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Building Immune Digital Twins: An International and Transdisciplinary Community Effort

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Abstract

Digital twins, initially developed for industrial applications, are set to make significant advancements in medicine and healthcare. They have demonstrated promising potential for drug development and personalised care, especially in cardiovascular diagnostics and insulin-dependent diabetes management. A particularly compelling application lies in immune responses and immune-mediated diseases, given the immune system's essential role in preserving human health, from fighting infections to managing autoimmune diseases. Creating Immune Digital Twins (IDTs) holds great promise for medicine and healthcare. At the same time, the development of a reliable and robust IDT presents significant challenges due to the inherent complexity and polymorphism of the human immune system, the difficulties in measuring patients' immune state in vivo, and the intrinsic difficulties associated with modelling complex biological systems and processes.
The Working Group "Building Immune Digital Twins" (BIDT WG) aims to address these challenges by fostering transdisciplinary collaborations among immunologists, clinicians, experimentalists, computational biologists, and engineers. The international network aims to leverage its cross-disciplinary expertise for building the components required for a working IDT model. Moreover, the BIDT WG works towards creating an open-access model repository for publicly available immune-related computational models and their required metadata. The group is also active in cataloguing open-access tools, methodologies, and software to identify interoperability gaps in the current modelling landscape.
Consequently, this work can drive transformative innovations in precision medicine, unlocking new possibilities for the diagnosis, treatment, and management of immune-mediated diseases.

Keywords: Digital Twins; Immune Digital Twins (IDTs); Precision Medicine; Immune-mediated Diseases; Research Data Alliance (RDA)

1. Introduction

Digital twins are gaining traction as promising tools for disease modelling and personalised healthcare. While we are still in the early stages of development and implementation, applications in cardiovascular diagnostics (1), (2) and insulin pump management (3–5) stand out as success cases. Along these lines, notable examples include the HeartFlow FFRCT Analysis, which utilises patient-specific 3D computational models to non-invasively calculate fractional flow reserve from CT angiography, thereby avoiding invasive catheterisation procedures, and the CardioInsight Mapping System (Medtronic), which employs personalised electrophysiological models for non-invasive cardiac mapping (6). Both systems have received FDA clearance and are routinely used in clinical practice. Beyond diagnostic applications, digital twins are actively improving procedural planning and treatment guidance through platforms like the HEARTguide (FEops nv, Belgium), which creates patient-specific models to predict outcomes of transcatheter aortic valve replacement, and the InHeart Platform, which uses patient-specific cardiac models to guide ventricular tachycardia ablation procedures (6). Current research, as demonstrated by Camps et al. in their cardiac digital twin pipeline, shows how patient-specific models can be automatically generated from routine clinical data to predict individual drug responses, with simulation results matching clinical trial data (7).

Another implementation example of a digital twin is the artificial pancreas, which has revolutionised the way patients with type 1 diabetes manage the disease. The artificial pancreas consists of three components: the continuous glucose monitor, the algorithm, and the pump. These parts work together to mimic how a healthy pancreas regulates blood glucose. The device can monitor a person's blood glucose in real-time, automatically calculate and adjust the amount of insulin needed, and then inject it into the patient through a pump. The advantage of the closed-loop system is that the patient does not need to calculate the insulin dosage: the pumps are fully autonomous. The National Health System (NHS) in the UK recently invested 2.5 million pounds to roll out the Hybrid Closed Loop system- artificial pancreas- in a world-first move, in April 2024 (8).

In a recent study (9), researchers from the University of Virginia took a step further by proposing human-machine co-adaptation for automated insulin delivery. They addressed a key limitation of current hybrid closed-loop devices: these systems do not adapt to the changing physiology of their users. In a randomised clinical trial, they showed that the improved digital twin technology can enhance glycaemic control beyond what automated insulin delivery systems can achieve alone.

While still a nascent methodology in the digital health space, medical digital twins will play a critical role in precision medicine, assisting in individualised therapy selection, targeted and timely drug delivery, and overall disease management based on patients' characteristics (10). The concept of medical digital twins represents a fundamentally new approach to medical science and practice. As a critical enabler of personalised medicine, these twins rely primarily on the computational modelling of the complexities of human biology. A robust, shareable, and scalable framework is required to support these computational models.

