Information models in healthcare: CAR T-cell therapy

Veronika Kostrouchová[1]

[1] *Prague University of Economics and Business, W. Churchill Sq. 1938/4, Prague 3, Czech Republic*

Abstract

The evolution of CAR T-cell therapy in cancer treatment represents a significant advancement in precision medicine, necessitating robust models for effective implementation. This article explores various modeling approaches to CAR T-cell therapy, ranging from high-level conceptual frameworks to detailed business process models. This work introduces three primary models: the Ontological Model, the PURO Model, and the MMABP Model. Each model serves distinct purposes: the Ontological Model provides a high-level framework of the domain, establishing foundational concepts and relationships. The PURO Model offers a flexible, graphical ontology sketching tool that enriches the initial conceptualization into detailed operational frameworks. Lastly, the MMABP Model delves into the specifics of the business process, detailing stages and interactions within the treatment workflow. These models collectively foster a comprehensive understanding—from theoretical underpinnings to actionable insights—enhancing the management and efficacy of CAR T-cell therapy.

Keywords

CAR T-cell therapy, MMABP, process map, conceptual model, PURO, ontoUML

1. Introduction

1.1. The goal

The goal of this work is to showcase different approaches to modeling a specific cancer treatment process (CAR T-cell therapy) from the most general to a more detailed business process model and then eventually leading to a particular application using a decision engine as a long-term vision of where to take this initiative. The use of these models represents a progression from a general to a more focused view. Each model serves a specific purpose and level of detail:

The Ontological Model provides a high-level, generalized view of the domain, outlining key concepts and their relationships. It sets the broad context and foundational understanding. An ontological model is a structured representation of knowledge in a specific domain. It defines the concepts, entities, and relationships within that domain, providing a framework to understand and analyze complex systems or processes.

The PURO model serves as a flexible, graphical ontology sketching tool that allows for an initial high-level conceptualization, which can be elaborated into more detailed and operationally significant ontological frameworks.

The MMABP (Methodology for Modeling and Analysis of Business Processes) Model offers a more detailed view, specifically focusing on the process aspect. It breaks down the general concepts into specific stages and steps, providing a clearer picture of the flow and interactions. It provides a structured approach for analyzing and representing business processes and involves identifying, documenting, and analyzing the sequences of activities within an organization to achieve specific business outcomes.

BIR-WS 2024: BIR 2024 Workshops and Doctoral Consortium, 23rd International Conference on Perspectives in Business Informatics Research (BIR 2024), September 11-13, 2024, Prague, Czech Rep.

kosv08@vse.cz (V. Kostrouchová)

0000-0001-8417-6721 (V. Kostrouchová)

This approach allows for a comprehensive understanding that starts from a broad theoretical base and narrows down to specific, practical applications. The following research questions were set to guide the study and focus the analysis: 1. What are the key concepts and relationships within the domain of CAR T-cell therapy? 2. What are the detailed stages and interactions within the CAR T-cell therapy workflow, and how does the MMABP model improve the understanding and optimization of these processes? 3. What potential challenges and outcomes can be identified in the CAR T-cell therapy process through comprehensive modeling, and how can these insights improve patient management and clinical decision-making?

1.2. Background

CAR T-cell therapy represents a significant leap in cancer treatment, shifting towards precision medicine and immunotherapy. It utilizes the body's immune system, specifically engineering T cells, to target and destroy cancer cells. This method is part of a broader category of targeted therapies, which include monoclonal antibodies and tyrosine kinase inhibitors, all designed to interfere with specific cancer cell processes. Immunotherapies like checkpoint inhibitors and cancer vaccines aim to boost the immune system's natural ability to fight cancer, marking a transformative approach in oncology.

Modeling CAR T-cell therapy is crucial for several reasons. It allows for more detailed understanding and representation of this complex treatment's mechanisms. Modeling aids in identifying potential challenges, side effects, and outcomes of therapy, facilitating the development of more effective strategies and management approaches. Furthermore, it supports the communication of complex information to researchers, clinicians, and patients, enhancing collaboration and informed decision-making in cancer treatment.

The following flow chart covers the major steps involved in CAR T-cell therapy, from initial patient reception to follow-up. It starts with a relapse of the patient's disease and proceeds with a referral from the patient's oncologist leading to a registration with a clinic that provides CAR T-cell therapy. Eligibility is screened, and upon consent, an appointment is assigned. The treatment phase includes cell collection through leukapheresis, cell manufacturing and proliferation, and then quality checks before patient preparation for the infusion of CAR T-cells (this step can include chemotherapy for some patients). Post-infusion, the patient is monitored, followed by care and response assessment. The flow chart was created based on the treatment process as outlined by the National Comprehensive Cancer Network[1].

