A Digital Twins Approach for Oncologic Pharmaceutical Supply Chain

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***Abstract*—Oncological treatments are especially challenging due to the high degree of therapy personalisation that calls for the on-demand preparation of drugs and accurate timing in the distribution and delivery process. The suitability of the patient's condition to carry on with the ongoing therapy is monitored periodically and bootstraps the whole preparation of a new iteration of the treatment. This makes pharmaceutical supply chain management very difficult to optimise since it needs to be responsive to sudden change while efficient in terms of costs and usage of resources. In this paper, we identify the main challenges of the domain drawing from the available related works and the experience maturated in collaboration with a public cancer care and research institute. We then propose how Digital Twins could be used as a way to engineer a system to support the accurate tracking of such a complex reality to monitor effectiveness and efficiency, as well as collect data and support decision-making using predictions and simulations to optimise the overall process.**

***Index Terms*—Pharmaceutical Supply Chain, Digital Twins, Healthcare**

I. Introduction

Pharmaceutical supply chain (PSC) concerns the process of sourcing raw materials, manufacturing, distributing, and delivering medications to patients [1]. It is a complex process that includes various stakeholders and requires careful coordination and adherence to regulatory guidelines at every stage to ensure patients receive safe and effective medications.

PSC is especially critical in the case of oncological treatments due to the consequences of shortages on treatment quality [2], [3], and challenging due to the high degree of therapy personalisation [4] that calls for the on-demand preparation of drugs and accurate timing in the distribution and delivery process. Moreover, patients can receive the treatment only after blood assessments. This can delay the administration and require to dynamically adapt the whole process. PSC management is then very difficult to optimise since it needs to be responsive to sudden change while at the same time efficient in terms of costs and usage of resources.

Digital technologies and infrastructures can play an essential role in supporting this process, helping to achieve the required responsiveness and adaptability [5]. The level of inherent complexity of the PSC makes the design of these digital infrastructure technologies an interesting problem that calls for innovative solutions from the IT and ICT point of view. Generally speaking, this PSC process involves the capability of tracking in real-time different kinds of physical assets (patients, therapy, vehicles, etc.), in different locations and with their own dynamics, enacting a process according to a plan that may need to be promptly revised and adapted depending on events and situations that concern those assets.

We propose a design based on *Digital Twins* (DTs) as a uniform approach to model and manage the ecosystem of heterogeneous physical assets involved in the oncologic PSC, enabling the development of smart digital systems to help achieve the proper level of responsiveness and adaptability. DTs are gaining momentum in digital healthcare literature, applied for different kinds of purposes ranging from the idea of creating digital patients that can simulate the behaviour of organs, to the simulation of the effectiveness of new chemicals for the pharmaceutical industry, to the management and administration of hospital structures [6].

In this paper, we consider DTs to track both the processes related to the preparation and distribution of treatments and the patient conditions to perform predictions on the suitability of the patient for new treatments and optimise the overall scheduling of the supply chain tasks. We first introduce the challenges of the domain and consider related works in the management of pharmaceutical supply chains and the application of DTs to both PSC and broadly to the care of oncology patients in section II. We then present a case study that takes inspiration from a real setting to identify the requirements of an ideal supporting system in section III. In section IV and V we present our solution based on DTs, first for tracking the relevant data during the overall process and then for predicting patient suitability for new treatments, discussing preliminary results. Finally, we highlight the main benefits and limitations of the approach and propose future work in section VI.

II. Background

The pharmaceutical supply chain may impact the quality of the service, the accessibility and costs of the process, as well as waste elimination. An efficient design of the whole pipeline, considering different risk components, is key for improving the service in terms of volume, network and population coverage [1], [7]. This paper focuses on the downstream of the process, namely, we are not interested in the enterprise production pipeline, but mainly in the in-loco drug preparation and timely administration [8]. In this section, we will discuss which are the challenges for a proper design in the context of oncologic treatment, present related works, and finally how and why we believe that the adoption of the DT approach may support the assessment and implementation of suitable strategies.

