RDA Working Group: Building Immune Digital Twins

Case Statement

WG Charter: A concise articulation of the issues the WG will address within an 18-month time frame and its "deliverables" or outcomes (including a Recommendation).

Digital twins, customised simulation models pioneered in industry, are beginning to gain ground in medicine and healthcare, with some significant successes in cardiovascular diagnostics and insulin pump control. Personalised computational models also assist in applications ranging from drug development to patient-tailored treatment optimisation. Advanced medical digital twins will be essential to make precision medicine a reality. Because the immune system plays a vital role in such a wide range of diseases and health conditions, from fighting pathogens to autoimmune disorders, digital twins of the immune system (IDTs) will have an exceptionally high impact. However, their development presents significant challenges stemming from the immune system's inherent complexity and the difficulty in measuring many aspects of a patient's immune state in vivo. A collaborative interdisciplinary effort involving immunologists, clinicians, mathematical modellers, and software engineers is required to achieve substantial progress.

The WG Building Immune Digital Twins aims to foster a network of collaborators and experts in all relevant research areas. The ultimate goal of the WG is to help create a long-term interdisciplinary immune digital twin community willing to take on the challenges of this exciting new field.

It is essential to understand that the field of medical digital twins is fundamentally new in its premise and ambition. It is a crucial tool for the realisation of personalised medicine. While computational modelling is an essential ingredient, it is far from the only one. However, it enables concrete steps quickly, making it the main focus of this WG and community building. As the recent report by the U.S. National Academies points out, it currently needs to be more challenging to distinguish what is aspirational and authentic in the digital twin field. The report lays out several foundational problems that need to be solved along the way, many related to the modelling component. This WG plans to focus efforts on some of these.

Within the 18-month timeframe, we will deliver clear outcomes that can be enlisted here:

- **Main Deliverable 1:** We aim to create an open-access library (using Zotero) where we will curate literature relevant to the human immune system.
- **Main Deliverable 2:** We will create an open-access catalogue and metadata of existing models and selected relevant literature. Given the WG time frame, we propose developing a prototype by establishing a simple data structure that enables the crowdsourcing of entries and an evolving ontology of labels and metadata.
- **Main Deliverable 3:** We will collaborate closely with Biomodels and the Virtual Human Twin infrastructure to create a collection of models focusing on the Human Immune System. We will create a sub-section using proper tags and the appropriate metadata.
- **Main Deliverable 4:** A dedicated webpage will contain all the relevant information about the project, the model/data, and the literature catalogues. We have started setting up a collaborative website and git to serve as our centralised resource.
- **Main Deliverable 5:** We will organise virtual workshops and webinars for a general audience, including WG members. The focus will be on creating specific work plans for IDT development in different contexts and a specific list of open problems to be solved, with steps toward their solution.
- **Main Deliverable 6:** We will organise a follow-up to the 3-week Institut Pascal workshop in 2023. Several possible venues, including the Institut Pascal, are available.

- **Main Deliverable 7:** The outcomes will be collected into a “manual” for IDT development. Over time, this manual can grow into a recommendation document that can serve as the foundation for this field.

Value Proposition: A specific description of who will benefit from adopting or implementing the WG outcomes and what tangible impacts should result.

Digital Twins can be a key technology for personalised medicine at different "levels": generic, population-specific, and subject-specific. To build a Medical Digital Twin (MDT), one would need to cross scales, propose hybrid methods, overcome computational costs, access data, integrate them, and build a system capable of receiving feedback and recalibrating. A MDT must combine computational models to simulate more than one biological process at a time. **Appropriate methodological advancements are needed for efficient model analysis, integration, and calibration**. Moreover, **guidelines and best practices must be included for building, hosting, adapting, simulating, and maintaining the Digital Twins.** The prospective WG will focus on these issues and try to tackle them by combining its members’ multidisciplinary and complementary expertise.

The outcomes of the WG Building Immune Digital Twins hold immense value for diverse stakeholders, encompassing researchers, clinicians, practitioners, patients and various entities in the medical and healthcare landscape. Intended adopters of the WG's outcomes include researchers and practitioners engaged in immune system research and professionals in epidemiology and healthcare technology.

