, that can be used for the development of DTs (UK biobank) have been mentioned with more than 100'000 entries.

3.4 Business models

Slides: EDITH_EM_Paris_Breakout_Business
Breakout chair: Enzo Fabiani (Pi School)
Breakout notes: Roberta De Michele (VPHi)

Starting from the definition of the VHT as a collaborative platform to accelerate the development, integration, and adoption of computer models, this breakout aimed to discuss the Virtual Human Twin (VHT) and potential business models for a platform representing Digital Twins of human pathophysiology.

First, an overview was provided of the general context for this topic within the EDITH project.

- Sustainability Work Package (WP) Goals:
  - Early prototype platform development with use cases.
  - Providing recommendations on business models and market place services
  - Expanding the ecosystem's roles and interactions.
- Business Model Canvas was completed for the different pre-selected use cases in EDITH
  - Utilized to interview use case providers.
  - Identified potential business models: tech transfer/spinoff, specific tech tools, intermediary businesses.

The discussion covered a range of items related to this context and wider possibilities

- For VHT Ecosystem: **Roles & Interactions**
  - Emphasize direct interaction with physicians/clinicians over IT departments.
  - Consider enhancing visualization techniques for highlighting different layers.
- Ecosystem **Sustainability**: Key Activities
  - Platform development and maintenance.
  - Collaboration with healthcare and researchers.
  - Scaling IT infrastructure and High-Performance Computing (HPC).
  - Continuous updates and data security measures.
- **Metrics**

  - Market size assessment.
  - Number of target customers and user adoption rates.
  - Revenue from VHT.
  - Customer satisfaction and VHT performance evaluation.
- **Resources**
  - Infrastructure for data collection, storage, and analysis.
  - Expertise in AI and computer science.
- **Partnerships**
  - Collaboration with healthcare institutions, universities, and research entities.
  - Engaging with technology providers.
- **Incentivization**
  - Phases of adoption: honour ledger, token ledger, and money marketplace.
  - Different VHT sub-platforms for academics, non-profits, and commercial entities.
- **Revenue Streams, Added Value, Opportunity**
  - Licensing and subscription fees.
  - Consultancy and data analysis services.
  - Integration with real-time record systems.
  - Collaboration opportunities between Pharma and medical device companies.
- **Major Costs**
  - Data acquisition and computing.
  - Personnel and experts.
  - Legal certification costs.
  - Necessity of clinical trials
- **Requirements to Use the Platform**
  - Discussion on cost efficiency players, reimbursement, and considerations for Health Technology Assessment (HTA) agencies.
  - Challenges in proving cost-effectiveness and ensuring credibility in open-source models.
  - Suggestions for proprietary models and platform robustness to address risks.
- **Participants' Perspectives**
  - Need to build the market for VHT.
  - Platform has core role in facilitating secure interactions with the market.
  - Various perspectives on cost-effectiveness, certification, and open-source model risks were discussed.

Conclusion

- Comprehensive understanding of VHT's potential and the necessary steps towards its implementation and sustainability.
- Emphasis on collaborative ecosystems, marketplace dynamics, and digital transformation.
- Focus on outcome-centric approaches, customization, and innovation.
- Proposed sustainability plan involving discussions with academia and industry, exploring funding possibilities.

3.5 Envisioned platform processes and services

Slides: EDITH_EM_Paris_Breakout_Platform
Breakout chair: Amaryllis Raouzaiou (ATHENA), Sabato Mellone (UNIBO)
Breakout notes: Artem Platonov (VPHi), Serena Moscato(UNIBO)

The breakout started with an introduction to the work done without EDITH on the envisioned platform processes and services and the governance. This included discussion of the preparatory phase (predefined use cases, scope/objectivities + technical aspects), the foreseen trinity of software (catalogue, repository, platform), cross-cutting directions (open source, distribution & federation, distributed platform) and main functionalities (loosely coupled soft and services, workflow, Jupiter notebooks). Next, the planned population of the VHT was explained (resource acceptance, role of community, recourses not accepted can go to EDITH-catalogue) along with legal aspects, copywriting (authorization), compliance and

standardization. The discussion evolved around specific questions related to the choices (to be) made for the realization of the platform.

- **Selecting model :** What are the criteria for choosing a best model (*e.g.* the accuracy might not be the best but has less parameters). What are the ways this can be implemented into the practice?
    - keeping one model only
    - model ranking
    - one can pick models and use them for different data from the platform and then choose the best model
    - the researchers have to go through the credibility assessment themselves
    - community involvement (*e.g.* if credibility is 50%, the community may say we have 2 datasets to be used for the verification). We might go to the community and tell that for the further progress we need a verification, and get the feedback from the community.
- **Data sharing:** the data stored in hospitals and they do not want to share. Is there a need for a platform to guarantee that these data though not on the platform must be somehow preserved?
    - Not tangible from the legal perspective
    - The decision should be made if we allow users not to share the data but still be able to use the platform
        - we can make it partial: *e.g.* without sharing the data the user will have to share the outcomes
        - Principle of reciprocity: more you take more you give back
    - Writing a paper is a good incentive for clinicians
        - the resource if it is valuable and reliable counts as publication increasing index > curation should be put in place
    - We need to have a clear picture of the process and how we can comply with all the ethical and legal requirements. Might require work from a lawyer sometimes. But we have to start doing it in a sustainable way in terms of the community
- **Standardization**
    - standardization is a software quality assessment available for commercial solutions
    - positioning yourselves as movers of standardization implies you provide the criteria/high-standards.
        - at the moment, the criteria are rare and not well established. It will take time but it is absolutely essential
        - it can then become an extension of the MDR making it even more powerful
        - platform may help creating these criteria through gradually improving recourses over time
    - the aim of end user is not publication but answering a question.
        - VHT must provide tangible benefit to clinician, otherwise it won't be used.
    - biology is very noisy – cleaning data means removing sensible data together with technical noise. Variability is a source of information. Clean data is approximation which does not fit biosystems. Standardization means cleaning the data and then we get the data that does not fit reality.
        - This is just one example of challenges that must be answered to make it a success. We do not deal with data we deal will complex biological data.
        - If VHT is not designed to overcome challenges like that than it is not useful for clinicians.
    - standardization means we standardize the format not the content
    - role of curators in metadata cleanup and standardization, acknowledging potential costs
    - Extension of the MDR - practice of DT and its usability (models cannot be just software as a service, but they can represent something more, following a set of guidelines, bringing value to the community)
        - In the meantime, people must be kept engaged in the process, since these requirements will be applied far in time. There must be some incentives (*e.g.*, writing papers, funding a DT journal)
            - Publishing a resource credible, reliable, *etc*. can be counted as a publication
- **Sustainability**
    - we have to begin targeting (even small) challenges that are not targeted by traditional approaches. Asking for specific points where we think VT is going to be better. Finding unmet needs will help promoting VHT.