A. Challenges in Oncologic Treatment

The diffusion of cancers and the consequent expenditure burden of cancer care, requires an effective management of the whole PSC [9]. To discuss this issue, of the whole PSC process, in this paper, we focus on the optimisation strategies to be deployed within the downstream domain, *i.e.*, the distribution to healthcare facilities so that treatments can be administered to patients. In this context, the process of preparation for cancer treatment begins after the medical prescription and patient's condition assessment, it involves multiple sub-tasks related to purchasing, stocking, picking, manipulating, scheduling and delivering treatment to the patient (in Hospital or other administration settings). It is a very complex process that should be optimised to reduce waste and guarantee a secure, right, and timeliness drug administration. The optimisation of this process faces a list of issues:

- *Optimised warehouse management:* it is necessary to maintain stock levels that respect the available spaces' physical constraints and guarantee the ability to manage the resources by providing precise information on the value (even forecast) of the materials in the warehouse.
- *Right time logistic:* the organisation, adaptation of and monitoring of transport both to the input and to the places of administration must guarantee punctuality and precision, guaranteeing safety and quality of access to care for patients.
- *Traceability and accountability:* the entire process must guarantee the traceability of materials and processes and accountability with respect to the professionals involved, to produce information for the continuous review of the processes and the reconstruction of any accidents in minimum times and with maximum precision.
- *Anticipation of information:* the digitalisation of the process guarantees the availability of information at all times and the connection between the different phases guarantees the anticipation of correct information for planning the subsequent phases.
- *Level of automation:* the availability of robots for efficient and safe production requires interfacing capabilities between automation tools and information systems to support the process.
- *Scenario simulation:* oncological treatments are characterised by a certain pace of updating with specific indications that vary from year to year; the different administration configurations and the different costs of the active ingredients produce effects on the entire organisation and impact on the sustainability of the organisation. For these reasons, the ability to simulate the impact of new therapeutic opportunities is a key element for professionals involved in programming.
- *Clinical trials:* the process of prescribing, confirming, setting up, administering and monitoring therapies in clinical trials requires particular attention and requires levels of guarantee of safety and traceability that are fundamental for the successful outcome of the research.

B. Related Works

Literature reports some work devoted to optimising the PSC, although mostly focused at the industrial upstream business level, mainly accounting for the product development to the demand points pipeline. Simulation is one of the most common approaches: e.g. [10] presents a multi-agent-based simulation of manufacturers, suppliers, and distributors. Mathematical approaches are also commonly applied to model the medication flow: under, for instance, a specific optimisation scheme in [11]. Interpreting the PSC as a manufacturing process to be optimised, the idea of applying DTs is quite straightforward, and some work is already available in literature [12]. However, none of the previous work and approaches discuss the issue in the context of the healthcare organisation, with a peculiar focus on drug preparation, patient needs and drug administration.

Moving from the production to the patient, DTs have been applied as a replica of the human [13], for instance, to support the precision and personalised medicine revolution [14], [15]. There, each digital counterpart is meant to store all the possible information on humans, from clinical data to -omics data, as a support to define highly personalised treatments and interventions. This idea is extremely promising in the context of cancer care, where the DT can store both biomarkers and models of their dynamics to analyse their dynamics [16]. However, creating a digital counterpart of patients envisions a 360-degree DT of a person where, for the digital copy to be always updated, the DT must interact with a vast type of services: integrating data into a unique framework requires interoperability, well-defined ontologies and, on top of that, advance cognitive services to manage and reason on these data for decision making purposes [17].

C. Digital Twins Ecosystems in Healthcare

DTs have been used to tackle the tracking, prediction and simulation of physical assets in several domains, and as discussed above this is true for the healthcare domain as well in which it is considered a true revolution [6], [18]. Whereas there is value in creating accurate representations and models of individual assets, they are rarely in isolated settings which makes considering the relationships among the assets and their corresponding DTs even more valuable. In this context, we can

envision a *Web of Digital Twins* [19] to support the vision for a connected network of assets mirrored in the digital world.

In the healthcare domain, this is even more interesting, given the broad range of diversity of the involved assets ranging from people to medical devices, to processes as well as the distributed nature of the management of a healthcare organisation [20]. The use of a general approach to design digital representation of the relevant entities can have benefits in terms of better interoperability and data management.

In this paper, we apply the Web of Digital Twins vision to the management of the oncologic treatment supply chain. Introducing an ecosystem of DTs is best suited for this domain given the high variety of assets involved and the relationships among different entities that concur with the overall complexity of the supply process.

III. Preparation and Delivery of Oncologic Treatments: a Case Study

Oncologic therapy preparation and delivery is a domain whose challenges are recognised by several works in the literature (Sec. II-A). In this section, we discuss the implications of such challenges describing a case study that has roots in the daily operations of an oncologic care and research centre.

The Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" (IRST) is a research centre located in Emilia-Romagna, Italy involved in the assistance and care for oncologic and onco-haematologic patients. IRST manage the whole PSC for more than 5.000 patients each year and registers more than 49,000 accesses for treatments. Oncologic pharmaceutic laboratories prepare more than 61,700 therapies by using more than 430 active substances. These elements help to better understand the complexity of a real setting and how digital systems could improve the management of the processes and facilities involved in the preparation of therapies.

We here then present a structural organisation that takes inspiration from the reality we studied, confident that this can serve as a generalisation of a much broader context. A typical care centre is organised as follows:

- *Production Units* are in charge of the preparation of treatments generally assembling personal packages by mixing active ingredients to produce personalised dosage as well as including ancillary drugs to support the specific patient and other medical equipment that may be necessary to perform the treatment. The process is only partially automatable (using fully automated production lines) since manual operations and checks are required especially for experimental treatments.
- *Warehouses* stock active ingredients, drugs, and other relevant medical equipment to be used in the production units. They may be physically separated from the production units and hierarchically organised to move the required stocks from bigger centralised warehouses to the smaller local ones.
- *Blood test facilities* are responsible for collecting samples from patients and analysing them to verify their suitability for the next iteration of the therapy. The sampling and the analysis could be carried out in different places, requiring the transport of the sample to the appropriate laboratory.
- *Therapy delivery facilities* are responsible for actually delivering the treatment to the patients. Depending on the treatment this may require the patient to stay at the facility so that medical staff can administer the treatment. Going towards even more personalised medicine, there is a plan to go towards home delivery of selected treatments, but this is not in action yet.

We now analyse a typical workflow to understand how the general challenges of the domain impact the production and distribution process and derive requirements for a system that could support the optimisation of such processes.

Patients under therapy usually follow monthly planned treatments, which are prepared and administered after a blood test aimed at helping the medical staff assess the effectiveness of the therapy and the suitability for a new iteration of (either the same or a different) treatment. In the reference context, patients are called into the therapy delivery facilities, where blood samples are collected. Samples are then analysed in a different laboratory. Production of the treatment starts as soon as results are positive, aiming to deliver the treatment as soon as possible so that patients can wait in the care centre and do not need to be given another appointment.

Given the strict time requirements for the overall process, it is clear how information should be tracked for it to be consistent and available at all times, to understand whether the available primary resources are available and whether the production process can handle the upcoming requests. Moreover, having an effective tracking of resources, ongoing therapies and patient conditions could help achieve better planning of the appointments, selecting the ideal moment for the patients to come and be checked to both maximise the probability they can accept the treatment and minimise the trips to the care centres as well as optimise the overall utilisation of centre resources such as hospital beds. Not only patients but also stockpile management in the warehouses can be improved. This is critical due to the medical equipment and drugs often having expiration dates and special conservation requirements such as temperature thresholds that need to be maintained even during transport from one facility to the other.

Finally, what has been described is of course an ideal setting. Often the medical staff may need to adjust or entirely re-evaluate the therapy given the patient's reaction, impacting the overall process. Additionally, advancements in oncological research can deliver new experimental treatments that may need to be taken into consideration. The system needs not only to track the current situation but also to react to unexpected variables and allow the simulation of new scenarios.

For all of these reasons, having evaluated the complexity of this field, in the next sections we suggest how a Digital Twin solution could tackle some of these problems.

IV. Supply Chain Tracking with Digital Twins

Having identified the complex nature of supply chain management for oncologic treatments, we propose a model for

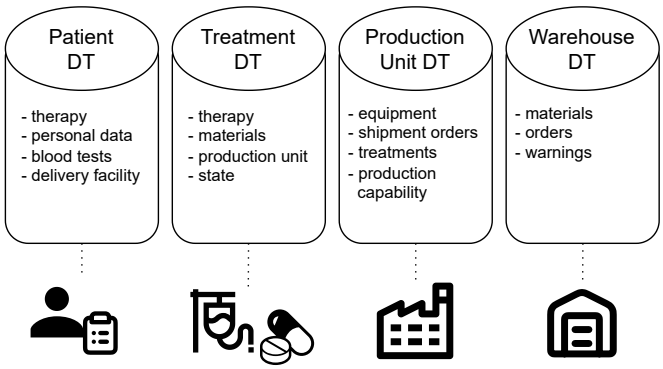

Fig. 1. The Digital Twins composing the system and the key properties they each keep track of.