Clinicians working on or searching for advanced tools for personalised medicine will find significant utility in this WG's deliverables. The beneficiaries extend to the broader healthcare ecosystem, including patient associations, NGOs, and companies invested in advancing healthcare technologies. The WG's inclusive approach and our stakeholder network ensure that adopters and beneficiaries are actively involved throughout the process. Researchers and clinicians are integral members, contributing expertise to developing catalogues, repositories, and best-practice guidelines.

Stakeholders will be actively included in workshops and stakeholder assessment meetings, including patient associations, NGOs, and companies. Our plans for Building Immune Digital Twins WG will consider their insights and needs. **Their contribution and active participation are critical factors to our success.**

The WG's strategy for broader adoption involves creating an open-access catalogue and repository, accessible through a dedicated webpage and a comprehensive recommendation document, facilitating easy access and dissemination of knowledge. In addition, research and perspective papers will be published within these 18 months, enhancing the visibility and broadening adoption of the material developed in our WG.

The second edition of the Building Immune Digital Twins Workshop and collaborations with other teams, projects and communities ensure broader engagement and dissemination of the produced materials.

The WG's holistic approach aims to foster a community-driven adoption strategy, ensuring that the benefits of Immune Digital Twins are accessible and applicable across a broad spectrum of healthcare stakeholders worldwide. Our Working Group aspires to become truly international, and we will work diligently to democratise access and facilitate the participation of scientists from underrepresented communities, either socially or geographically.

The ultimate beneficiary, and our main goal for developing this work, is the patient. By adopting MDTs, the healthcare ecosystem can provide more accurate and personalised therapies, faster diagnosis, and improved outcomes. On a global level, this can accelerate new drug development, address personalised needs in therapies, and reduce healthcare costs.

We aim to identify several areas where Immunodiagnostics and Therapeutics can improve the diagnosis, treatment, and monitoring of immune-related conditions.

Engagement with existing work in the area: A brief review of related work and plan for engagement with other activities.

Our WG aims to facilitate the gathering of scientists from different backgrounds, such as immunologists, biologists, engineers, bioinformaticians, biocurators, modellers, computational biologists, and clinicians. Building an Immune Digital Twin of the Human Immune System requires the cooperation and communication of scientists with complementary expertise.

Our goal is to facilitate communication and collaboration. To this end, a three-week workshop was organised with the support of the Institut Pascal, Paris Saclay (https://www.institut-pascal.universite-paris-saclay.fr/en/scientific-programs/building-immune-digital-twins). The highly interdisciplinary community of the workshop will be the core of our prospective WG. We are organising frequent workshops, tutorials and webinars to communicate and exchange best practices across systems biology communities and boost transparency and reproducibility in computational modelling in life sciences. We organise our workshops and tutorials as satellite events or integrated events in major Bioinformatics conferences such as ECCB, ISMB, VPH, CMSB, and [BC]2, to name a few, and publish community papers on best practices for accessibility, reusability, interoperability and reproducibility of computational models in systems biology. Here are some recent examples:

1. *Immune Digital Twins Working Group. (2024). Building an international and interdisciplinary community to develop immune digital twins for complex human pathologies. Building Immune Digital Twins (BIDT), Institut Pascal, University of Paris Saclay. Zenodo. https://doi.org/10.5281/zenodo.10783684*
2. *Laubenbacher Reinhard , Adler Fred , An Gary , Castiglione Filippo , Eubank Stephen , Fonseca Luis L. , Glazier James , Helikar Tomas , Jett-Tilton Marti , Kirschner Denise , Macklin Paul , Mehrad Borna , Moore Beth , Pasour Virginia , Shmulevich Ilya , Smith Amber , Voigt Isabel , Yankeelov Thomas E. , Ziemssen Tjalf, Toward mechanistic medical digital twins: some use cases in immunology, Frontiers in Digital Health, VOLUME=6,YEAR=2024; DOI=10.3389/fdgth.2024.1349595*
3. *Laubenbacher, R., Adler, F., An, G. et al. Forum on immune digital twins: a meeting report. npj Syst Biol Appl 10, 19 (2024). https://doi.org/10.1038/s41540-024-00345-5*
4. *Laubenbacher, R., Niarakis, A., Helikar, T. et al. Building digital twins of the human immune system: toward a roadmap. npj Digit. Med. 5, 64 (2022). https://doi.org/10.1038/s41746-022-00610-z*
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. doi: 10.1109/JBHI.2023.3323688*
6. *Rodríguez Martínez et al, Computational modelling of immunological mechanisms: From statistical approaches to interpretable machine learning,ImmunoInformatics,2023,100029,ISSN 2667-1190,doi.org/10.1016/j.immuno.2023.100029*
7. *Niarakis et al, Addressing barriers in comprehensiveness, accessibility, reusability, interoperability and reproducibility of computational models in systems biology, Briefings in Bioinformatics, Volume 23, Issue 4, July 2022, bbac212, https://doi.org/10.1093/bib/bbac212*
8. *Niarakis et al, Setting the basis of best practices and standards for curation and annotation of logical models in biology—highlights of the [BC]2 2019 CoLoMoTo/SysMod Workshop, Briefings in Bioinformatics, Volume 22, Issue 2, March 2021, Pages 1848–1859, https://doi.org/10.1093/bib/bbaa046*
9. *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8170388/*
10. *https://www.embopress.org/doi/full/10.15252/msb.20209982*