  - the data must be very user friendly otherwise no one will use it. Thus, it must be very understandable and easy to use for clinicians (not developers).
  - the only way to promote VHT is to make its usage mandatory. It should not be just 'nice to have': 'nice to have' is not enough
  - we need feedback from policymakers how to enforce these processes
  - the platform should be able to help people to do what their grants tell them to do *i.e.* conducting the study (*e.g.* clinicians want the position of the tumor and need to compare a fully automated against manual identification). The platform could help identifying key parameters or drawbacks in the model
  - VHT usability concerns: simplicity, understanding by users, and the impact on limited healthcare budgets.
- **Miscellaneous**
  - in the future we will be able to accept software from outside of EDITH, in such a case the software should follow the guidelines provided
  - one of the challenges is demonstrating efficacy of the workflow. Every single model will be making approximation to one flow
  - the platform can be modified – *e.g.* the results from step1/user1 will become a part of the workflow for step2/user2

3.6 User roles & identities

Slides: EDITH_EM_Paris_Breakout_Users
Breakout chair: Gökhan Ertaylan, Elfi Goesaert, Frederic Jung (VITO))
Breakout notes: Martina Contin (VPHi)

The breakout session started by two presentations with (1) a short introduction on EU legislation and data and (2) User Profiles and Access. This was followed by a demo & a questionnaire session that attendees were individually filling in on their phone. Finally, the other half of the session was dedicated to a semi-structured discussion on the feedback collected during the various presentations.

- **Intro into EU legislation and data**: the first presentation went through the European strategy for data and the connection with the Digital Twins. The presentation was an opportunity to answer questions about the European Health Data Space (EHDS), explaining further how DT connect to data spaces and map to the current legislation.
- **User profiles and access**
  - A user Profile is a collection of settings and information associated with a user.
  - User roles is a collection of capabilities that can be used to give access to concrete part of the system. In the EDITH environment we can have following roles:
    - Patients/Citizens Category: Patient: Patient Advocate: Citizen Scientist:
    - Healthcare Professional Category (Doctors, Specialists, *etc*.): General Practitioner; Medical Specialist; Medical Researcher; Medical Educator
    - Creator/Model Developer Category (can upload new model version, train the models): Data Scientist: Simulation Engineer: Model Developer/Owner
    - Platform Administrator Category: System Administrator; Data Curator; DevOps specialist: Software Developer
  - A simple way to understand user roles is to imagine it as a building block that contains capabilities. Each role is a different block with different capabilities. One individual can have different roles which means to assemble different blocks together.
- A **demo** was shown in order to give a visual overview of what was presented previously. There is nothing on the demo that is promised however everything presented is part of the vision of a platform where users can access with various profiles/ roles.
  - A wireframe prototype was implemented with FIGMA showcasing a user journey using the VHT platform. The mock-up demonstrated how a user login on the platform, using the Itsme Belgium national provider system and landing on its user profile. Depending on their roles users have access to a slightly different interface with different components.

        - The first user, Miles Hickman has different roles listed as tabs on the top of the screen. Under Medical Researcher, the user can access to the Simulation Platform & Data Repository - under patient, the user can only see the Personal Pod application.
        - Lana Shelton (second example) has only the role of patient. This patient is only able to use the personal pod. This example also illustrates a bit further how the user can interact with the platform and display with the "More Info" feature.
        - Tomas Calderon an Administrator and Patient. As an Administrator, the user unlocks the Administration Panel application. From this panel the administrator can manage user roles and access.
- **Access Questionnaire**: right after the demo, a user Access questionnaire was presented to collect feedback from the attendees. The questionnaire was made to collect information about user expectation regarding the access. The questionnaire was designed as a tree where the questionnaire helps the user to define its profile and maps it to one or multiple roles. Finally, the user ends up on a final page where features & access have been listed. In a multiple-choice checkbox list the questionnaire user can select the components he find relevant according to his profile.
    - Examples of access features & their description
        - View Personal Health Data: Users can view their own personal health data.
        - Access Applications: Users have access to applications using the computational models.
        - Submit Personal Data: Users can voluntarily submit their personal data for processing.
        - Perform Cohort Analyses and Studies: Users can perform cohort analyses and studies.
        - Dedicated GUIs: Users have access to dedicated Graphical User Interfaces (GUIs).
        - Feedback and Comments: Users can provide feedback and comments on platform features.
    - The output of this questionnaire will help to identify missing key roles and features and also to map roles to the right features. Moreover, various visualization has already been implemented to visualize overlaps between and within the different categories (see results section).
    - Following the breakout session, a larger questionnaire taking into account feedback from the breakout session will be send to a larger EDITH public. The questionnaire will be shared through the coming newsletter and/ or social networks. In this regards, the form should reach a high number of people and allow us to shape better access.
    - Initial results from session: in anticipation of the wider distribution of the questionnaire, the breakout session mostly provided the opportunity to highlight certain point of the questionnaire and open further discussion.
        - One such discussion point was about nationality of the users (European and non-European citizens), and the usage of national ID providers.

The final part of the breakout session was an open discussion on following points

- Foreseen discussion points
    - We envision a EU citizenship based access to the VHT platform.
    - The profiles and roles are defined based on individual needs.
    - Each role category calls for a dedicated set of access tools.
    - They are complemented by Grants and affiliations to allow customization and dynamical allocation.
    - Ultimately, distinct access interfaces would need to be exposed by an EDITH-inspired catalogue/repository/platform infrastructure, each tailored to a specific user group
    - The purpose of this presentation was to present our vision and get your valuable feedback.
- Additional discussion points
    - **Identity Providers**
        - How to solve issue with national identity providers? → This is a relevant question; this will need to be solved and consider in the access. There is a European identity that should be happening in the coming years. To data there is no clear timeline on when it will be available.
        - What happened if you are from a EU country and living in another one? (*i.e.* French person living in Belgium) -> which provider should I be using?
        - Not EU users?
            - If you can be authenticated, you can still have a profile.
            - Prevent unauthorized access to the system.
            - Record what the individual is doing to check unusual behaviours.

- **Role assignment**: How do we envision the assignment of roles?
  - Role curation
  - Same roles can have different permissions in different countries.
  - If you use the affiliation, it is up to that organization to take internal decision on the access level.
  - Single users can have multiple affiliations.
- **New roles**: new roles might be taken in consideration in the future as the needs arise.
  - How many roles do we need?
  - How much does it cost to have one more role in the system?
    - This might have a cost in development and resources, to create new roles specific UI
    - We would need to set up a committee to define the roles as well.
- **Granting access** – assign to role: How can people explain and justify why they want to have access to a specific role?
  - Email address part of an institution?
  - Proof of affiliation? Who should check it? Another committee?
  - What does it cost the system to give a certain role? (in terms of security risk) For specific roles the level of scrutiny should be different (ask the 12 labours project who they do it)
  - What if you need more access that granted by your affiliation?