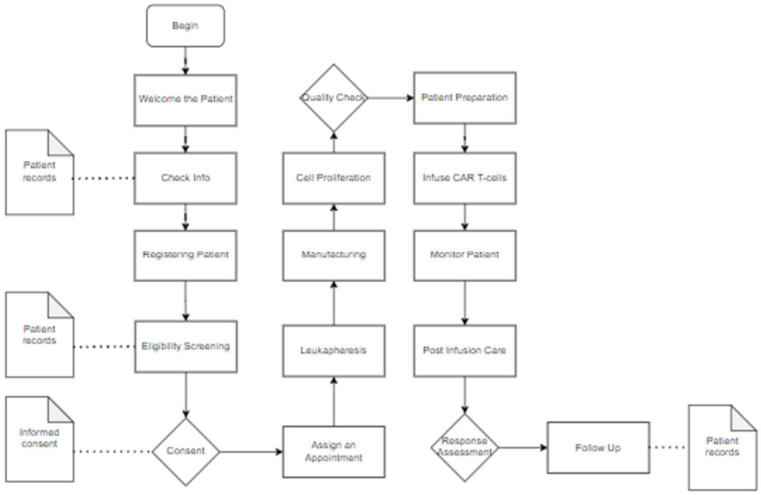

Figure 1: Simple CAR T-cell Therapy Treatment flowchart.

This above treatment flow chart is obviously lacking crucial information. One of its main disadvantages is that it does not consider the various other possible outcomes besides successfully continuing the process. In clinical or treatment processes, particularly for complex procedures like CAR T-cell therapy, it's essential to include potential contingencies and alternative outcomes at each stage. Potential failures at key steps should also be taken into account, as they realistically represent risks and possible need for intervention.

It is also important to understand that typically CAR T-cell therapy is only recommended after the patient has undergone previous unsuccessful treatments. The following diagram outlines the process flow specifically related to Myeloma. It encompasses different stages, starting with the diagnostic workup and progressing through various treatment pathways. The diagram details the clinical decision-making process and the potential referral for CAR T-cell therapy based on the patient's specific disease progression and response to other treatments, based on the National Comprehensive Cancer Network guidelines for Multiple Myeloma, Version 4.2024[2].

Modeling clinical processes holds the potential for automation in practical applications. Automating parts of the process could streamline the coordination of treatment phases, improve the efficiency of patient data management, and ensure timely interventions. This would be especially beneficial in complex cases where multiple treatments have been tried, and quick decision-making is crucial. Integrating these models into healthcare systems could enhance adherence to treatment protocols, reduced errors, and optimized patient outcomes, aligning with the best practices set forth by the National Comprehensive Cancer Network guidelines.

Figure 2: Treatment diagram for Myeloma based on the NCCN guidelines.

2. Modeling approaches and integration of models

2.1. Methodology

In this section, the process and importance of the models is described. The process of creating an ontological model involved defining the scope (determining the boundaries and focus of the domain being modeled. As outlined in the article “Semantics, Ontology and Explanation” by Giancarlo Guizzardi and Nicola Guarino[3], an important part is a process they call "ontological unpacking," which focuses on revealing the ontological commitments of conceptual models to enhance understanding and interoperability. The article supports defining the domain of interest through its emphasis on identifying the relevant domain for which the ontology is to be developed, particularly in ensuring that the ontology supports semantic interoperability tasks); identifying key concepts and entities (enumerating the fundamental elements within the domain) and establishing relationships (linking concepts and entities to show how they interact or are related).

The domain of interest of the project is focused on CAR T-cell therapy. This sets the primary domain of the ontological model. The boundaries of the domain are medical aspects (types of cancers and subtypes), the treatments (classical and advanced treatment), and the outcomes and side effects of the treatment.

Using OntoUML, as mentioned in the article, allows for the representation of the ontology in a formal, machine-readable format. OntoUML is designed to provide semantically rich modeling primitives that are aligned with ontological distinctions, which supports the creation of more precise and expressively powerful ontological models. OntoUML is a specialized modeling language aimed at capturing and representing ontological distinctions in conceptual models. It draws heavily from the Unified Foundational Ontology (UFO), which provides a rich set of ontological categories and relations. OntoUML distinguishes among various class stereotypes to represent different types of universals that exist in reality. These stereotypes are grouped into three main categories: Sortals, NonSortals, and Aspects[4]. The conceptual model in this article concerns the following sortals:

Sortals are foundational for categorizing things that have a clear identity criterion, meaning they can be individuated and counted. They include:

Kind: The most general type of thing in a domain of interest. Kinds provide the principle of identity for their instances. An example from the ontological model is Person.

Subkind: A specialization of a kind, where the instances still comply with the identity principle of the kind but differ in some specific characteristics. For example, Multiple Myeloma is a subkind of the kind Myeloma.