Our aim is now to focus on Building Immune digital twins and use our significant expertise to advance the field. We would like to provide a textbook guide for Building Immune Digital Twins with concrete application best practices and standardisation in most steps. In this direction, we have fostered close communication with EDITH-CSA (https://www.edith-csa.eu/). This project envisions the building of the Virtual Human Twin, and we will develop our IDT according to the specifications of the broader community to maximise its value to society. There is no existing WG at

the RDA currently working on this emerging topic of immense value for personalised treatment. Our WG could complement the work of the Health Data Interest Group and bring significant value to the discussions and topics addressed, as we already have a core community of scientists with inter- and multidisciplinary backgrounds. The HDIG held a plenary session, "The usage of digital twins in healthcare for personalised care", in February 2022. It addressed the challenges of Digital Twins for Health (DTH) and the stakeholders needed to address them. **We genuinely believe that our prospective WG can complement this work and fill in a much-needed space to further advance in emerging technology, personal data and personalised care.**

UN Sustainable Development Goals (SDGs) (An explanation of how the Group and its activities will contribute to the United Nations' Sustainable Development Goals (SDGs).

Goal 3: Good Health and Well-being: The project makes a direct contribution to the enhancement of health outcomes through the creation of advanced medical digital twins that model the immune system. This technology can transform personalised medicine by providing individualised treatment optimisation and disease diagnosis advancements. The effort to improve the comprehension of the immune system and its involvement in diverse medical conditions consistently ensures good health and well-being.

Goal 5: Achieve gender equality and empower all women and girls: Our community is dedicated to achieving Goal 5 (Gender Equality) by promoting inclusivity and diversity. The project ensures gender balance in representation, particularly in leadership roles, fostering an environment where women scientists actively inspire other scientists. Moreover, the deliberate selection of prominent women as chairs for the WG and as speakers for our workshops breaks stereotypes, inspires women to pursue STEM careers and contributes to dismantling biases in the field. By actively working towards gender equality, the project aligns with Goal 5. It plays a crucial role in empowering women within the realm of the many fields of expertise in the project.

Goal 10: Reduce inequality within and among countries: Our WG recognises the complexity of the immune system and the challenges associated with many aspects of a patient's immune state, diagnosis and treatments (when available). Through the implementation of collaborative interdisciplinary initiatives, the project has the potential to help mitigate disparities in healthcare by tackling these challenges. The rise and availability of advanced medical digital twins may have extensive positive effects on individuals worldwide, reducing the costs of diagnosis and therapy by providing means of personalised and more precise care in an open-science-aligned philosophy, accessible to everyone worldwide, aiding in the mitigation of health inequalities both domestically and internationally.

Goal 17: Partnerships for the goals: Establishing the WG Building Immune Digital Twins underscores the importance of partnerships and collaboration. By bringing together experts from various fields, the project aims to create a network of collaborators in immune system research and digital twins, as well as diverse stakeholders, aiming to accelerate and implement the adoption of the developed DTs. This collaborative effort promotes knowledge sharing, resource pooling, and a collective approach to address the challenges of developing immune digital twins. Such partnerships are crucial for achieving sustainable development goals by leveraging diverse expertise and resources.