Proposed follow-up actions

- **Questionnaire:** Spread the questionnaire via Social Networks / Newsletter
- **Roles Implementation**
  - Investigation national ID providers:
  - Define user rules for EU a non-EU individual with different EU providers.
  - Investigate on setting up a committee for roles / profile approval.

3.7 Standards for digital twins and their implementability

Slides: EDITH_EM_Paris_Breakout_Standards (1+2)
Breakout chair: Martin Golebiewski and Gerhard Mayer (HITS)
Breakout notes: Martin Golebiewski and Gerhard Mayer (HITS)

This breakout session aimed to give some answers to questions related to standardization, harmonisation, terminologies/ontologies, metadata standards, quality, standardization gaps and roles of standard defining organisations and communities of practice. The focus was most specifically on the practical application and implementation of domain-specific standards.

The breakout started with an overview of the current landscape and VHT requirements identified to date

- Standardization requirements for the VHT: Focus on data integration into models and model validation
- Forest of standards: formats, terminologies, metadata guidelines
  - Example for community standards: COMBINE
  - Standard for data formatting and description: ISO 20691
  - Standard for biological material and data provenance: ISO 23494 series
  - Standard for modelling in personalised medicine: ISO TS 9491
- EDITH Standards document (as a complement to the roadmap)

The session introduced and demonstrated the EDITH **FAIRsharing collection**[9] as an online resource to find appropriate and relevant standards, and introduced a practical VHT standardisation landscape[10] and **implementation guide**[11] that has been developed specifically

[9] https://fairsharing.org/4787
[10] https://zenodo.org/records/10492796
[11] https://zenodo.org/records/10524795

for the users and stakeholders of the EDITH infrastructure. The implementation guide focusses on all aspects of building and applying VHTs

- Data handling
  - Data preparation
  - Data integration
  - Annotation with metadata
  - Check of data quality, plausibility, and completeness
- Executing models on patient/healthcare data
  - Model parameterization
  - Model execution
    - Model description
    - Model solver
    - Targeted execution environment
    - Execution as workflow
  - Validation and verification of modelling results
  - Reporting and visualization of modelling results
  - Archiving
  - Electronic Health Record data
  - Clinical decision support systems (CDSs)
- Building an approved model
  - Model building
  - Getting regulatory approval
  - Execute the approved model

During the discussion, following points were addressed

- How should that all work in practice with all those different subdomain- and technology specific data and metadata standards? How should they all **interoperate**?
  - Covid-19 disease maps community as a good example that only worked based on standards (but implementation needed in tools/platforms to support standards
  - Standardization of data and modelling is a cultural change and needs time. It starts where the data is gathered/recorded (already at the patient side)
- It is almost impossible to **implement** it all in hospitals, not to speak about data transfer between institutions
  - Interfacing supported by standards is the key (*e.g.* HL7 FHIR)
  - Sometimes already small recommendations have a great impact (*e.g.* the use of units for measurements/parameters
- How to **connect** the VHT standardization to the GDPR?
  - GDPR is base for everything, especially important for standardization/harmonization of data access for sensitive data
- How users can be **supported** in the standardization?

Following gaps were identified that require additional work when implementing the VHT

- Specific standard for model **validation** and reference data/reference models for validation
- Process for standardized model **approval** as medical devices, if used for clinical decisions/treatments or for drug approval
- **Implementation** in tools/platforms - technical help needed to achieve **interoperability**

3.8 Clinical engagement

Slides: EDITH_EM_Paris_Breakout_Clinical
Breakout chair: Caroline Roney, Elisa Rauseo (cardiologist), Laura Bevis (QMUL)
Breakout notes: Artem Platonov (VPHi)

The clinical engagement breakout session was attended by an audience with mixed backgrounds, with just under half being clinical. Questions were produced taking into account

the responses of VPHi's previous clinical survey[12] and with the input of our clinical collaborators, and presented to the audience as one large group (rather than smaller groups). Notes were recorded collaboratively using Google Jamboards[13] and by the note taker. The session focused on the current understanding and perceptions of the DTs and their potential applications in healthcare, the complex challenge of integrating patient-specific data into digital twins, and ended with an open discussion on the factors to be addressed by EDITH.

Discussion started with the audience's current understanding and perceptions of DTs and their potential applications in healthcare.

- Although a fully integrated, multi-scale DT was said to be difficult to imagine as a clinician, it was thought that DTs could be **useful in reducing the noise and bias of human decision** making, in teaching, and the quantification of risk/complexity for surgery.
- The **uncertainties of clinicians** around DTs were thought to be a result of: disparities in language used, models not meeting clinical needs, and lack of inclusion of clinical figures at the head of DT initiatives.
- It was said that **involving clinicians at the forefront** of these projects, and approaching the problems from the clinical point of view (to be cost effective and improve patient outcomes, which are often clearly defined for a disease/treatment in clinical practice) will increase trust, engagement, and the uptake of DTs in clinical practice.

Next, we confronted the complex challenge of integrating patient-specific data into digital twins.

- Key concerns included **data accessibility** and the complexity of **combining heterogeneous** datasets for building models.
- It was also recognized that **privacy and security** concerns are major obstacles, affecting not only the sharing of data between institutions but also the subsequent reuse of that data. This is especially true given that anonymization processes may not always comply with the stringent requirements of GDPR or similar standards.
- An additional challenge noted was the **scarcity of annotated datasets** for effective training.
- Despite these hurdles, there was a collective interest in **exploring synthetic data** as a potential solution.
- The group emphasized the **need for rigorous validation** of these models through prospective clinical trials to ensure clinical reliability before their implementation. This validation is crucial for building trust and securing regulatory approval, which could lead to broader adoption of digital twins.
- The discussions also highlighted the importance of **collaboration among various institutions**, involving clinicians in the data selection and collection process, and ensuring data harmonization to enable effective modelling.

In summary, the group voted that **clinical involvement** was the most important factor for EDITH to address. Suggestions were made as to a clinical workgroup, having clinical figures at the top of EDITH, dissemination at clinical conferences/events by EDITH representatives, more clinical breakout sessions at future meetings, breakout sessions/task groups led by clinicians, advertisement of clinical involvement, and research into current funding areas and research topics in medicine in order to improve the involvement of clinicians in the project. A collaborative effort between modelers, clinicians and regulatory bodies to determine clear **standards and regulations** of DTs in healthcare was also highlighted as a key barrier to the implementation of DTs in clinical practice. Attendees were encouraged to fill in the current clinical survey and to disseminate it to their colleagues (cfr section 5.2).