Phase: Represents stages or temporal segments of an individual's existence that are mutually exclusive and exhaustive for a particular kind. For example, Healthy person and Unhealthy person could be phases of the kind Person.

Role: Temporary roles that instances of kinds or subkinds can assume during certain relations or situations, without altering their identity. For example, Oncological patient as a role people (Person) can assume.

Relator: Represents relational entities that mediate associations between two or more individuals, providing the basis for their connection. An example is the Diagnosis that links a Oncological patient to a Treatment.

The subsequent model is the PURO model. PURO is introduced as a graphical ontology sketching approach that utilizes a first-order axiomatization. It employs a set of primitives akin to those used in the Web Ontology Language (OWL), but with greater flexibility. In PURO, elements such as objects, types, relations, and attributes are treated as foundational ontological distinctions rather than merely as data modeling options. This helps in achieving a higher semantic quality of models. Furthermore, PURO is used for creating initial sketches that can later be developed

into more rigorous reference ontologies in languages like OntoUML or into semantic web vocabularies in OWL. Apart from its use in formal ontology engineering, PURO also serves as a standalone graphical language for mapping out real-world situations, which is particularly useful in discussions and explanations among human users [5]. A web-based tool called PURO Modeler supports the PURO methodology, providing functionalities to transform sketches into different ontology formats or to lift them to more complex models.

The final models are the MMABP models. According to the Philosophical Framework for Business System Modeling [6] the development of an information system should be grounded in real-world facts that exist independently, thus ensuring that the system effectively mirrors the intricacies and operations of the business it is designed to support. The framework proposes a four-dimensional model of the business system, which includes real world modality, real world causality, model of collaboration and model of acting.

The real world modality represents the static view of being, detailing the system of real-world objects and their potential relationships (the conceptual model), the model of Collaboration captures the static view of behavior, illustrating the system of business processes and their relationships (the process map). According to Repa, the real world causality focuses on the temporal view of being, showing possible states in the life cycle of specific real-world objects and the transitions between the (object life cycle). MMABP models help in optimizing and standardizing business processes for efficiency and effectiveness. According to the article a process map is a high-level representation of the interactions and relationships between different business processes within an organization. It provides a global overview of the entire system of processes, highlighting how they collaborate to achieve defined business goals.

2.2. Ontological model

The conceptual model reflects some of the principles discussed in the article "Semantics, Ontology, and Explanation" by Giancarlo Guizzardi and Nicola Guarino. The model uses a variety of ontological distinctions such as kinds, phases, roles, and relators, which are consistent with the ontological theory of relations as outlined in the paper. The main concepts identified in the CAR T-cell therapy treatment domain were cancer types, treatments, mechanisms of action, patient characteristics and treatment outcomes.

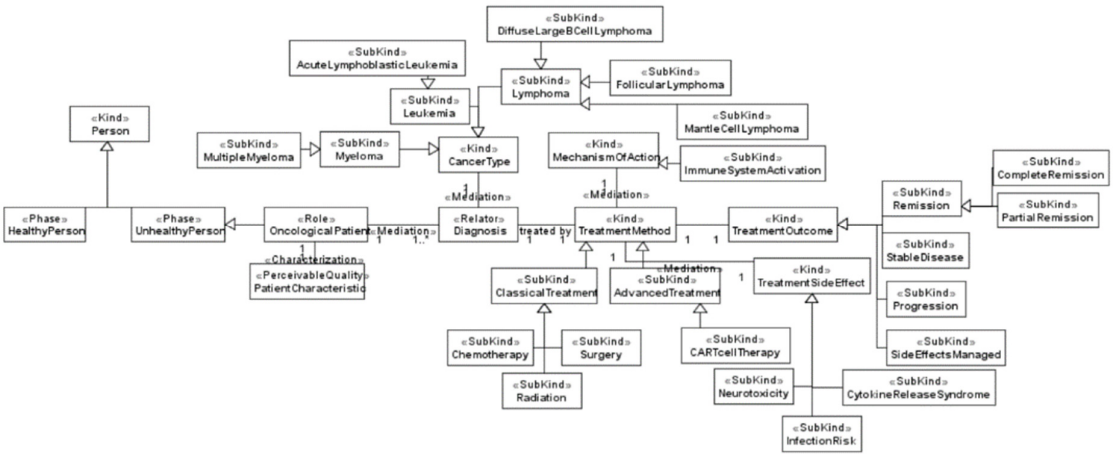

Figure 3: Ontological model made using Menthor Editor

Using OntoUML stereotypes, these concepts have been classified:

CancerType as kind: Represents general categories of cancer that provide the identity principle for their instances.

Treatment as kind: Diverse treatment methods form distinct categories with a clear identity. ClassicalTreatment and AdvancedTherapy as subkind: These are specific types of treatment methods, inheriting the identity criteria from TreatmentMethod but differing in certain characteristics.