Work Plan: A specific and detailed description of how the WG will operate, including:
As previously stated, we will collaborate closely with Biomodels to create an open-access repository for models of the Human Immune System. We will start with curated metadata and create an accessible Git repository. We will also create a new tag for the DigitalTwin-RDA in BioModels, which could mean all relevant models can be pulled through a single URL. We could also curate new models for BioModels and tag them with DT-RDA tags or something similar. We could also create a page for this unique collection within BioModels with a description and the URL. We will also work on producing a written document that will serve as a Recommendation for the development of IDTs. The recommendation will include best practices, tools, platforms, available resources, standards, interoperability issues, use cases, and a stakeholder assessment to provide insights into key challenges and possible solutions. We will create intermediate documents for every subgroup to monitor progress and exchange between the groups working on different deliverables. A deliverable development plan and expected dates for completion can be found in Table 1.

Conflict management: The conflicts will be addressed with an open mind and open discussion with all WG members until a consensus is reached. If a consensus is not apparent, a poll and a voting session will be proposed to proceed. All discussions and conflicting arguments should be registered and addressed to the community through further publications to open the discussion and be able to incorporate other perspectives until we reach a consensus. We already use polls to vote for different matters that arise within our community; people are open to using this tool to exchange opinions. Voting can be anonymous if needed to avoid further conflict.

Communication and dissemination: We already have a shared space with shared documents (Google Drive and GitHub) and a Slack channel where the IDT members exchange daily in a more informal setting. This environment is the embryo of our stakeholders' network, which can be developed further with the progress of the project and the next IDT workshop and stakeholder assessment meeting. The IDT members come from all over the world. Alternative time slots for online meetings will be proposed to accommodate everyone. Dissemination of the work at conferences and meetings of relevant communities, like the Disease Maps Community, the COMBINE community, and the EDITH -CSA community.

Expected meeting frequency: All members meet online once every two months. Subgroups meet twice a month online, and there is an on-site meeting every six months for chairs, and everyone is available. There is also an on-site meeting for everyone on the first-year milestone at the IDT workshop.

Table 1. Deliverables development planning

Deliverable	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**M13**	**M14**	**M15**	**M16**	**M17**	**M18**
	Data curation and repository																	
D1. Literature repository						***D1***												
D2. Model metadata								***D2***										

catalogue																		
D3. Model repository - Dedicated BioModels section																		*D3*
	Communication and Dissemination																	
D4. IDT git and webpage										*D4*								
D5. IDT virtual 1-day workshops				*D5*			*D5*			*D5*			*D5*					
D6. IDT Summer school																*D6*		
	Recommendation document																	
D7. Building IDTs best practices Recommendation document																		*D7*

Adoption Plan: A specific plan for adopting or implementing the WG Recommendation and other outcomes within the organisations and institutions represented by WG members and plans for adoption more broadly within the community.

Who needs to adopt the Recommendation?

The WG Building Immune Digital Twins aims to make immune digital twin technology a reality. Our primary purpose is to bring together researchers across disciplines for activities ranging from extended active teamwork on specific immune digital twin projects, webinars, workshops and tutorials organisation, new collaborative projects and collaborations on an international level through relevant funding calls. We also aim to produce a written document suitable for publication that will detail the state of the art and essential milestones of an IDT roadmap, highlighting its scientific, technical, and organisational challenges.

Digital Twins can be a key technology for personalised medicine at different "levels": generic, population-specific, and subject-specific. To build a Medical Digital Twin (MDT), one would need to cross scales, propose hybrid methods, overcome computational costs, access data, integrate them, and build a system capable of receiving feedback and recalibrating. An MDT must combine computational models to simulate more than one biological process at a time. Appropriate methodological advancements are needed for efficient model analysis, integration, and calibration. Moreover, guidelines and best practices must be included for building, hosting, adapting, simulating, and maintaining the Digital Twins. The prospective WG will focus on these issues and try to tackle them by combining its members' multidisciplinary and complementary expertise.

The prospective WG will focus on the human immune system as a proof of concept and use case. Most of its members are active leaders and coordinators of relevant communities, so the WG can

lead in European and non-European initiatives. The WG's outputs will significantly impact the medical digital twin field, mainly focusing on the human immune system.