Recent reports by the U.S. National Academy of Engineering (NAE), the National Academies of Sciences, Engineering, and Medicine (NASEM) and the EDITH-Coordination and Support Action consortium (the European Coordination and Support

Action (CSA) for building an Ecosystem of Digital twIns in healTHcare (EDITH[1])) underscore the difficulty in distinguishing between aspirational concepts and near-term applications (11), (12). The report identifies several foundational challenges directly tied to the advancement of modelling biological systems and processes. The human immune system plays a central role in numerous health conditions, from combating infections to managing autoimmune diseases. Immune Digital Twins (IDTs) have the potential to transform precision medicine and healthcare. However, their development is particularly challenging due to the complexity of the immune system, the heterogeneity of immune system attributes between patients, and the difficulty of measuring the diverse aspects of an individual patient's (or a patient community's) immune state *in vivo*. Addressing these challenges requires a coordinated, transdisciplinary effort involving immunologists, clinicians, mathematical modellers, experimental and computational systems biologists, and software and biomedical engineers. Ethical, regulatory, and patient awareness and participation challenges also need to be addressed.

With over 100 members from 22 countries, the Research Data Alliance's (RDA) Working Group on "Building Immune Digital Twins" (BIDT WG) comprises an international, transdisciplinary, and collaborative network of experts dedicated to bringing IDTs from the workbench to the clinic. One of the key characteristics of this community is inter and transdisciplinarity, as our members are mostly interdisciplinary researchers, such as biologists working on data curation and bioinformatics analyses, mathematicians working on biological problems, engineers and computer scientists building software and developing formal methods to address immunological questions, all supported by dedicated groups of domain experts, from clinicians to researchers in the immunology field. Besides the interdisciplinary scientists, we also welcome scientists working in complementary fields needed for the development and deployment of an IDT, such as immunologists, oncologists, clinicians, and experimentalists. We also include a dedicated team of scientists with a philosophy, humanities, and law background to help us address questions regarding policy, regulation, and ethics. In addition, the interactions with the Virtual Physiological Human Institute enable discussions on the involvement of patient support groups.

While focused on the human immune system, advancements in this area could lead to a scalable paradigm for other human digital twin models in human biological and health-related systems. BIDT shares the NAE and NASEM aspirations for digital twins while also developing concrete outcomes to address their foundational challenges in a stepwise approach intended to achieve a limited working model that demonstrates the application and utility of digital twins in immunology.

This article describes the BIDT WG's activities and a five-year plan, focused on data and model infrastructures, community building, and societal impact (**Figure 1)**. The BIDT WG represents an example of bottom-up community building to accelerate the development of DT technologies in immunology. With a primary target of creating the foundational infrastructure needed for functional systems-specific digital twins in clinical and preclinical settings, BIDT WG will identify gaps and missing information, enhance collaboration

[1] https://www.edith-csa.eu/edith/

across scientific communities, reinforce links with industrial partners, and support training and technology transfer. By developing the framework in a community-driven, collaborative fashion that leverages prior and emerging knowledge and achievements, the BIDT WG aims to accelerate the translation of DT technologies to human healthcare. Concretely, this project goes beyond IDTs by supporting and coordinating efforts with similarly oriented communities, such as the Virtual Human Project (13)-(14), while creating opportunities for collaborative research projects and fostering interdisciplinary exchanges.

2. The RDA ecosystem

The Research Data Alliance (RDA)[2] is a global community-driven organisation that builds the technical infrastructure needed to drive innovation in data sharing and interoperability, advance open science research, and cross-fertilise education in the digital space. RDA working groups (WGs) and interest groups (IGs) collaborate to develop data and digital technology solutions that advance science and broader societal goals, as well as technical and science-community infrastructure solutions, while promoting these outputs to European, American, and global stakeholders. In return, the RDA helps its communities by fostering dialogue within and across regions and governing or regulatory bodies, including instances like the European Commission and the US National Institutes of Health (NIH). Members from across Europe and the globe significantly contribute to the RDA's efforts by engaging in its core activities such as plenary meetings, IGs and WGs, workshops, and collaborative cross-fertilisation activities that lead to its recommendations and other outputs. This diverse community brings region-specific challenges forward while collaborating internationally to identify and implement workable solutions. In this context, we aim to utilise the RDA's platform resources to address the challenge of developing Immune Digital Twins (IDTs).