In the context of a CAR T-cell therapy ontological model, categorizing Treatment into subkinds ClassicTreatment and AdvancedTreatment allows for a distinction between more traditional forms of cancer treatment (such as chemotherapy, radiation, and surgery) and newer, more innovative therapies like CAR T-cell therapy. CAR T-cell therapy, given its novel approach to leveraging the body's immune system to fight cancer, falls under AdvancedTreatment. This differentiation helps in understanding and organizing the range of treatment options available for different cancer types within the model.

MechanismOfAction as kind: Different mechanisms by which treatments work represent distinct categories.

TreatmentOutcome as kind: Outcomes of treatments form distinct categories with clear identity principles.

In this model focused on CAR T-cell therapy, possible subkinds of TreatmentOutcome include Remission, Stable Disease, Progression, and SideEffectsManaged. Remission indicates that the cancer signs and symptoms are reduced or absent. Stable Disease means the cancer has not significantly changed. Progression indicates that the cancer has grown or spread. Side Effects Managed implies that any adverse reactions to the treatment have been successfully controlled. These outcomes can help in evaluating the effectiveness of CAR T-cell therapy for different cancer types.

TreatmentSideEffect is modeled as a separate kind with a mediation relationship to Treatment. This distinction is important because treatment outcomes and side effects are conceptually different aspects of the treatment process. Outcomes relate to the effectiveness of the treatment in addressing the disease, while side effects are unintended consequences of that treatment. By modeling TreatmentSideEffect as a separate kind with a mediation relationship to Treatment, the model can more accurately reflect the complexity of treatment processes, including both the intended effects (outcomes) and unintended adverse effects (side effects).

Regarding side effects, they are critical for understanding the full impact of treatment. The approach chosen includes a kind TreatmentSideEffect with subkinds representing specific side effects CytokineReleaseSyndrome, Neurotoxicity, and InfectionRisk. This allows the model to encompass the range of potential adverse reactions to CAR T-cell therapy, providing a comprehensive view of treatment implications.

Person is a kind with phases HealthyPerson and UnhealthyPerson indicating changes in state that do not alter the underlying kind. Patient is a role that a person can take on under certain conditions (being unhealthy). The element PatientCharacteristic has been modeled as a perceivable quality as it represents aspects of a patient that can be observed or measured, such as age, weight, or the presence of certain symptoms. Perceivable qualities are properties that can be attributed to an individual and can vary from one individual to another. Modeling patient characteristics in this way allows for a nuanced representation of the attributes that may be relevant to their treatment or diagnosis, consistent with the principles of ontological modeling.
Diagnosis is a relator that establishes specific relations between entities like a Patient, a CancerType, and Treatment.

Next, the relationships between these concepts were established using OntoUML's relation stereotypes: mediation connects CancerType to Diagnosis. This is a mediation relationship

because the diagnosis mediates the effect on the cancer type, mediation also connects Treatment to MechanismOfAction, indicating the method's mechanism.

A mediation relation is used to connect two entities that are existentially dependent on a third entity, which is often called a relator. This relator, in the healthcare context, could be a diagnosis, a medical construct that substantiates the relationship between a patient's condition and the method of treatment prescribed. The diagnosis is what mediates the relationship between an oncological patient and the treatment. The treatment is chosen based on the diagnosis, and the appropriateness or validity of the treatment method is grounded in the diagnosis. Without the diagnosis, the connection between the patient and the treatment method does not exist in a justified or medically sound way.

Association links the Diagnosis to the Treatment, and also links Treatment to TreatmentOutcome, showing the possible results of the treatment.

The specifics of the Mechanism of Action for CAR T-cell therapy can vary among different types of cancers such as Diffuse Large B-cell Lymphoma (DLBCL), Follicular Lymphoma, Mantle Cell Lymphoma, Multiple Myeloma, and B-cell Acute Lymphoblastic Leukemia due to the unique characteristics of the cancer cells in each disease. For example, the antigen target for the CAR T-cell therapy may be different, reflecting the distinct cell surface proteins found on cancer cells of each type. The model implies that while the overarching mechanism involves immune system activation, the precise pathway or target could differ based on the specific nature of the cancer being treated, affecting the design and application of the therapy for each cancer type.

This approach leverages OntoUML's capabilities to model the cancer treatment domain, providing clarity on the types of entities involved, their properties, and the complex relationships between them.