3.9 Large infrastructures & networks

Slides: EDITH_EM_Paris_Breakout_Infrastructures

[12] Lesage R, Van Oudheusden M, Schievano S, Van Hoyweghen I, Geris L, Capelli C. Mapping the use of computational modelling and simulation in clinics: A survey. Front Med Technol. 2023 Apr 17;5:1125524. http://www.doi.org/10.3389/fmedt.2023.1125524.
[13] https://jamboard.google.com/d/17RUCym9HBvY29X4K1XbEsRNSgegGK9DOwaQRCwz0v8g/viewer?f=0

Breakout chair: Amaryllis Raouzaiou & Evita Mailli (ATHENA)
Breakout notes: Janaki Raman Rangarajan (VPHi)

The breakout session started with a discussion on the existing infrastructures, networks and initiatives, deriving from that the main learnings and possibilities of alignment for the VHT infrastructure. During the discussion, additional initiatives were identified by participants. The main needs were discussed for the interactions, as well as the perceived bottlenecks and challenges.

Overview of **existing infrastructures, networks and initiatives**.

- Infrastructure: EHDS, EBRAINS, EOSC, ELIXIR, OpenAire
- Computing: EuroHPC, LUMI, PRACE, Fenix, EGI, GEANT, National grids, CompBioMed, PerMedCoE
- Other initiatives: EUDAT, GDI, RDA, EUCIAM, Gaia-X, Virtual Brain Twin

EDITH **learning & alignment** from/with these infrastructures, networks & initiatives: Technology, Standards, workflows, federation, governance

Related **initiatives & needs identified** during the break-out

- Initiatives: .
  - STRATIF-AI - digital twins for stroke
  - Multi-organ, across time
  - DARWIN-EU
  - SURF: Alzheimer Genetics Hub
- Needs
  - Accreditation for repository: *e.g.* CoreTrustSeal
  - Standards to connect with large infra (*e.g.* OMAP)
  - Standard in data collection

Perceptions from the audience related to infrastructures & networks

- Is **computing resource** is bottleneck: No…
  - Technical (feasible, available), legal (critical)
  - BUT most crucial is financial part for resource utilization
- Overcoming **legal challenges in sharing data**
  - Solution: Patient owns the data (GDPR) > to be developed further by legal experts in EDITH/ecosystem
    - Patient has personal vault to collate data from hospital/companies
  - Constraints:
    - Patients can opt out
    - Patients are conservative or hesitant to share
    - Patients are not informed

Major challenge identified during breakout: "HEALTH is heavily **dependent on lifestyle**"

- We DON'T have the correct data for improving the predictive capacity of models
  - Longitudinal data
  - life style and behavioural data (private tech companies)
- NEED of public infrastructure for patients to SEEK lifestyle data from wearables/sensors

3.10 New use cases : how to?

Slides: EDITH_EM_Paris_Breakout_UseCases
Breakout chair: Sabato Mellone (UNIBO)
Breakout notes: Serena Moscato (UNIBO), Lorenzo Cristofaro (Lynkeus)

The key questions addressed in the session were "what can I do for EDITH/VHT?" and "what can EDITH/VHT do for me?". The objective of this session was to present the application process for new use cases to be integrated into the EDITH repository and/or catalogue: how the evaluation takes place, what levels of integration are possible and what requirements need to be met. Discussions covered on points of attention such as intellectual property, standards, incentivization and data protection.

Key Points from **Trinity of Software**:

- Limited functionality with a connected Platform to HPC facilities, first repo version, and a federated Catalogue.
- Criteria for integrating external services based on maturity levels and standards adoption.
- Smart resource search with manual or graphical selection.
- Compliance and legal considerations addressed through metadata annotations.
- Defined roles: Provider, User, and Administrator.

Key Points on **Populating the VHT**:

- Open call for external use cases with legal requirements as a filter.
- Seventeen contributions received via website[14] (dd 18/1/2024), including computational models, platforms, datasets, and technology for data conversion.
- Example integration of the BBCT use case explained (cfr slides).
- Discussion on model and data object separation, certification, and metadata for certified status.
- Discussion on external project connections, tools for integration, and the complexity of technical training.
- Patient-specific cases, credibility, hackathons, and incentivizing resource sharing discussed.
- Consideration for distributed datasets, connection to Zenodo, and community-building.
- Role of the Catalogue in providing visibility and enabling the ecosystem's primary objective.

Overall **Discussion and Impressions**:

- Challenges with technical complexity, training, and proprietary software integration.
- Incremental approach to resource uploading and the need for standard formats.
- Importance of incentivizing collaboration, diversity, and building the community.
- Primary objective of the ecosystem is visibility, emphasizing the role of the Catalogue.
- The procedure for populating the VHT was showcased

3.11 Role of AI in the VHT

Slides: EDITH_EM_Paris_Breakout_AI
Breakout chair: Gökhan Ertaylan, Simon Denil (VITO)
Breakout notes: Goran Stanic (VPHi)

The breakout session started with a presentation reviewing the sections of the EDITH roadmap currently referencing the use of Artificial intelligence (AI). This was followed by an interactive questionnaire to collect feedback from the participants on the topic. The bulk of the session was dedicated to a semi-structured discussion on broad categories of use cases for AI as it pertains to Digital Twins or the Virtual Human Twin (VHT) platform.

The presentation covered

- the **aim of the breakout session**
  - Review the envisioned role of AI in the context of VHT in healthcare and clinical practice.
  - Though incorporating AI will certainly lead to ethical, legal, societal and inclusiveness challenges, these were not to be addressed here (covered by other sessions).
- the **definition of AI** as spelled out **in the draft roadmap**[15]

[14] https://www.edith-csa.eu/call-for-use-cases/
[15] https://zenodo.org/records/8200955

    - "AI can refer to the advanced computational technologies that will enable the simulation, prediction, and replication of human physiological and pathological processes."
    - "This encompasses Machine Learning (ML) algorithms, data analytics, and neural networks that can process vast amounts of health data. AI in this domain should be characterized by its ability to learn from and adapt to new information, leading to better prediction of health outcomes, provide personalized medical insights, and support clinical decision-making."
    - "Its role extends to the continuous updating and refining of the virtual twin as new data becomes available, ensuring an ever-evolving and accurate digital representation of the individual's health status. This form of AI will be pivotal in advancing precision medicine, enhancing patient care, and contributing to the broader understanding of human health and diseases."
- **foreseen use cases** in digital twins
    - Ability to assess more systems (heart models based on image processing, candidate compounds for drug treatment, ...)
    - Surrogate models or ML based PDE solvers in multiscale models or clinical decision support
    - Parameter tuning for personalised mechanistic models based on the individual's data
    - Automating iterative approach to hypothesis generation and testing for mechanistic multilevel models
    - *Note*: DT use cases may be limited by the inherent tension between data driven predictive AI/ML models and the need to be explainable (*e.g.* integration of prior mechanistic knowledge).
- **foreseen use cases in supporting the VHT platform** and its users.
    - Data and model integration (knowledge graph)
        - data-data: harmonisation of formats
        - data-model: take given input data and convert to a suitable input for relevant model(s)
        - model-model: map outputs from one model suitable as input for another
    - Resource orchestration & continuous updating of DTs
    - Evaluation (and credibility scoring) of data and DT model quality for imported within the platform
    - Chatbot interface to the VHT platform with LLM tailored to the VHT platform