One of the strong aspects of the BIDT WG is the support it receives from the RDA. This platform, with more than 5000 experts engaged from across the globe, ensures that everyone has an opportunity to contribute to this (or any other) RDA working group. All interested parties can join RDA BIDT by first signing up as a member of RDA (there are no fees) through the dedicated RDA Membership webpage (https://www.rd-alliance.org/) and then joining the WG. BIDT WG was awarded Research Data Alliance facilitation of Targeted International working Groups for EOSC-related Research solutions (RDA TIGER) support, which includes facilitation, communication, landscape analysis, and output support services. A dedicated facilitator assists with the project, providing feedback to the community while monitoring the work plan and timeline (15). Throughout the stages of the WG's progression, RDA TIGER assists in recruiting the required expertise, provides a platform for intra-group communication during the work period, and helps disseminate deliverables. The Landscape Analysis Service provides an overview of similar international initiatives and research outputs, offering up-to-date information and establishing connections across the various expertise needed to build the prototype of an IDT. Further, a helpdesk supports the alignment and implementation of European

[2] https://www.rd-alliance.org/

Open Science Cloud (EOSC) policies with the needs of the BIDT WG. The sustainable management of the WG's deliverables is a key objective of RDA TIGER. BIDT WG's focus (**Figure 1**) further aligns with key RDA priorities, such as

- **Shared digital infrastructure:** Recognising that computational models integrate multiple layers of data and knowledge, BIDT WG emphasises the importance of creating a shared infrastructure for cross-disciplinary and cross-institutional model management and sharing. This resource will foster a collaborative digital infrastructure supporting diverse inputs when modelling an IDT. To this end, the BIDT WG is the recipient of an RDA-supported Expert Grant to conduct a technical report and analysis on the development of the group's digital platform.
- **Standards and the application of the FAIR DATA Principles:** BIDT is committed to the FAIR and CARE Data Principles. Its works and outcomes are conducted entirely within the framework of open science as found in the UNESCO 2021 Recommendation on Open Science. BIDT WG fosters dialogue between different systems modelling communities to identify gaps in standards and ontologies required to face the complexity and the different scales involved in building digital twin technologies for the human immune system. The WG works to assemble a set of relevant standards, meta-standards, and ontologies that can support data and knowledge exchanges across communities. For example, the GO ontology[3] developed for the human immune system could be employed by BIDT to describe its organisational chart (see Section 3). Another example is the standards implementation guide[4] and FAIRsharing collection[5] assembled by the EDITH consortium. The BIDT WG is the recipient of the RDA-supported Cascading Grant, which aims to facilitate the adoption of RDA WG recommendations in tangible and quantifiable outputs.
- **Broader engagement:** As the requirements for digital twins extend beyond computational modelling, BIDT also engages with other initiatives to develop digital twins in the biomedical space (e.g., EDITH). We are working diligently to establish communication channels and foster inter- and intra-community dialogue, supported by open-access materials and tools, with the systems biology communities (**Figure 2**). We work closely with members of the COMBINE (16,17), SysMod (18,19), Disease Maps (20), Multiscale Modelling and Viral Pandemics WG[6], COVID-19 Disease Map project (21,22), SBML (23), SBGN (24–27), CoLoMoTo (28,29), VPHi[7], Avicenna Alliance[8], and the Systems Biology Community of ELIXIR (30) communities. Many members of the BIDT WG are also active in the working groups and communities listed above, facilitating exchanges and output dissemination.

[3] https://www.ebi.ac.uk/QuickGO/term/GO:0045087
[4] https://zenodo.org/records/10524795
[5] https://fairsharing.org/4787
[6] https://www.imagwiki.nibib.nih.gov/working-groups/multiscale-modeling-and-viral-pandemics
[7] https://www.vph-institute.org/
[8] https://www.avicenna-alliance.com/