We aim to provide a guide of best practices for developing a FAIR environment for the building, development, hosting and deployment of IDTs. As mentioned, one of our aims is to develop standards for Digital Twin technology to facilitate the reusability and integration of computational models across scales and the technology development that would need to implement these standards to maximise interoperability. Many members of our prospective WG are active members of various Systems Biology communities (COMBINE, CoLoMoTo, SysMod, Disease Maps, Viral Pandemics, COVID-19 Disease Map project, SBML, SBGN communities, ELIXIR, etc.) and are fervent supporters of Open Access. We use publicly available repositories, such as GitLab or GitHub, Zenodo or Figshare, to share data and files, use Jupyter Notebooks to facilitate reproducibility and transparency where possible, and use FAIRDOMhub web-accessible registry for storing, sharing and publishing research results and projects. We are actively promoting FAIRness in science. **We want to focus on bringing FAIRness to the immune digital twin technology in a well-coordinated and open fashion.**

Initial Membership: A specific list of the WG's initial members and a description of its initial leadership.
We already held a 3-week workshop in May-June 2023 that had 90 participants from 18 countries, including France, the Netherlands, the USA, India, Spain, the UK, Norway, South Africa, Switzerland, Luxembourg, Greece, Denmark, Israel, Germany, Portugal, Belgium, Italy, and Sweden. We continue to hold Zoom meetings with the workshop participants, and our goal is to create a working group to continue our exchanges and interactions.
Our RDA group now has over 40 subscribed people.

Working Group Chairs

The WG Chairs are responsible for the work's quality, scope, timeliness, and usefulness. The Chairs ensure an effective organisational structure in place for the WG and that there are individuals, groups, and processes that can ensure progress in infrastructure, the development and editing of policy and written documents, and other tangible outcomes. The responsibilities of the WG Chairs, other leaders and members should be described in the WG Case Statement and followed during the operation of the Group. The chairs would not necessarily need to lead subgroups (or task forces), but they could. We need to identify some leadership (to take the lead on each deliverable) and form smaller groups to work on each deliverable. Some of the deliverables require a more defined profile. For example, for the webpage, we will need people with skills in web development, design and illustration; for the catalogue, we need trained curators; and so on. Everyone is welcome to join every group, but we need at least one person with the right skills for each task in each subgroup.

Group Chairs:

1. Dr Anna Niarakis, Full Professor of Computational Systems Biology, University of Toulouse III, Paul Sabatier, Centre of Integrative Biology, Toulouse & Lifeware, INRIA Saclay
2. Dr Reinhard Laubenbacher, Dean’s Professor of Systems Medicine, Director, Laboratory for Systems Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, University of Florida

3. Dr Gary An, Green and Gold Professor of Trauma and Critical Care, Vice Chair of Surgical Research, Department of Surgery, University of Vermont Larner College of Medicine
4. Dr Liesbet Geris, Professor of Biomechanics, Skeletal Biology & Engineering Research, University of Liège, Belgium, KU Leuven, Belgium
5. Dr Kristin Reiche, Head of Biomarker Center and Bioinformatics Unit,Fraunhofer IZI
6. Dr James Glazier, Professor of Physics, Adjunct Professor of Informatics and Biology and Director of the Biocomplexity Institute at Indiana U., Bloomington.

Perspectives

This RDA WG aims to lay the foundation for a rigorous implementation of use cases of digital twin technology focused on the Human Immune System.

Short-term goals: We will work on providing a repository of computational models focusing on the Human Immune System, and developing an open access metadata catalogue of them to help understand what is missing and were the future efforts should be directed. We will also work on putting together a Recommendation document that could serve as a “text book” for scientists aiming at a “clean and fast” implementation of IDTs in their research projects.

Medium-term goals: We will also focus on identifying the particular unmet needs in diagnosing and treating immune-mediated diseases to enhance the present tools for early identification. We will select a use case and focus on data collection and analysis for solving an existing clinical problem. The goal here is to showcase how we can improve outcomes using current prediction tools and personalising the current immunotherapies.

Long-term goals: We plan to create a digital platform/ portal to utilise existing datasets, collect new data to enhance current prediction tools and develop outcome-based therapies for patients with immune-mediated disorders.