Discussion with audience

- **Draft definition**: no disagreement was raised about the draft definition of AI in the context of VHTs.
- **Use of AI in DTs**: there was little disagreement that AI will find more uses here but that they will arise at their own pace without the need of active input from the EDITH/VHT perspective.
- **Use of AI to support a VHT platform**: most of the discussion centred around AI in a supporting role and identified several shortfalls in terms of terminology and conventions that would be required for AI to function well in this context.

Questionnaire & results

- A **survey of the participants** found that most of those attending had an academic background (in AI or other fields) or a background in computational infrastructure. The participants expected AI to certainly play a significant (but not all-encompassing) role in DTs and the VHT platform.
    - AI in DTs: As demonstrated by several existing use cases the participants had encountered in their respective fields, there is expected to be an increase in the usage of AI to model (parts of) human physiology. Although a large majority felt that explainability remains an essential factor in the adoption of AI, a few participants argued that this will not always be the case.
    - AI in support of a VHT platform
- The participants were asked to **rank the proposed supporting functions according to utility and feasibility**.
    - Most participants saw a useful role for AI in the integration data and models, followed by quality assessment and resource orchestration. In terms of feasibility the options of quality assessment, data-model integration and a supporting chatbot were ranked nearly equally.

AI as "glue" for a VHT platform

- It was noted that a **more comprehensive dictionary** may be necessary to ensure that all stakeholders can communicate in a shared language. This may be necessary both in terms of conversational terminology but also in terms of a well-structured ontology of all components of a VHT platform. Take for example the term 'data'. Depending on the context of use, this may refer to raw signal acquired from

devices, pre-processed data ready for analysis, model generated data, model weights (and architecture) as a form of data stored in a computational environment, synthetic data (generated by statistical or AI methods) ...
    - Data-data relations:
        - Furthering the identified need for more nuanced naming of data types above, a few other dimensions were found to be relevant. Initially the term "data hierarchy" was suggested, but it was quickly rejected due to concerns about perception of relative importance. Data "types" and "relationships" were found to be more useful concepts. This framework could serve to record what a data set's provenance is, which transformations it has undergone, what additional (linked) information was added *etc*.
        - It was noted that properly annotating data (to maximise the utility and re-usability), in practice is often the most time-intensive part of a DT project. Developing AI tools to support or take over part of this work would provide significant benefit to the VHT community. A significant step towards this goal would be the harmonisation of data formats supported by (potentially) AI-based tools for conversion to an acceptable standard.
    - Data-model relations
        - Provided that a good standard is available for cataloguing the disparate data types that would be part of a VHT environment and a similar framework is in place for models, the participants expect that AI techniques will then be able to support researchers in identifying available input data in the VHT ecosystem. Missing input data could potentially be generated (by deterministic or AI-based means).
    - Model-model relations
        - With standardized model specifications, it becomes more feasible to check compatibility between the outputs of one model and the inputs of another. Participants remarked that relations between models could be built up both 1) based on a well-defined set of input and output characterizations of any DT in the VHT environment and 2) by automated retrieval and curation of published VHT literature and data. AI techniques could aid in both approaches.
- Participants raised the possibility of AI (similar to product recommendation systems) to aid researchers in **choosing appropriate DTs for assembling a VHT**.
- **Resource orchestration & continuous updating** of digital twins (DTs)
    - Utilising AI as a means to solve the optimisation problem of running VHT computations in a cost or speed optimised fashion was agreed to be both feasible and useful (high utility). This would require a machine-readable overview of available resources, pricing and computational requirements of the various computational sub-tasks required to achieve a given VHT result.
- **Evaluation and credibility** scoring
    - The evaluation and credibility scoring of data / DT models was the subject of animated discussion. In fact, the term "credibility" itself was found to be inadequate. The participants agreed that there is utility in this concept but that one cannot approach this problem with AI, if there is no agreement on what exactly is meant by credibility in the first place. This subject should be further refined by the EDITH consortium. If a sufficiently clear definition or scoring criteria are available, an AI system could score models and/or provide text-based feedback for points of improvement.
    - The following, non-exhaustive list of **dimensions of credibility** was suggested:
        - Context of use / field of application (in general, but especially for AI-based models, the nature of the training data may limit a model's wider applicability)
        - Need for data normalisation
        - Potential biases
        - Privacy evaluation
        - Validated ranges for input parameters
        - Validated ranges for output values
        - Evaluated on direct observations/surrogate endpoints/simulated data/...
        - Quantification of uncertainty (potentially for use in error propagation)
        - Tracking of data provenance (raw data-> annotated data -> standardized data *etc*.)
- **LLM chatbot tailored to VHT purposes**
    - There is currently a demonstration version of an LLM-based chatbot interface to the VHT platform. This LLM was (re)trained on a corpus of literature and legal text relevant to VHTs. There was consensus that this is a beneficial use of AI technology but that a distinction should

be made in the purposes served by such a chatbot in a full-fledged VHT platform and the associated practical implications:
    - Helpdesk functionality (tailored towards model developers, data providers and VHT composers)
    - Educator functionality (tailored towards citizens, medical professionals *etc*.)
    - Accessibility functionality (serving users of different languages but also translating electronic health records which are usually maintained in national/regional languages)
- Which types of knowledge/training data an AI should be given access to may differ significantly for the respective purposes. One potential solution is the inclusion of data usage tags/ontology (*i.e.* can an AI access this or is this information too sensitive?). One participant suggested the SPARC project as an example of data curation protocols for this purpose.

Other topics of discussion

- Participants remarked that AI will likely spontaneously finds its way into DT simulation but that a more **pro-active stance** may be necessary to speed adoption in the field of healthcare (lagging many other fields where data access is less sensitive or impact on any single individual is lesser).
- There was some discussion on the topic of how to go from a data/model repository and a simulation platform to an **identification system for missing components in the VHT platform**. Knowledge graphs are a plausible route, but this was not explored in further depth.
- Participants remarked there **might be a role for AI in "post-market" monitoring** of an operational VHT platform to identify points of improvement.