2.3. PURO model

The PURO model represents various entities and their relationships within a CAR T-cell therapy cancer treatment context. It includes different cancer types (Myeloma, Leukemia and Lymphoma), as well as an instance of Follicular Lymphoma (Pat1FL). CAR T-cell therapy (a subtype of Advanced Treatment) is connected to the cancer type subtypes through "treats" relationships, indicating these cancers can be treated by this advanced treatment. The type Patient has an instance Patient 1. Patient characteristics include previous treatment count and age, as these are key attributes that impact treatment choices. Overall, the model attempts to reflect the complexity and interrelated nature of patient characteristics, cancer types, treatments, status in cancer care. Contrary to the conceptual model, this model does not have TreatmentOutcome but rather DiseaseStatus. This model is only the starting point and it is planned to build upon this model in the future, as well as alter the conceptual model to reflect certain aspects that are and will be uncovered using PURO.

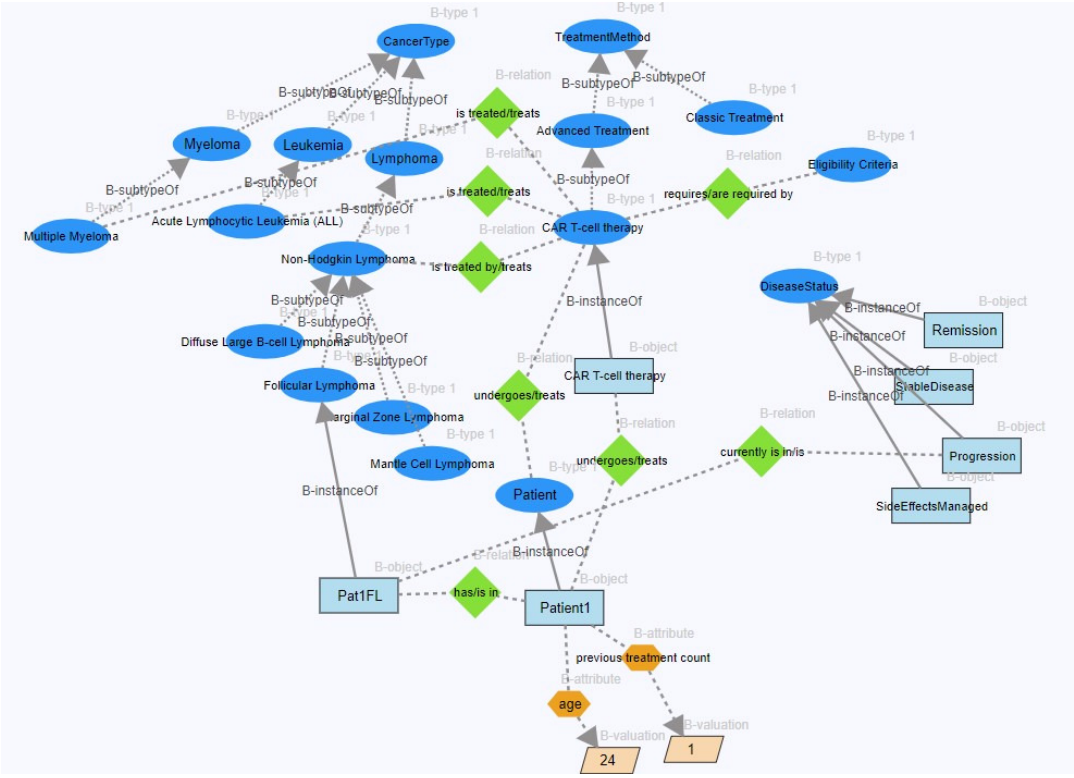

Figure 4: PURO model made using PURO Modeler.

2.4. MMABP model

The Process map offers a system-level perspective, showing the constituent processes and their relationships and emphasizes the interrelationships between processes, showing how they work together. Process maps help distinguish between key and support processes based on their roles in the business system. These models are essential for understanding the broader context and collaboration of processes within a business system, ensuring that all processes align with the organization's goals and function cohesively.

Creating a process map for CAR T-cell therapy treatment involves visualizing the high-level workflow of the entire treatment process, from the start event of the relapse and the patient referral to the actual CAR T-cell therapy process. The objective of this process map is to outline the end-to -end CAR T-cell therapy process. The models were created using TeamAssistant software after reviewing extensive literature on CAR T-cell therapy [7][8][9][10][11][12] and building upon the research of my master thesis[13].

The process begins with the patient's relapse or referral from the patient's oncologist (while it could be argued that these events would follow one after the other, it could also be argued that the patient could have a relapse and contact the clinic without having the referral). The CAR T-cell therapy process involves several supporting processes (Medical History Evaluation, Laboratory Tests, Chemotherapy, Pre-infusion Monitoring, the Infusion procedure and Monitoring during and after infusion). After the starting event is the Patient registration, following which is the eligibility screening that is done via the supporting processes Medical History Evaluation and Laboratory Tests, once these are completed the Patient Screening Assessment determines whether the patient is eligible or not eligible for treatment. If eligible for treatment, the clinic must obtain the patient's consent for treatment, if obtained the clinic can schedule an appointment for the treatment. After the appointment is scheduled, there are several possible progressions: the favorable one (that the patient shows up for the treatment, and thus

the process leads to leukapheresis), or the less favorable version (that the appointment has to be rescheduled either due to the patient or due to the clinic) to the least favorable option (the patient not showing up for the planned appointment without rescheduling, leading to the final state Cancellation).