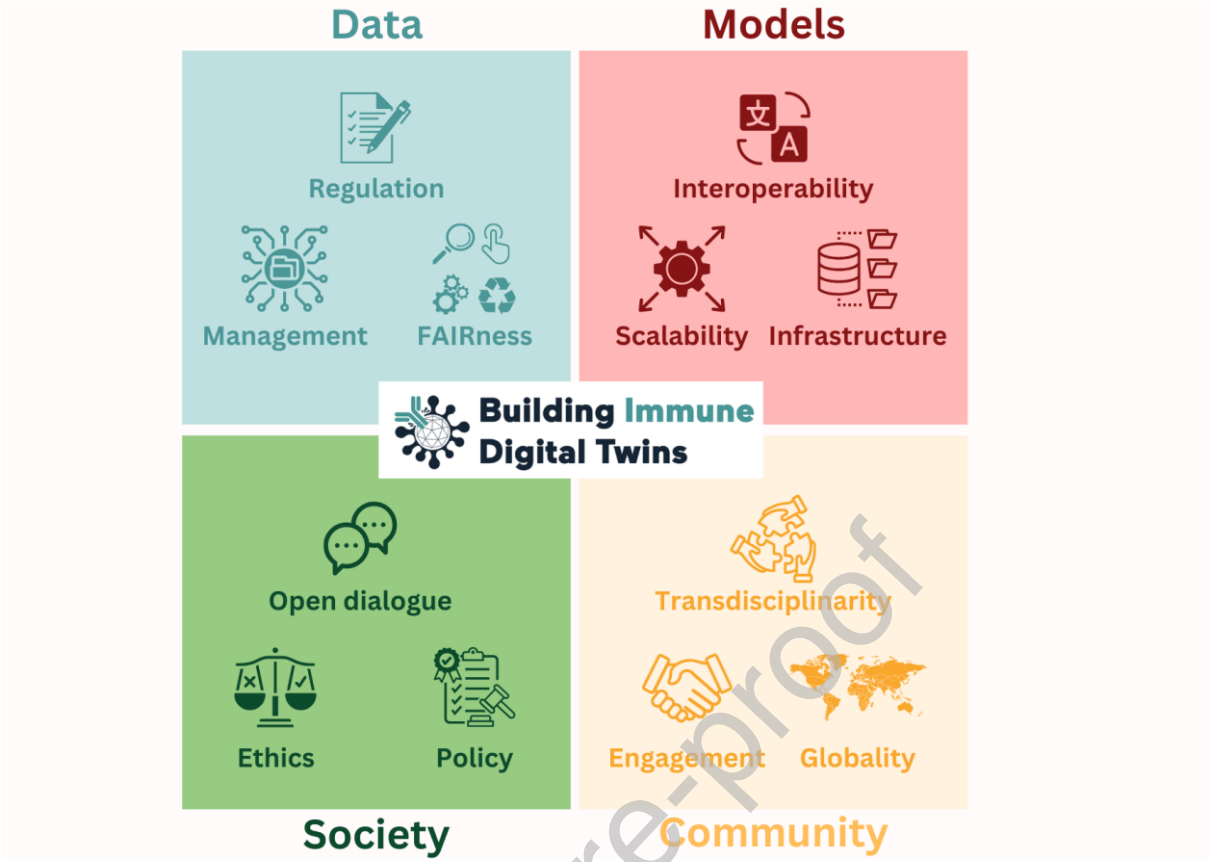

Figure 1. The four different pillars of interest of the BIDT WG.

3. Building an open-access repository of immune system-related models and their metadata across scales

The computational systems biology community has built various mechanistic models of immune system components. These models span different scales, from intracellular regulatory networks to system-level immune processes. As of now, there is no easily usable repository or platform for such models. An essential activity of the BIDT WG is to develop an "organisational chart" of the immune system supported by a database of computational models tagged to the different parts of this organisational chart. Additional tags for the models will include information about the functions of the models, particularly in the context of specific diseases. The development of an underlying prototype model of the IDT will follow the roadmap by Laubenbacher et al. (31) while implementing the FAIR Data Principles (32), (33). The core computational models should also comply with community standards where such standards exist and, where not, be used to identify which new standards need to be developed. The models should include sufficient annotation to allow for reproducibility and reusability (34) alongside the development of aligned methodologies properly adapted to quantify uncertainty while also evaluating the reliability and robustness of predictions for research and clinical decision-making. Specifically, BIDT works to accomplish the following:

1. Build a shareable Zotero library with curated literature on the human immune system, medical digital twin technology, and modelling efforts. The library is

currently being populated with a literature collection of state-of-the-art publications describing model building and simulation, data generation analysis, methodological development in model and data integration and analysis, and their appropriately curated metadata.

2. Identify gaps in the coverage of computational and mathematical models and parts of the immune system that have yet to be modelled.
3. Catalogue simulation platforms, tools, and software; identify interoperability and gaps. Eventually, supporting simulations across multiple platforms to assess the robustness of *in silico* results.
4. Identify interoperability gaps and missing parts to create an integrated modelling pipeline across biological scales from molecules to tissues, organs, and whole/entire systems.
5. Build a focused model repository and a model metadata catalogue. This will link the IDT-developed resources to relevant BioModels (35) and virtual human twin resources by creating appropriate IDT-tagged sections, covering immune-related mathematical models of various scales that can be used as modules for a wider IDT. A prototype is now available on the WG's Git repository[9]
6. Write a recommendation document that could serve as a textbook guide for researchers interested in employing digital twin technology when studying various aspects of the human immune system and its responses (see section 4).

We will host the WG's resources using the BIDT GitHub Website[10] and Repository[11]. Moreover, we use publicly available data and file-sharing repositories like GitLab, GitHub, Zenodo, and Figshare. We will also use Jupyter Notebooks to facilitate reproducibility and transparency, as well as FAIRDOMhub (36), a web-accessible registry for storing, sharing, and publishing research results and projects. The collaborative website and repositories serve as our centralised resources, while we are designing the IDT interoperable digital platform.