Proposed follow-up actions: overall, the roadmap makes modest reference to AI as it is not at the core of the conception of a VHT platform. It is however the consensus among participants that **AI can make key contributions to realising a well-functioning platform**. We have identified the following potential follow-up actions to improve the quality of the roadmap and the VHT platform project:

- Elaborate the discussion of model (and data) quality/reliability/trustworthiness
- Expand discussion of terminology/ontology of data and models to create a shared vocabulary amongst stakeholders
- Make note in roadmap that AI might be used to identify "missing links" in the VHT platform (both in terms of models and data)
- Highlight the potential utility of AI in information retrieval from literature/measurements to incorporate into a knowledge system
- Addition of a paragraph on the role of synthetically generated data (including but not limited to generative AI) and the implications for model evaluation and data labelling. (Could be a breakout session at the upcoming Amsterdam EDITH meeting.)
- Achieve consensus on standards that should be required or at least supported by a VHT community/platform.

3.12 Incentivization

Slides: EDITH_EM_Paris_Breakout_Incentives
Breakout chair: Irene Vignon-Clementel, Anna Niarakis, Roel Meiburg (Inria)
Breakout notes: Martina Contin (VPHi)

The objective of this session was to brainstorm on the challenges of creation, coupling & adoption of VHT, and on creative ways to incentivize stakeholders to go beyond these challenges. Questions addressed were the following: What are challenges to create the missing part of the VHT puzzle? What are the barriers to couple existing VHTs? What are challenges to adopt VHT in the clinics? Are these challenges different in different communities (Biology, Medicine, Computer Science)? How creative can we be about rising to these challenges? During the break-out report, all attendees participated in the wooclap questionnaire.

Identified challenges

- **Alignment on the goals** for different stakeholders : clinicians, regulatory, patients, industries

- **Resources** (time & money)
- Start the **virtuous circle** :
  - from clinician's decision to patient benefits
  - cascades their wishes of the VHT to be part of the clinical workflow
- **Common language & meaning** among the different stakeholders
- **Resistance to innovation**/changes: from certain groups of clinicians
- **Resistance to data sharing**: even an electronic Health record is not fully admitted yet > though this might not be due to patients' resistance but rather due to other organisations
- **Heterogeneity of cultures within Europe** (access/sharing of data; clinical registries)
- **Identify stakeholders**: academia, industry, patient advocacies / orgs., governmental bodies, payers/med. insurances, medical doctors + hospital management
- **Categorize the needs** / what they look for incentivisation
- **Fight the inertia** (!)
- approach to **outreach** for the different stakeholders (end-users)

How to address the challenges

- Start with the **patients advocacy groups**
- **Scientific proof** (proof of concept) - successful examples
- **Collaboration** between clinicians and modellers (and other stakeholders)
- Approach it like a drug test: small scale proof, pilot study, in silico trial, small cohorts, scale up
- Meet the patients, think about application **early on** in designing a VHT project
- **Become aware of difficulties** in clinical and modelling reality - build a common language (communication/ comprehension barriers)
- More **interdisciplinary** training, projects, conferences - opportunities to bring all stakeholders together
- Now the research style is too introspective—> change paradigm: **more real world** (patient-centric)

3.13 Preconditions for a thriving ecosystem

Slides: EDITH_EM_Paris_Breakout_Ecosystem
Breakout chair: Edwin Morley-Fletcher (Lynkeus)
Breakout notes: Claudio Capelli (UCL, Lynkeus)

This session looked into the economic preconditions to facilitate a thriving ecosystem. The initial premise is based on the work of Jean Tirole, 2014 Nobel laureate for his pioneering job in digital market, *i.e.* multi-sided platforms. He saw the great developments in Amazon, eBay,… for offering something free or underpriced is a very competitive move to establish a network effect which ultimately causes the one takes it all. The session investigated the similarities and differences between multi-sided platform and ecosystems.

Platforms and ecosystems

- **How do platforms and ecosystems differ**? Several authors have started to question whether the market as a unit is becoming obsolete as a unit of analysis and should be replaced by interconnected ecosystems..
- In economics, the term ecosystem refers to a group of interacting entities that depend on each other's activities. All together they form a symbiotic community capable of converging on the adoption of strategies by which each entity reinforces each other, overcome multiple co-evolution challenges.
- But ecosystems are not easy to build. In a way, you engage into an exercise of designing the coexistence of emergence and intentionality. Planning the spontaneous attainment of an intentional outcome may seem an oxymoron.

Lessons learned on innovation and platform ecosystems

- An **innovation ecosystem** aggregates all actors whose contributions are essential to generate interrelated innovations.
- A **platform ecosystem** aggregates developers of complementary and interdependent products required to extend the value of a core platform technology.

- Both are characterised by:
    - their "**generativity**"— *i.e.*, the capacity for the continual creation of variant system components offering new affordances to the technology user.
    - a **modular interorganisational architecture** that enables a non-hierarchical alignment of actors' interests.
    - **governance arrangements** that are functional to internalize the externalities of these cooperation interdependencies.

Discussions

- ecosystem analogy: we need to be aware of all the other living parts being sure not to reinvent the wheel. And react faster for the evolution. The concept of **constructive competition**. However, which are the **limitations on sustainability**? Following on the analogy with amazon – the globalization might affect the local markets (example: cardiologist virtually operates from California rather than the local French one)
- **Standards and ecosystem**: standards are necessary but there are also a barrier. Standards can be considered as institutions that can be created through purposive actions.
- The question for the VHT is how we can configure a setting which is not competition but more on the **coopetition** (mix of competition and collaboration).
    - A Distributed Ledger Technology can allow trace all types of assets exchanged, track their provenance, secure their findability.
    - Blockchain technology: emphasizes the value of knowledge and automated smart contracts. This is a digital approach to trust. Transaction costs are therefore reduced. Remember that money is a form of trust. Reducing such costs can favour more attention to costs.