Leukapheresis can lead to three possible routes: leukapheresis being completed, the need to redo it (or reschedule due some circumstances that however allow the possibility of rescheduling) or a failure requiring an alternative treatment strategy. The next steps (manufacturing, cell proliferation and quality check) all have similar three possibilities: being unsuccessful and thus needing to repeat the leukapheresis (and scheduling the appointment to do so), being unsuccessful but with failure requiring an alternative treatment strategy or being successfully completed leading to the next step.

The successful quality check leads to Patient Check, this can lead to the patient having to undergo chemotherapy (which can also lead to the patient not being able to continue treatment) and being evaluated if still suitable further CAR T-cell therapy treatment. If the patient is suitable, the patient will be monitored pre-infusion, the patient can be ready or not ready for infusion (leading to treatment cancellation). If the patient is ready for infusion, what follows is the infusion process and simultaneously patient monitoring during and directly after the infusion. The infusion can have these possible outcomes: the patient has an acute reaction during the infusion leading to the treatment being stopped; the infusion being unsuccessful leading to treatment cancellation; the infusion and monitoring being successful leading to post treatment monitoring that can have three endings: a positive response to treatment, the patient having adverse effects (Cytokine release syndrome, neurotoxicity or other complications) or the patient having a relapse.

2.5. Analysis and results

The paper focuses on three types of models: the ontological model provides a high-level understanding of CAR T-cell therapy by defining key concepts and their relationships. The PURO model provides a different look at specific elements in CAR T-cell therapy, demonstrating how the patient, treatment methods, and outcomes interrelate. The process map offers a detailed view of the actual treatment process, breaking down the stages into more granular steps.

The ontological model helps clarify the kinds of categories and their ties that are assumed to exist for CAR T-cell therapy, the PURO model can serve as a tool for further ontological analysis. During the creation process of this model, it was discussed that a more detailed PURO model should be created in the future and also that a revised conceptual model should also be created, reflecting the truths unearthed through the PURO model. The process map specified each step of the CAR T-cell therapy, detailing possible outcomes (even those that are not typically mentioned in literature concerning CAR T-cell therapy).

The models give comprehensive insights into the therapy, illustrating the end-to-end process from the relapse to post-treatment monitoring. The models assist in understanding the therapy's workflow, identifying challenges as well as various outcomes, and ensuring optimal treatment strategies and answer the set questions of what are the key concepts and relationships within the domain of CAR T-cell therapy and what are the detailed stages and interactions within the CAR T-cell therapy workflow. The MMABP model improves the understanding and optimization of these processes by specifying each step along with assumed possible outcomes.

