RDA Working Group: Building Immune Digital Twins

Case Statement

Version 2.0, 30th July 2024

1. 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).

Introduction: Digital twins, customized 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. Personalized computational models also assist in applications ranging from drug development to patient-tailored treatment optimization. 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 modelers, 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 realization of personalized medicine. While computational modeling is an essential ingredient, it is far from the only one. However, developing a robust, shareable, and scalable data infrastructure for computational models that can be expanded to form medical digital twins enables the quick implementation of concrete steps, making it the main focus of this WG and its associated community building. As the recent report by the U.S. National Academies points out, it is currently challenging to distinguish what is aspirational and what is closer to actual deployment in the digital twin field. The report lays out several foundational problems that need to be solved along the way, many related to the modeling component.

The IDT WG plans to focus on some open questions regarding deploying Digital Twin technology for precision medicine, especially for diseases involving the human immune system. These questions and points that we want to address are of particular relevance to the RDA: 1) we recognize that computational models embody multiple tiers of knowledge and data and that providing an infrastructure for this data as a shared data resource is essential in fostering a scientific community aimed at developing medical digital twins, 2) achieving this goal is consistent with the overarching theme of the RDA by establishing standards and guidelines by which such data and knowledge can be stored, accessed and added to in a fashion that is compliant with FAIR Principles and 3) recognizing that the construction of medical digital twins that expands beyond the computational models, it is to the benefit of the nascent medical digital twin community to be engaged in the broader activities of the RDA with respect to the additional data resources needed to develop and implement medical digital twins. Given the potential biomedical applications of digital twins, our WG has chosen to focus on a particular subset of biology, the human immune system - involved in numerous biological processes in health and disease. We hope that

developing the basic data infrastructure for Immune Digital Twin development can serve as an example that can be expanded to other biologically relevant applications.

Deliverables and Milestones: We have identified the following deliverables as necessary components for developing Immune Digital Twins. For each Deliverable, we list specific Milestones that will be met within the 18-month timeframe:

- **Main Deliverable 1. Literature repository:** We will create a series of open-access data and model repositories to form a shared community resource to facilitate the development of Immune Digital Twins. We will create data structures for open-access metadata libraries for the types of data objects needed to develop Immune Digital Twins. These libraries include curated literature relevant to the human immune system, including an index of existing models and their associated metadata that model the human immune system. The creation of these data structures will include the initial development of ontologies relevant to the development of Immune Digital Twins. 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 in an expandable and adaptable format. We aim to have at least 100 articles in the library of relevant literature accompanied by the appropriate curated metadata by the end of 18 months. This deliverable will inform Deliverable 2 and Deliverable 3 (final recommendation).
    - **Milestone 1. :** Reaching 50 curated scientific papers relevant to developing digital twins for immune-related processes in the human body.
    - **Milestone 2. :** Reaching 100 curated scientific papers relevant to developing digital twins for immune-related processes in the human body.
- **Main Deliverable 2. Model repository and Model metadata catalog:** The IDT-developed resources will be linked to relevant Biomodels and Virtual Human Twin resources by creating appropriated IDT-tagged sections. We will use our GitHub website (https://immunedt.github.io/) and repository (https://github.com/ImmuneDT) to host the WG resources. The collaborative website and git will serve as our centralized resource.
    - **Milestone 1a:** We will create an interface between our Git and Biomodels and the Virtual Human Twin infrastructure to create a collection of models focusing on the Human Immune System. This model collection will be in concert with the curated open-access catalog and metadata of Deliverable 1. We will create a sub-section using proper tags and the appropriate metadata, and we plan to have at least 50 models included by the end of 18 months.
    - **Milestone 2b:** A dedicated webpage hosted will contain all the relevant information about the project, the model/data, and the literature catalogs.
- **Main Deliverable 3. Building IDT best practices recommendation document:** 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. The first draft suitable for distribution will be produced by the end of the 18 months. We will perform a series of community-building activities to engage potential collaborators and facilitate the development of the multidisciplinary research teams needed to develop Immune Digital Twins. At the same time, these events will provide opportunities. This document will be put forward for official endorsement and community review.
    - **Milestone 3a: Kick-off meeting for writing the recommendation/ best practices document:** The chairs and more senior members of the WG will discuss and exchange the document's structure and pinpoint essential aspects that should be included in the recommendation article. They will also decide on different chapters and share the workload depending on interest and expertise. They will also plan writing activities

within a 6-month window.