4. Recommendations for IDTs

The BIDT WG will develop recommendations regarding the appropriate data, infrastructure, and methodologies needed to develop an IDT. This includes identifying what is already available and achieved while addressing the scientific, technical, and organisational challenges in building a fully operational IDT. The recommendations will be widely distributed for consultation across interested and related scientific communities, including within the wider RDA community. With community input and support, these recommendations will serve as a foundational resource for IDTs and other digital twins related to human biology.

[9] https://immunedt.github.io/models/
[10] https://immunedt.github.io/
[11] https://github.com/ImmuneDT

The recommendations will provide a reference framework for research into personalised medicine at different levels: generic, population-specific, and patient-specific. Building an IDT requires adaptability across scales, hybrid methods, resources for computational costs, data access and integration, and interoperable systems capable of receiving feedback and recalibrating. An IDT must combine computational models that simulate multiple biological processes. Appropriate methodological and technological advancements are needed for efficient model analysis, integration, and calibration. Moreover, specific policies, best practices, and guidance are needed for building, hosting, adapting, simulating, and maintaining IDTs. The BIDT WG will tackle these issues based on its broad experience, competencies, and multidisciplinary and complementary expertise.

Importantly, these recommendations will include the requirements for developing data and model infrastructures based on the FAIR Data Principles. This complements and supports a core need described above: developing standards and ontologies for digital twins that facilitate the reusability and integration of computational models across biological scales while also maximising interoperability.

As mentioned in previous sections, we have open communication channels with a significant number of systems biology communities (**Figure 2**) (16,17,30). Besides our close ties with the "Computational Modelling in Biology" (COMBINE) network, which aims to coordinate the development and adoption of model standards, we are also working closely with the Centre for Reproducible Biomedical Modelling[12]. A recent collaborative publication focuses on FAIR and CURE guidelines for computational models of biological systems (37), a complementary work to previous community-driven efforts on addressing barriers in comprehensiveness, accessibility, reusability, interoperability and reproducibility of computational models in systems biology (38). Ongoing collaborative efforts with the centre and the CoLoMoTo consortium are focused on bringing clarity to standards for qualitative models in biology, as a follow-up on previous efforts (28). The cross-community collaboration allows us to work towards FAIR models directly relating our BIDT WG activities and deliverables to broader international initiatives.