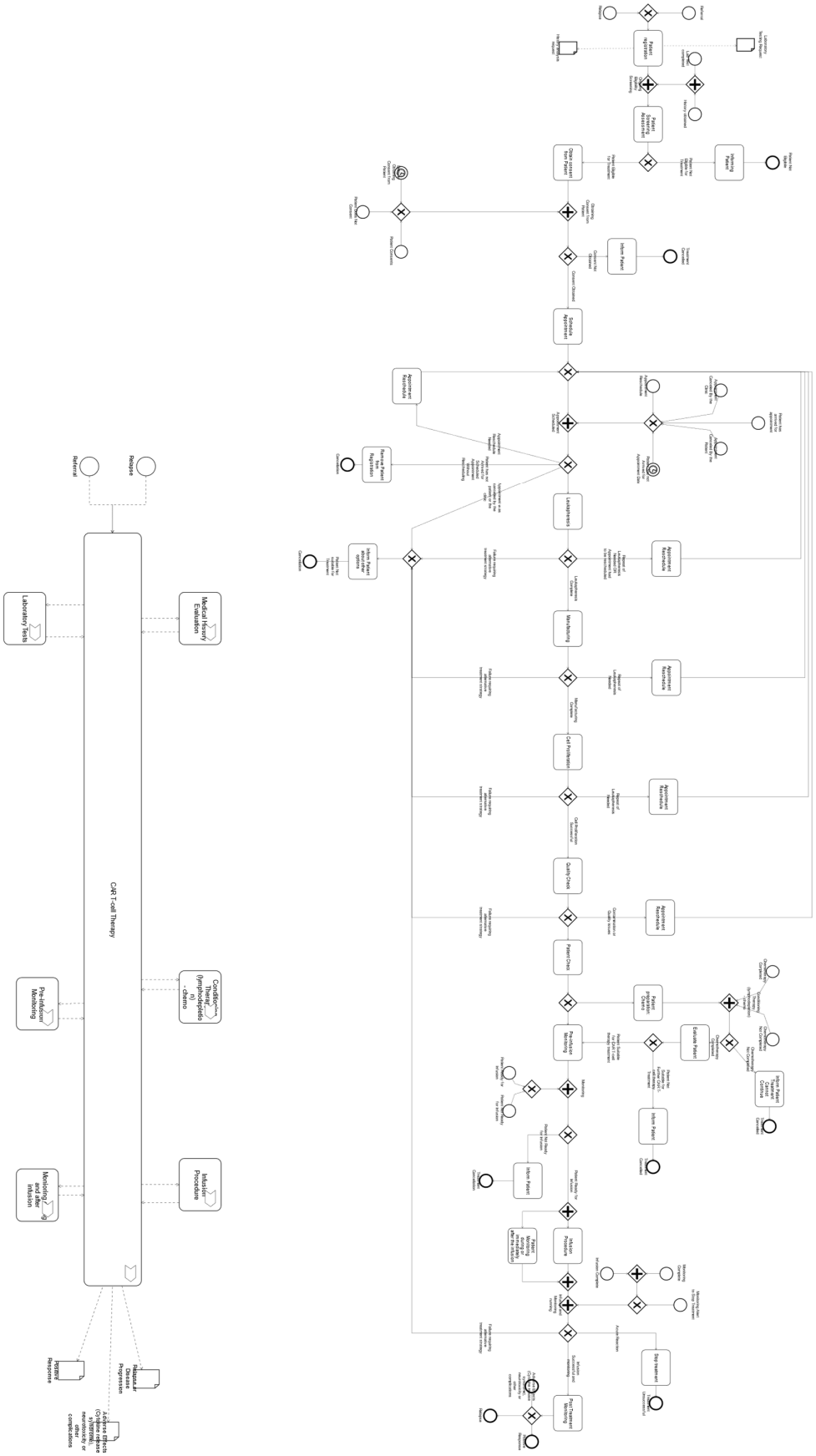

Figure 5: CAR T-cell therapy process map (left) and process (right) created using TeamAssistant.

3. Discussion and conclusion

3.1. Discussion

The different models analyzed in this article contribute to understanding the CAR T-cell therapy treatment process. The Ontological Model, PURO Model, and MMABP models each contribute to a comprehensive understanding of CAR T-cell therapy by providing distinct perspectives and levels of detail. While the ontological model provides a high-level conceptual framework that identifies the primary entities and relationships within CAR T-cell therapy and serves as a foundational framework by defining key concepts like patient, treatment types, and treatment outcomes, it also lays the groundwork for the more detailed models, ensuring a consistent conceptual base for all subsequent analyses. The PURO model offers a different view of the entities, relationships, and specific elements of CAR T-cell therapy. The Process Map provides a practical, visual guide to the workflow of CAR T-cell therapy. It translates the conceptual insights from the Ontological and PURO Models and the simple flow chart into actionable steps. It allows healthcare professionals to visualize the entire therapy process, identifying handoffs, bottlenecks, and areas for improvement based on the framework provided by the other models. The Ontological and PURO Models establish a clear conceptual and detailed framework, while the Process Map offers a visual translation of these frameworks into the actual workflow. Together, these models help understand the CAR T-cell therapy process from broad concepts to specific details, offering a holistic perspective for planning, analysis, and optimization. Using these models in conjunction provides a layered understanding of CAR T-cell therapy that can help refine the treatment process, enhance patient care, and improve outcomes.

3.2. Conclusion

Using multiple models to map out CAR T-cell therapy aids in efficiently managing the treatment process by clarifying the relationships between processes, understanding the therapy's mechanisms, and ensuring patient safety. These models form a basis for creating decision-making tools that can improve clinical outcomes.

The paper thus emphasizes the value of detailed process mapping and conceptual modeling to improve CAR T-cell therapy's management and decision-making. Using multiple models to map out CAR T-cell therapy aids in efficiently managing the treatment process by clarifying the relationships between processes, understanding the therapy's mechanisms, and ensuring patient safety. These models form a robust foundation for creating decision-making tools that can significantly improve clinical outcomes. The comprehensive nature of this approach—integrating ontological models, PURO models, and process maps—provides a multifaceted perspective that is essential for enhancing precision in treatment planning and execution.