- **Milestone 3b:** The working group will meet to assess the writing progress, the possible new literature and achievements in the field that would need to be implemented and propose a plan within a 5-month window to achieve the first draft of the recommendation document. This will allow us to identify potentially missing expertise in specific areas and the need for external contribution. We could also reach out to the various systems biology communities for their input regarding areas such as FAIRness, ontology and standard development, ethical aspects, and regulatory policies, and increase the inclusivity of the WG.
- **Milestone 3c:** We aim to have the first draft of the recommendation document ready by month 13. This will leave us enough time for discussions, improvements, and exchanges between all stakeholders. The goal is to provide a document that will be useful, detailed, and quickly adopted. Hopefully, by then, we will also be able to include tangible use cases as proof of concept.
- **Milestone 3d:** Document refinement session during the workshop activities. We plan to dedicate at least one day for an in-person meeting to refine and complete the recommendation document. This meeting can be organized either as a stand-alone working day, as a satellite event of the planned workshop, or as a collective activity during the workshop. The aim is to have a satisfactory version of the recommendation document that can be submitted for community review and endorsement. We will make different versions of the draft available via Zenodo and encourage contributions from other RDA groups and members. The milestone is planned for month 15, which will leave at least 3 months for community review and ensure the document's endorsement within the 18-month lifespan of our WG.

2. Value Proposition

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

Innovation and groundbreaking research: Digital Twins can be a crucial technology for personalized 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 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 personalized 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 catalogs, 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 catalog 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 democratize 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 personalized therapies, faster diagnosis, and improved outcomes. On a global level, this can accelerate new drug development, address personalized 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. For example:

1. This will provide greater precision in characterizing the specific immune profiles and associated dynamics for chronic inflammatory diseases such as osteoarthritis, rheumatoid arthritis, and inflammatory bowel disease. This increased descriptive and predictive detail can help identify which type of therapy best suits an individual patient.
2. Since digital twins represent a data link between the real world and the virtual one, simulations with digital twins can provide insight into the types of sensors/diagnostics needed to potentially update a particular individual's condition in real-time.
3. The digital twin concept, which can involve the addition of control modalities and guidance, is particularly well-suited to capturing and potentially treating acute disorders of inflammation and immunity, such as sepsis or cytokine-release syndrome.

FAIR - Open access - data sharing - visibility and usefulness for the broader community
The IDT WG members will strive to promote and -when possible and relevant- align their work to:

- The FAIR Data Principles: Findable, Accessible, Interoperable, and Reusable
- TheTRUST Principles for Data Repositories: Transparency, Responsibility, User focus, Sustainability and Technology.
- The CARE Principles for Indigenous Data Governance: Collective Benefit, Authority to Control, Responsibility, and Ethics.
- The RDA Guiding Principles: openness, consensus, inclusiveness, harmony, community-driven, non-profit, and technology-neutral.
- The RDA Code of Conduct**.**

We will also collaborate with relevant Systems Biology communities (biocuration, modeling, standard and ontology development, etc.) to ensure the relevance, coherence, feasibility, and usability of our deliverables and maximize the adoption and implementation of the created resources and documents.

Our collaboration with other RDA groups and Systems Biology communities will also help with the sustainability and updating of the resources.

3. Engagement with existing work in the area

A brief review of related work and plan for engagement with other activities.