[12] https://reproduciblebiomodels.org/

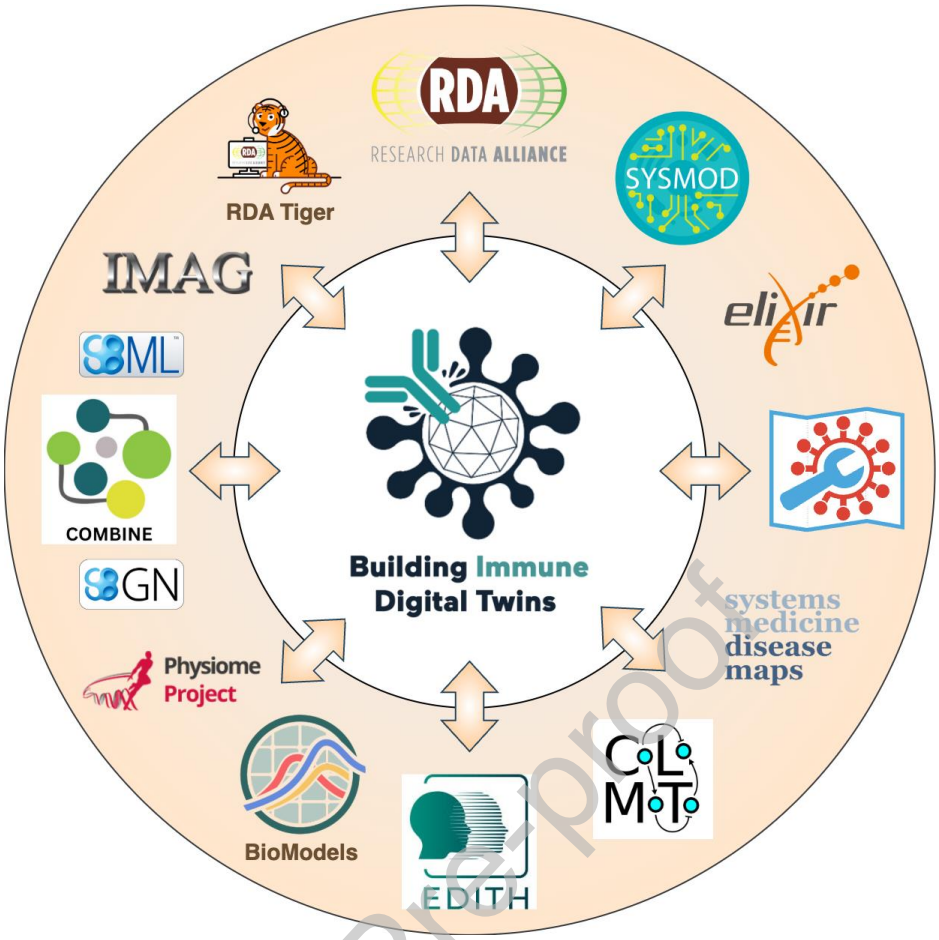

Figure 2: The BIDT WG and connected Systems Biology communities.

5. Sustainability through proof of concept and collaboration

The collaboration with BioModels, the Virtual Human Twin advanced simulation platform[13], and related RDA IGs and WGs creates a foundation for the long-term viability of the BIDT WG's outputs. BioModels is a repository of mathematical models of biological and biomedical systems (35). It hosts a vast selection of existing literature-based physiologically and pharmaceutically relevant mechanistic models in standard formats, such as SBML (23) and BioPAX (39). BioModels is supported by the European Bioinformatics Institute (EBI) and is one of the most popular repositories in systems biology. Together, we will create a sub-collection focused on the human immune system, using the appropriate tags and the curation system used by BioModels (35). Likewise, we are collaborating with EDITH[14] to support this large-scale European initiative for virtual human twins (VHT) (40). The EDITH project, a coordination and support action funded by the European Commission under the DigitalEurope program, has brought together the entire ecosystem related to digital twins in healthcare, including the IDT community. It has also coordinated the writing of the roadmap to realise the VHT. The roadmap discusses all aspects of the VHT and its future advanced simulation platform (currently being procured by the European Commission), including technological, clinical, social, ethical,

[13] https://digital-strategy.ec.europa.eu/en/policies/virtual-human-twins
[14] https://www.edith-csa.eu/

legal, standardisation, regulatory, and sustainability elements. In addition, BIDT is a use case within the EDITH consortium, included in the EDITH catalogue and roadmap.

We also plan to work closely with RDA WGs of similar interests, developing standards and ontologies, metadata, data-sharing, data visitation, and artificial intelligence (AI) applications for IDTs. Examples include the Metadata IG and the FAIRsharing Registry: Connecting data policies, standards, and databases, RDA WG, the EOSC-Future/RDA Artificial Intelligence and Data Visitation (AIDV) WG and the newly minted WGs on Health Data Commons and Global Open Research Commons. This will help us accelerate progress towards our deliverables and join forces with existing RDA WGs to ensure that our work is relevant, timely, coherent with other efforts and sustainable, all central to RDA's scopes.

6. Ethical considerations, data governance and privacy protection

IDT development raises several ethical and regulatory issues, especially regarding handling sensitive data and using artificial intelligence. These issues relate to the security and confidentiality of data/metadata and their sharing and reuse. We plan to develop our framework by considering data management and privacy protection, ensuring respect for ethical and legal standards in all processes. Governance frameworks for data, models, and infrastructure require attention to the sovereignty considerations of the various stakeholders, mainly due to the sensitive and complex nature of immune data. Governance and sovereignty are interdependent concepts that ensure the ethical, secure, and effective use of data, models, and infrastructure to develop IDTs. Sovereignty ensures control and rights over data, models, and infrastructure, while governance provides the operational frameworks to manage and enforce these rights. Together, they are indispensable for designing ethical, trustworthy, and scalable IDTs, enabling innovation while respecting privacy, security, and collaboration.

Furthermore, close collaboration with projects such as the Physiome Project[15], EDITH, and the RDA IGs "EOSC-Future/RDA AIDV", "Ethics and Social Aspects of Data" and "Sensitive Data" can help us fill the knowledge gaps. This will ensure that our approach aligns with ethical guidelines, regulatory standards and legal frameworks, including the General Data Protection Regulation (GDPR) in the European Union and other relevant regional or national guidelines, such as those of the U.S. Health Insurance Portability and Accountability Act (HIPAA). A comprehensive overview of the legal and ethical frameworks in the European Union relevant to digital twins in healthcare has recently been published[16].

By engaging regulators and advocacy groups early in the development process, we aim to create a scalable, consistent approach that can evolve with shifts in policy and societal expectations. This proactive engagement will help the WG design a scalable and consistent governance framework that supports innovation in IDT development while respecting legal and ethical standards.