This paper underscores the critical value of detailed process mapping and conceptual modeling to improve the management of and decision-making in CAR T-cell therapy. The insights derived from these models not only support current clinical needs but also pave the way for the development of advanced analytical tools that can predict treatment outcomes, customize patient care plans, and mitigate potential risks associated with therapy. The research questions addressed in this work aimed to clarify how fundamental concepts and relationships can be structured and understood within the context of CAR T-cell therapy, how the detailed modelling of the business process can provide clarity and enhance the workflow of the treatment and how the entire modelling approach aims to identity challenges, possible outcomes and improvements in patient management and decision-making process. The overall objective of integrating different modelling approaches provides a more detailed understanding of CAR T-cell therapy.

Moreover, the methodologies discussed herein have broader implications for other complex medical treatments and can be adapted to enhance systems in various therapeutic areas. Future

research should focus on refining these models through real-world data integration and exploring their applications in other contexts to validate their effectiveness and adaptability. It is imperative that the medical and research communities continue to collaborate in evolving these models, ensuring they remain relevant and responsive to emerging clinical challenges.

Acknowledgments. I would like to thank professors Václav Řepa and Vojtěch Svátek for guidance and discussions regarding the MMABP and PURO models.

Disclosure of Interests. The author has no competing interests to declare that are relevant to the content of this article.

References

[1] National Comprehensive Cancer Network, Immunotherapy Side Effects CAR T-cell Therapy, (2024). Accessed: April 13, 2024. [online] URL: https://www.nccn.org/patients/guidelines/content/PDF/immunotherapy-se-car-tcell-patient.pdf.

[2] National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Multiple Myeloma. Version 4.2024, (2024). Accessed: April 13, 2024. [online] URL: https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf.

[3] G. Guizzardi, N. Guarino, Semantics, Ontology and Explanation, (2023). doi:10.2139/ssrn.4673400.

[4] M. Suchanek, OntoUML Specification, (2018). Accessed: February 21, 2024. [online] URL: https://ontouml.readthedocs.io/en/latest/classes/index.html.

[5] V. Svatek, M. Vacura, PURO: Stretching a Rope between Ontology Sketching, Foundational Distinctions and Linked Data Vocabularies. (2024).

[6] V. Repa, Philosophical Framework for Business System Modeling. In: 2023 IEEE 25th Conference on Business Informatics (CBI). pp. 1–6. IEEE, Prague, Czech Republic (2023). doi:10.1109/CBI58679.2023.10187427.

[7] American Cancer Society, CAR T-Cell Therapy and Its Side Effects. Accessed: April 20 2023. [online]. URL: https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/car-t-cell1.html.

[8] W. Aiman, M. A. Ali, H. Zubair, S. K. Butt, M.Y. Anwar, M. Hamza, N. Nanjundaiah, V. S. Chemarthi, H. Shaaban, G. Guron, M. Maroules, F. Anwer, Advances in CAR-T Cell Therapy in Re-lapsed/Refractory Multiple Myeloma: A Systematic Review and Meta-Analysis of Clinical Trials in the Last Two Years, Clinical Lymphoma Myeloma & Leukemia, (2023) Vol. 23, S485–S486. doi:10.1016/S2152-2650(23)01427-1.

[9] M. Hong, J. D. Clubb, Y. Y. Chen, Engineering CAR-T Cells for Next-Generation Cancer Therapy. Cancer Cell, (2020), Vol. 38, no. 4, 473–488. doi:10.1016/j.ccell.2020.07.005.

[10] M. Jogalekar, R. L. Rajendran, F. Khan, C. Dmello, P. Gangadaran, B. Ahn, CAR T-Cell-Based gene therapy for cancers: new perspectives, challenges, and clinical developments. Frontiers in Immunology, (2022). Vol. 13, 925985. doi:10.3389/fimmu.2022.925985.

[11] M. Omar, P. Strati, L. Feng, R. Sun, A. Ayers, R. E. Steiner, R. Nair, C. Flowers, J. L. Ramdial, N. Saini, S. A. Srour, R. E. Champlin, P. Kebriaei, L. J. Nastoupil, M. A. Rodriguez, E. J. Shpall, Y. Nieto, J. Westin, S. S. Neelapu, S. Mandayam, S. Ahmed, Real-world analysis of safety and efficacy of CAR T-cell therapy in lymphoma patients with decreased kidney function, British Journal of Haematology (2023). doi:10.1111/bjh.19152.

[12] S. S. Raikar, L. C. Fleischer, R. Moot, A. Fedanov, N. Y. Paik, K. A. Knight, C. B. Doering, T. Spencer, Development of chimeric antigen receptors targeting T-cell malignancies using two structurally different anti-CD5 antigen binding domains in NK and CRISPR-edited T cell

lines, Oncoimmunology. (2018) Vol. 7, no. 3, e1407898. doi:10.1080/2162402X.2017.1407898.
[13] V. Kostrouchová, The Use of Technology Intelligence Processes in the Management of Research and Production of New Drugs, Diplomová práce. Vysoká škola ekonomická v Praze. Vedoucí práce Jan Černý, (2023).