A platform for exchanging ideas, data, and expertise: Our WG aims to provide a safe space for scientists from different backgrounds, such as immunologists, biologists, engineers, bioinformaticians, biocurators, modelers, 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 organized 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 is the core of our prospective WG. We organize frequent workshops, tutorials, and webinars to communicate and exchange best practices across systems biology communities and boost transparency and reproducibility in computational modeling in life sciences (see Annex). We organize 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:

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 standardization 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 maximize its value to society. There is no existing WG at the RDA currently working on this emerging topic of immense value for personalized 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 personalized care," in February 2022. It addressed the challenges of Digital Twins for Health (DTH) and the stakeholders needed to address them. Additional RDA groups that are sources for potential collaboration include the FAIR for Machine Learning (FAIR4ML) Interest Group, the multi-omics metadata standards Working Group, and the Artificial Intelligence and Data Visitation (AIDV) Working Group, all of which address topics that will be integral to the development and maintenance of medical digital twins. **We genuinely believe that our prospective WG can complement the work of these existing Working/Interest Groups and provide a complementary space for further advances in emerging technology, personal data, and personalized care.**

4. UN Sustainable Development Goals (SDGs)

Contribution of the IDT RDA Working Group to the United Nations' Sustainable Development Goals (SDGs).

Goal 3: Good Health and Well-being: The project directly contributes to enhancing health outcomes by creating advanced medical digital twins that model the immune system. This technology can transform personalized medicine by providing individualized treatment optimization 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 recognizes 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 personalized 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.

5. Work Plan

A specific and detailed description of the IDT RDA WG modus operandi.

Brief description of the objective: 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 also aim to 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. Given the inherently translational and patient-facing nature of IDTs, it will be essential that these solutions comply with the principles of FAIRness in handling the data needed for IDTs, and also address the issues of equity, diversity, and security inherent in the deployment of IDTs. We will create intermediate documents for every subgroup to monitor progress and exchange between the groups working on different deliverables. A deliverable and milestones 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, could enhance visibility and coordinate advancements.
During the WG's lifespan, we will organize at least three virtual events to discuss open problems and steps toward solving them. By the end of the 18 months, we will provide at least two virtual webinars that will inform of our activities and results. We will also organize a follow-up to the three-week Institut Pascal workshop which took place in Paris in 2023. Several possible venues, including the Institut Pascal, are available for a date around spring 2026.

Working Group Chairs and Task Managers: The WG Chairs are responsible for the work's quality, scope, timeliness, and usefulness. The Chairs ensure an effective organizational 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 catalog, 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.

Expected meeting frequency: All members meet online monthly to arrange additional meetings when needed. Subgroups meet monthly 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.

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. Noriko Hiroi, Professor, Kanagawa Institute of Technology/Visiting Researcher, Keio University, Japan (New Chair)
3. Mohit Kumar Jolly, Professor, Indian Institute of Science, Bangalore, India (New Chair)

4. 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
5. 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
6. Dr Liesbet Geris, Professor of Biomechanics, Skeletal Biology & Engineering Research, University of Liège, Belgium, KU Leuven, Belgium
7. Dr Kristin Reiche, Head of Biomarker Center and Bioinformatics Unit,Fraunhofer IZI
8. Dr James Glazier, Professor of Physics, Adjunct Professor of Informatics and Biology, and Director of the Biocomplexity Institute at Indiana U., Bloomington.

Additionally to Prof Hiroi, Japan, and Prof Kumar Jolly, India who accepted, an invitation was also sent to :

1. Osbaldo Resendis Antonio, Professor, National Institute for Genomic Medicine at Mexico City, INMEGEN, Mexico

to diversify the membership of the WG.

6. Adoption Plan

A specific plan for adopting or implementing the WG Recommendation and other outcomes within the organizations 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 to webinars, workshops, tutorials organization, 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 state-of-the-art and essential milestones of an IDT roadmap, highlighting its scientific, technical, and organizational challenges.

Digital Twins can be a crucial technology for personalized medicine at different "levels": generic, population-specific, and subject-specific. To build a Digital Twin of the human immune system, 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 IDT 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 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 that 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, as well as the technology development needed to implement these standards to maximize 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 way.**

All produced material, catalogues, metadata, repositories, and libraries will be curated and shared openly with the community.