[15] https://physiomeproject.org/
[16] https://zenodo.org/records/14516807

7. Impact, implementation, dissemination and knowledge transfer

BIDT provides a unique interdisciplinary space for scientists from different backgrounds, such as immunologists, biologists, engineers, bioinformaticians, bio-curators, modellers, computational biologists, clinicians, and other experts, to exchange and collaborate. The work relies on frequently organised workshops, tutorials, and webinars to share knowledge, exchange best practices across systems biology communities, and boost transparency and reproducibility of computational models of human biology. These workshops and tutorials are frequently organised as satellite or integrated events in major bioinformatics and *in silico* medicine conferences, such as the European Conference on Computational Biology (ECCB), Intelligent Systems for Molecular Biology (ISMB), Computational Methods in Systems Biology (CMSB), and Basel Computational Biology Conference [BC][2] to name a few. BIDT WG further publishes community papers on best practices for accessibility, reusability, interoperability, and reproducibility of computational models in systems biology (28), (38), (41). In the last few years, we have published several scientific articles focusing on Immune Digital Twins (31,42–44).

The outcomes of the BIDT WG are highly valuable to various stakeholders, including immune system researchers, epidemiologists, healthcare technology professionals, and clinicians seeking advanced tools for personalised medicine. Additionally, the broader healthcare ecosystem, including companies focused on healthcare innovation, patient associations, and NGOs, stands to benefit significantly.

Our inclusive approach ensures that WG members and stakeholders are actively involved throughout the process. Researchers and clinicians contribute directly to developing catalogues, repositories, and best practice guidelines, while patient associations, NGOs, and companies participate through workshops and assessment meetings. These engagements provide critical insights, ensuring the WG's deliverables are practical, relevant, and aligned with user needs.

To promote broader adoption, the WG plans to develop a dedicated online portal and a recommendation document, facilitating access to the WG's resources and enhancing dissemination. A second edition of the Building Immune Digital Twins Workshop (42) and collaborations with other teams, projects, and communities will ensure broader engagement and dissemination of the produced materials, which will also be shared via dedicated publications. The patient is the ultimate beneficiary. By adopting IDTs of mechanisms underlying healthy or pathological immune responses, the biomedical community will support the discovery and development of innovative treatments for immuno-inflammatory diseases. In the same vein, the second edition of the workshop is planned for Spring 2027, with support from the Institut Pascal, Paris-Saclay, and the active participation of members (clinicians) from the Hospital/ University Institute IHU Prometheus[17], focusing on Digital Twin for sepsis, the Hospital/ University Centre CHU CARE, focusing on Immuno-oncology, and Paris Institute for Transplantation & Organ Regeneration, PITOR[18], focusing on organ regeneration and transplants.

At the same time, members of the BIDT WG work on representing the complexity of

[17] https://www.fhu-sepsis.uvsq.fr/ihu-prometheus-3
[18] https://paristransplantgroup.com/pitor/

immune disorders, identifying highly relevant therapeutic targets, selecting and optimising treatments, and evaluating performance in virtual patients.

Overall, these efforts can foster precision medicine approaches that better address individual patient needs with more effective and safer therapies while reducing healthcare costs.

8. Perspectives

The BIDT WG aims to lay the foundation for a rigorous implementation of digital twin technologies focused on the human immune system. The short, medium and long-term goals are briefly discussed below, with a tentative roadmap with deliverables and milestones for the next 5 years (**Figure 3**).

Short-term goals: We will conduct a systematic review of the scientific literature relevant to available datasets and computational models of the human immune system and work on building an interoperable repository of computational models, their metadata and the corresponding articles. This repository will adopt standardised data formats and reference architectures, enabling researchers worldwide to contribute models that can be seamlessly shared, compared, and integrated. By gathering this information in one place, we aim to understand what is missing and where future efforts should be directed. We will also work on producing a recommendation document that could serve as a textbook to guide the development of open-source, FAIRly shareable, and clinically viable IDTs. Finally, we will actively work towards expanding our WG with new members and fostering further collaborations with existing initiatives, research networks, and public health entities worldwide. This will ensure our alignment with established workflows and allow us to leverage existing expertise.