Evolutionary ecosystem

- In the current draft of the VHT Roadmap, the only question raised until now regarding the ecosystem has been the following: "Can we figure out an evolutionary transition leading the VHT community from a pre-competitive setting to a mature market system?"
- **Three evolutionary phases**:
    - **Honour ledger**: the DLT infrastructure will host exclusively pre-competitive transactions and work on incentives based on forms of reputational scoring.
    - **Token ledger**: pre-competitive and competitive transactions will coexist, and exchanges will be facilitated through the issuance by the distributed ledger technology (DLT) infrastructure, of digital tokens with no direct monetary value, but operating as the scaffold on which symbolic prices can emerge through supply and demand of all assets traded, included the DLT services.
    - **Money marketplace**: the ecosystem will mature and specialise: while some entities dealing mainly with pre-competitive transactions will continue to exist, a growing number of entities will increasingly focus on competitive transactions in the form of B2B exchanges, with prices set in Euros and no-more in tokens.
- **Implications for VHT**
    - The idea of using **tokens** can contribute to resources to the ledger exchange system and the paying out of tokens. The VHT ecosystem will use its growing token economy to experiment with how it can become progressively self-sustained. This is a symbolic currency (VHT currency?) that can be exchanged for assets or services within a community of practice, allowing such an ecosystem to experiment allocating and tracking symbolic value exchanges among its actors. This can ensure long-term sustainability.
    - **Why using tokens and not real money**? In the creation of business models, there is for example in assigning a value to personal data. Monetization is very complex. Tokens can facilitate overcome this barrier.
    - VHT needs a **metric**. The tokens can contribute to the definition of such matric. So, this could be an idea. Should we have this to explore the market? Do we have elements to benchmark this? We can think of a repository. But we have something maybe even more direct. We have the web app developed on the EDITH website by which you can ask questions and get answers based on a knowledge-base based on existing scientific literature. This is not an hallucination (such as GPT) because it's strongly dependent on the real literature. We have an agreement with openAir to keep developing it. this can be used to create thematic summary on specific topics. So, this can be used to create the needed metrics.
- **Feasibility** (legal)

  - Contribute to VHT (with data) and receiving tokens in return: is this legal?
    - depends on which kind of data. It might not be possible to use their own data (GDPR). If this is solved, another question/issue. How the data are going to be used afterwards? There is a concept of altruism. But there is a difference (substantial) between altruism and given in return of something. We need to have an explicit consent?
  - Does it make sense to focus (in the next 6 months) in investing in developing in such model? Can we find solutions which can remove such roadblocks either technological (*i.e.* synthetic data) or with law? The definition of personal data differs from EU and US. in the US, personal data are already considered assets to create values. In EU, we are discussing about principles. We need to inform patients. But what if we cannot reach them out any more. With anonymization we might offer an alternative but there are other issues.
- **Is there a value?** If so, can we do it?
  - There might be an issue in purchasing these tokens from outside. There is an issue in giving a monetary future value. It's like in issuing share. If I have contribute with data because I want returns – so this can be issue. So, there could be also a recirculation issues.
  - There is a distinction between tokens and security and tokens issued by startups (with no value). When there is a value problem arise. Is there therefore a possibility of a transition symbolic phase.
  - Assigning a monetary value in the future can become an issue. The conversion (2nd phase) can be an issue. It depends who is giving the money.
- **Data altruism & donation**
  - You cannot you sell your personal data, it is a right. You can donate – not sell. Facebook analogy.
  - what about talking of virtual donations? Donations are in general non conditional.
  - Use of personal data is a donation so they should be used for "good purpose". Is there a body which controls this? Risk assessment needs also to be taken into account

3.14 Trust in VHT

Slides: EDITH_EM_Paris_Breakout_Trust
Breakout chair: Zita Van Horenbeeck (VPHi), Ine Van Hoyweghen, Elisa Lievevrouw (KU Leuven)
Breakout notes: Zita Van Horenbeeck (VPHi)

The objective of this session was to engage in thought-provoking discussions that promise to shed light on the diverse social facets of virtual human twins (VHT). Leaving the technical complexity of VHTs behind, this session explored what it takes for a VHT to be deemed trustworthy. It aimed to better understand what is important for someone to be able to engage with VHTs? Recognizing the complexity and context-dependency of trust in this context, this session sought to gain insights into the dynamics of why different stakeholders are willing (or not) to engage with VHT. What challenges building trust in the VHT ecosystem? As such, this session did not aim to establish trust in the field, but to understand what it takes for stakeholders to be able to trust the respective VHT within their medical environment (whether it be in a hospital setting, at home, in a medical regulatory setting, in a research centre, *etc*.?), what does it mean? This session invited participants to explore and share their own perspectives and experiences with the help of 3 practical scenarios to enhance our understanding of trust dynamics for the advancement of virtual human twins.

SCENARIO 1 Mr. Platel & Heart-Twin (*Patient is unwell and goes to hospital. Model is used to combine input from various measurements. Use of Virtual Reality to communicate model results to patient.*)

- **Virtual Reality** (VR): could increase trust in the surgical process. VR visualisation tools are also for patients to have more info -> even more trust in the surgical process.
- **Health literacy**: it requires health literacy for the patient to understand because visualisations may not be evident for the patients.

- **Patients' preferences**: VR could be good for the doctor to understand what are the patient's preferences
- Timing: the patient should be taken to VR screening before the decision-making process. Other persons commented that the VR should be separate, to be used after the decision, to be used after for the patient to be used to feel more comfortable.
- **Human oversight**:
    - Is it "strange" that VR proposes something and the surgeon may make changes? It could also make patients them feel safer, as it keeps the human oversight.
    - When human makes changes, it means that the model was perhaps not optimal and should be re-evaluated. Regardless, having the human oversight of the tool was still deemed important. You cannot just blindly rely on the tool, not just making interpretation. Important to have oversight.
- **Liability and trust**: "What if the patient doesn't trust the VR?"
- **Misleading practices/insurance**: reference was made to the US system
    - VR may even come up with a problem of insurance. Risk: Patient being pushed to get a treatment. The patient could be encouraged by the VR.
    - risk that other insurance companies can use it as an obligation to be used in the clinic. *E.g.*, use of wellbeing programs to get a better insurance rate. That becomes a stick to punish people for bad behaviour. We do not have it in Europe because of anti-discrimination laws
- **Self-determination & Patient involvement** in the decision-making process. Willingness should be respected for what patients want to see and what they do not want to see.
- **Integrated information**: With medical device developers.
- **Opt-out & Digital Twin**: Should patients be able to opt-out from using heart twin?
- **Access to VHTs**. Do doctors have to share the model with the patient? Doctors already use electronic devices, but do not tell to the patients. For VHT: how to ensure access to VHT? Should be perhaps part of electronic health records files.
- **Information**:
    - VHT information should be accessible for patients
    - At the same time, what's the difference with surgeons when consulting trial studies. "New technology should not question old aspects".
- **VHT, Doctors & scientific process**: Doctors do not always make decisions alone. *E.g.* for ask for another opinion. Depends on where they are. If they work alone. *E.g.* in university hospitals they have

SCENARIO 2 Jenny & Bone-Twin (*based on own-initiative genetic screening, patient contacts physician who orders tests (including model) but judges results are insufficient to recommend treatment*)