Sustainability will be achieved through collaboration with structures such as BioModels and the EDITH platform, as well as collaboration with RDA IGs and WGs, ensuring the long-term viability of our work. BioModels (https://www.ebi.ac.uk/biomodels/) is a repository of mathematical models of biological and biomedical systems. It hosts a vast selection of existing literature-based physiologically and pharmaceutically relevant mechanistic models in standard formats. Together, we will work on creating a sub-collection focused on the Human Immune System, using the appropriate tags and the curation system that BioModels uses so that our collection is fully compliant with the repository. BioModels is supported by the European Bioinformatics Institut (EBI), and is one of the most popular repositories in Systems Biology. Likewise, we are collaborating with EDITH (https://www.edith-csa.eu/), to make sure that our efforts are compliant with the European initiative for vitual human twins, and we have submitted a request to become an official use case of the EDITH consortium (https://www.edith-csa.eu/call-for-use-cases/), and be included in the EDITH catalogue and federated repository.

We also plan to work closely with our facilitators of the RDA TIGER services, to identify RDA WGs with similar interests and pursuits, and available structures (ontology efforts, data sharing recommendations, metadata specifications) that we could adopt to a) accelerate the progress towards our milestones and deliverables, and b) create communities and join forces with existing RDA WGs to ensure that our work is relevant, timely and coherent with other efforts.

Finally, we plan to seek external funding where possible, to continue working on the IDT field well beyond the 18 months period.

Using the produced material of our WG for educational purposes, is also a way of ensuring sustainability and community maintenance.

7. Initial Membership

A specific list of the WG's initial members and a description of its initial leadership.

Initial members: We already held a three-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 hold Zoom meetings, use our Slack channel almost daily, and produce working shared documents. Dr Anna Niarakis also sends an IDT Newsletter bimonthly to over 100 recipients.

Our RDA group now has over 50 subscribed people, and we aim to increase this number once fully endorsed.

8. 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 catalog to help understand what is missing and where future efforts should be directed. We will also work on putting together a Recommendation document that could serve as a "textbook" 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 to solve an existing clinical problem. The goal is to showcase how we can improve outcomes using prediction tools and personalizing the current immunotherapies.

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

ANNEX

Relevant literature published by IDT members

Here are some examples of collaborative publications among many Systems Biology communities:

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, 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*
3. *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.*
4. *A Niarakis, M Ostaszewski, A Mazein, I Kuperstein, M Kutmon, et al., Drug-Target identification in COVID-19 disease mechanisms using computational systems biology approaches, Front. Immunol. Sec. Systems Immunology; Volume 14 - 2023 | doi: 10.3389/fimmu.2023.1282859*
5. *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*
6. *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

7. *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*
8. *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*
9. *Rodríguez Martínez et al., Computational modeling of immunological mechanisms: From statistical approaches to interpretable machine learning, ImmunoInformatics,2023,100029, ISSN 2667-1190,doi.org/10.1016/j.immuno.2023.100029*
10. *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8170388/*
11. *https://www.embopress.org/doi/full/10.15252/msb.20209982*

Mini symposia organisation:

a. *IDT mini-symposium on July 15th from 9:00 a.m. to 12:00 p.m. in Amsterdam. Building Immune Digital Twins mini symposium - Google Docs*
b. *JOBIM mini-symposium: Digital Twins for Human Health – The Role of Bioinformatics and Computational Biology - June 27, 2024 - 16h30 - 18h30 https://jobim2024.sciencesconf.org/data/3B_english_Programme_Symposium_DTs_JOBIM.pdf*
c. *FEBS Digital twins for precision medicine symposium, July 2nd https://2024.febscongress.org/program#enlaceCabeceraDia10_1*

Table 1. Deliverables, milestones, and activities of dissemination and communication development planning

Deliverable	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**	**M13**	**M14**	**M15**	**M16**	**M17**	**M18**
	Deliverables and Milestones regarding Data curation																	
D1. Literature repository										***D1***								
Milestones			***M1 a***				***M1 b***											
	Deliverables and Milestones regarding the Model Repository																	
D2. Model repository - Model metadata catalog															***D2***			
Milestones								***M2 a***				***M2 b***						

	Deliverables and Milestones regarding the Recommendation document																		
D3. Building IDTs best practices Recommendation document																			***D3***
Milestones		***M3 a***						***M3 b***					***M3 c***			***M3 d***			
	Communication and dissemination activities																		
Virtual Events		***E1***			***E2***			***E3***				***E4***	***E5***						
Two weeks workshop																***W1***			