Medium-term goals: We will focus on identifying the unmet needs in diagnosing and treating immune-mediated diseases to enhance the existing tools for early identification. Collaboration with clinicians, researchers, and advocacy groups to pinpoint diagnostics bottlenecks and therapeutic challenges will be one of the main points to address the application of IDTs to clinical practice. Suitable immune-mediated diseases will be selected as use cases, leveraging systems biology, machine learning, and computational modelling. The goal is to showcase how our collaborative, interdisciplinary effort and expertise can improve clinical outcomes using prediction tools. Focusing on specific pathological conditions associated with inflammation (where dysregulation has distinct local and systemic manifestations, cellular interactions involving immune cells are more measurable and quantifiable, and multi-omics data are available) appears to be a valid starting point for initial “proof of concept” IDT implementations. As such, the research groups associated with our consortium work to address inflammation in different cases and timescales, using various modelling approaches and formalisms. Rather than providing one IDT implementation, we aim to present different ways of building an IDT to address inflammation-related questions in a variety of pathologies, such as autoimmune diseases, where inflammation is chronic, or in sepsis, where inflammation is acute, or in certain infectious diseases, where inflammation presents as both acute and chronic.

Furthermore, besides temporality, we also address different biological scales (from genes to proteins, to pathways, to cells, to tissues, to organs, to systemic full body manifestations) that can be represented in virtual patients. Several scientific articles have been published by our members, focusing on these pathologies and their modelling efforts since 2020 (21,44–53).

Furthermore, because inflammation is pervasive in many disease contexts, it could serve as a foundational immune response model, adaptable to a wide range of cases. This working example will lead to solutions for model integration and combination, addressing real-world challenges of interoperability, scale differences, and mismatching input-output reads. To build such a pipeline, we will engage previous works and efforts (54). For example, the Atlas of Inflammation Resolution (AIR) provides a curated resource that integrates molecular interaction maps across multiple scales of inflammation (52). Its standardised, machine-readable structure and compatibility with multi-omics and time-series data enable mapping of immune dynamics. This supports the further development of predictive, patient-specific models, making AIR a foundational starting point for early IDT prototypes focused on inflammatory dysregulation.

Long-term goals: We plan to enable collaboration among researchers by creating a digital portal to collect and build digital immune models, leveraging relevant datasets, and stimulating the collection of new data to enhance diagnostic, prophylactic, and therapeutic models while also contributing to outcome-based interventions for patients with immune-mediated disorders. This process involves engaging stakeholders (including regulatory bodies, academia, industry, and patient organisations) in facilitating development and implementation. Ultimately, we aim to cultivate long-lasting and synergetic collaborations with consortia such as the ImmPort consortium[19], for sharing immunological data that could be used to train, validate and boost the development of immune-related models, and pave the way to the realisation of an IDT prototype, advancing the frontiers of immunology and resulting in novel therapies and personalised medical care.

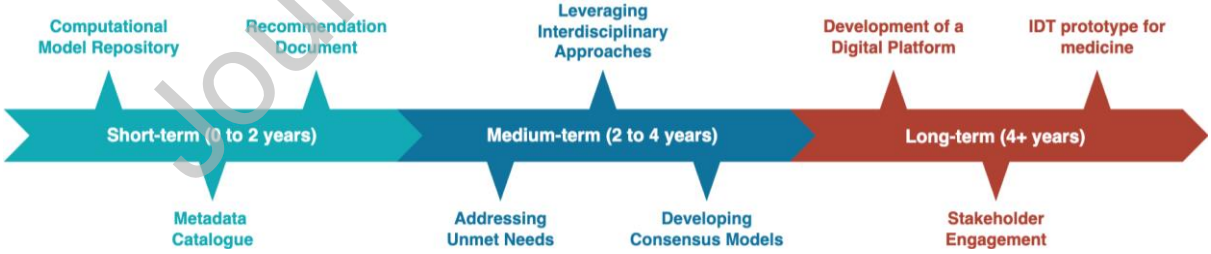

Figure 3. BIDT 5-year plan and roadmap.

9. Limitations

[19] https://www.immport.org/home

We acknowledge the uncertainty associated with different steps of building an IDT, ranging from inter-individual data variety and incomplete mechanistic understanding of the immune system, to challenges of integrating heterogeneous data modalities at different scales. While a fully integrated meta-model is not yet within immediate reach, the current phase is focused on foundational work: standardising data types, validating submodels, and establishing interoperable frameworks. These steps are essential precursors to more ambitious integration.

Regarding the scale of collaboration, progress requires a dual approach: individual investigators contribute deep expertise and innovation at the component level, while larger consortia focus on harmonisation, shared infrastructure, and integration strategies. In this sense, a “mega-consortium” is not about centralising all research, but rather about coordinating distributed efforts to ensure they can eventually converge meaningfully.

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Conflict of interest

The authors declare no competing interests.

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Declaration of Interest Statement

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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