- **Trust**: It seems that, in the scenario, patient trust the tool but the doctor can be more skeptical.
- **Transparency**: From the doctor perspective, the model that is a black box, they cannot understand what made the digital decision.
- **Division of work**: is there a risk for possible adverse reactions by physicians when patients come with results of tools they are unfamiliar with
- **Reliability**: it is important to understand which tools are reliable for which purposes.
- **Education at citizen level**: it would be important to educate citizens to provide proper context now that more and more tools are becoming available (*e.g.* genetic screening).
- **Balance**: balance is important between suggestions by tools and trust in doctor.
- **Education at healthcare professional's level**: Patients could become more and more demanding because of these digital tools. It could be a challenge for doctors > doctors need to be trained to deal with these tools.
- **Health literacy + education** on digital devices

SCENARIO 3 Alex & 'Gluco-Twin' (*use of gluco-twin to enhance independent life*)

- **Trust from trusted organisations**: The gluco-twin programme comes from the university hospital, so trust in the institution is transferred onto trust for the tool.
- **When tools are DIY**: these tools are already in use by patients with diabetes. There are also cases where patients developed their own devices based on their read-outs. The diabetes patients are well-known for being independent and therapy-compliant.
- **Trialogue**: conversation between doctor, digital device developers & users to understand what the other wants.

- **Quality of data** is also important: make sure doctors are trained concerning that. And then the ability of the doctor to be able to explain the tool in the language of the patient.
- **Trust and personal data**: are there considerations to make about data protection for VHT? Should be protected as personal data and be part of electronic health record?
- **Role of private companies** involved in modelling.

4 Plenary sessions: clinical implementation and other initiatives

The second day of the meeting was kicked off with a presentation by Eric Vibert (Greater Hospital in Paris AP-HP) showing how virtual human twins are used in clinical practice. The day was concluded with presentations by Konrad Lang (BBMRI-ERIC), Victor Jirsa (Inserm, EBRAINS) and Thiranja Prasad Babarenda Gamage (AIB, 12 Labours) presenting the large scale initiatives/infrastructures they are involved in.

4.1 CLINICAL UPTAKE

Slides: EDITH_EM_Paris_clinical_VIBERT

Eric Vibert (Greater Hospital in Paris AP-HP, Université Paris-Saclay) presented the concept of the Digital Twin in Liver Surgery, a digital quantification to identify complexity and improve safety in surgery by adapting the patient journey and anticipating the anatomical and hemodynamic consequences of the treatment.

4.2 BBMRI-ERIC

Slides: EDITH_EM_Paris_other initiatives_LANG-BBMRI

Konrad Lang (BBMRI-ERIC) gave an introduction into the BBMRI-ERIC, the BioBanking and Molecular Research Infrastructure ERIC. BBMRI-ERIC provides tools and services for samples and data, making them findable. It provides services to negotiate on sample and data exchange.

4.3 EBRAINS

Slides: EDITH_EM_Paris_other initiatives_JIRSA-EBRAINS

Viktor Jirsa (Inserm, Aix-Marseille) presented the EBRAINS platform, the infrastructure built by the Human Brain Project. EBRAINS was built to enable brain research, building the digital twin brain, merge science & technology, and integrate heterogeneous data & sources. The Virtual Brain Twin (2024-2027), using the EBRAINS-RI, aims to provide a platform for personalized treatment of psychiatric disorders.

4.4 12 Labours

Slides: EDITH_EM_Paris_other initiatives_BABARENDA GAMAGE-12LABOURS

Thiranja Prasad Babarenda Gamage (Auckland Institute for Bioengineering) presented the 12 Labours DigitalTWINS platform, a project geared towards translating digital twins into the clinic. As the leader of the DigitalTWINS Tech Platform, he explained the basic principles, the core services and exemplar workflows.

5 Next steps, timeline & prioritization

Slides: EDITH_EM_Paris_ masterfile

The end of the Paris meeting marked the start of the public discussion & writing phase of the roadmap, facilitated through online meetings and the InSilicoWorld Community of Practice slack channels. All of this work will be brought together and translated into a tangible 10-year plan during the second public VHT ecosystem meeting (15-16/7/2024 in KIT, Amsterdam).

5.1 General conclusions

- Continue the interactions between the different stakeholders. Much work has been done in various places related to outreach, stakeholder engagement, patient interactions, collaboration with clinicians, but this is not always visible enough to the entire community. Use our champions!
- Further work is required on the business modelling (focusing on outcome-centric approaches, customization, and innovation) and the investigation of economic preconditions to create a thriving VHT ecosystem
- Further work is required on deepening the role of AI in the context of the VHT (in all its diversity).
- Much work is being done on the development of new data generator technologies – in the context of VHT this should be supported but prioritization is required (based on cost, need, TRL)
- EDITH should continue to learn from and align with existing large-scale infrastructures, networks & initiatives regarding technology, Standards, workflows, federation, governance
- Further investigation on user roles and identities is required, along with the way to grant access through national/European identity providers.
- In terms of standardization, additional work is required on standards for model validation (including reference data/model development), development of a process for standardized model approvement (SaMD) and inclusion of standards during implementation to achieve interoperability.
- An Ethical Manifesto on ethical and social responsibilities related to model development and use should be developed, which can serve as a sort of compass for in silico/community.

5.2 Ongoing activities

Several activities are currently ongoing that will strengthen the ecosystem and the development and realization of the Virtual Human Twin.

- VHT manifesto - please help your organisation sign up: https://www.virtualhumantwins.eu/
- Call for use cases: https://www.edith-csa.eu/call-for-use-cases/
- Clinical community survey - please forward to your clinical collaborators: https://www.surveymonkey.com/r/vphcs2a

5.3 Future activities

A range of activities is foreseen to further develop different elements of the roadmap and its validation. Communication of these activities will happen through the EDITH newsletter which is published on the EDIHT website and sent to all people registered to the EDITH mailinglist and all participants of EDITH events and activities. These will include the following.

- Dedicated **online meetings** on Use cases, Platforms, Infrastructures, Clinical community, Patients
- Additional surveys to gather input and suggestions
  - A User profile/roles survey is in preparation and will be communicated through slack and the newsletter
- **Roadmap writing**
  - A public Google Docs is available with the latest version of the roadmap and several comments that require further discussion. After requesting access, you can make your comments and suggestions directly in the document.

  - For the elements that require a more lively discussion with the entire community, please post them in the dedicated channel on the In Silico World community of practice on Slack: https://insilico.world/community/join-the-community-of-practice-channels/. If you are already in the ISW_CoP, you can go to the public channel 'edith_public_discussion' or any of the other EDITH related channels that will be created.
- **Amsterdam Ecosystem Meeting**: 15-16/7/2024 at the Royal Institute of the Tropics. The registration will open soon. The aim of this meeting is to
  - Provide space for final brainstorming on outstanding elements
  - Finalise the writing process
  - Reach consensus on the recommendations included in the roadmap