a DT-based system to improve the tracking of resources in the production and distribution processes. Following the ideas presented in Section II-C the benefit of using Digital Twins to model this ecosystem comes from the possibility of offering an integrated view of the involved entities. Moreso, this view on the overall supply chain is updated in near real-time through the DTs, thus empowering stakeholders in better and timely decision-making. Figure 1 illustrates the Digital Twins that compose the system and the main data each of them keeps track of to map the supply-chain process. We selected the minimum set of entities to reify as DTs to implement the system. Thus we model patients, treatments, production units and warehouses as Digital Twins. Their role and responsibilities are described in the following paragraphs. Blood test and therapy delivery facilities are considered out of the scope of the live tracking of the process and are indirectly tracked by their interaction with the patient. Future extensions of the system could include them as well as the medical staff involved in the delivery of the treatments for an even more precise overall picture.

a) Patient DT: keeps track of patient's personal data, the therapy they are prescribed and the blood tests that are performed periodically to monitor the suitability for new treatments. The patient DT also keeps track of the delivery facility where patients are in care, and can thus be used to monitor the use of resources. The DT can offer a prediction service to foresee the conditions of a patient, usually assessed with blood tests, and schedule the new iterations of treatments accordingly. This service is described in the next section.

b) Treatment DT: has the most dynamic nature and is used to track the whole process following the evolution and interaction with other components of the system.

Each treatment DT starts in a `scheduled` state for a given date depending on the therapy, then is moved to the `confirmed` state if the corresponding blood test is positive. This starts the production process and has the treatment `assigned` to a production unit depending on the local availability of resources and the current production capability. Each treatment DT stores information about the required materials and is linked to the actual resources used in the production to guarantee tracking of the batches. The DT is then moved to a `production` state when in preparation and, once ready, to a `distribution` state and keeps track of its travel towards the therapy delivery facility at which the patient is in care. Finally, it changes to a `delivered` state once the treatment is administered to the patient.

c) Production Unit DT: is responsible for monitoring and estimating the production capability of a unit so that planning algorithms can distribute treatments to optimise the selected performance indicators. When treatments are assigned to a production unit, the necessary resources need to be fetched by the warehouses, so the production unit may need to emit shipment orders. This DT should offer simulation services to test the impact of new requests or failures in the production process on the overall efficiency of the unit.

d) Warehouse DT: monitors the stockpile of medical equipment, active ingredients and ready-to-deliver drugs to keep track of the stored quantity, and expiration dates as well as the environmental conditions in which special resources need to be kept. This DT can emit warnings to notify if stocks are below some set thresholds, if the expiration date for a given resource is close or if the required environmental conditions are not matched to either emit new orders or redistribute the resources to avoid waste.

Listing 1 shows the representation in Turtle syntax for RDF of the data collected by the system. We adopted the Hl7 FHIR[1] standard as it is one of the most comprehensive vocabularies for electronic health records and is a great tool for granting interoperability of the collected data. Using FHIR resources we were able to model the therapies for each patient as `CarePlan` resources and treatments as `MedicationRequest` resources that can be fulfilled by a `SupplyRequest` that are handled during production and distribution and a `MedicationAdministration` to represent where and how the produced treatment is administered to the patient during an `Encounter`.

The resulting scheme enables accurate recording of all the events tracked during a patient therapy and since using a standard vocabulary the data is guaranteed to be in interoperable format and enriched by useful semantics. This data can then be used to measure and monitor process KPIs, as well as to train models and make predictions as we will show in the next section.

V. Data-driven Predictions of Patients Suitability

Each DT of the ecosystem can embed knowledge-based and data-driven models of the corresponding physical asset. The analyses that are thus enabled, allow for a comprehensive view of the ecosystem dynamics and support informed planning.

Among all the DTs, in this paper, we focus on the Patient DT and present the first data-driven model we designed. The model embeds data including patient anthropometric measures, cancer properties, blood test results and treatment administration. As a result, several data-driven analyses are enabled,

[1] http://hl7.org/fhir

Listing 1
DATA COLLECTED FROM THE SYSTEM ENCODED IN RDF USING THE HL7 FHIR STANDARD

```
@prefix fhir: <http://hl7.org/fhir/> .
@base <http://example.com/test/> .

# a Patient resource with it's ID
<patient/1234> a fhir:Patient .

# the Therapy for a Patient
<therapy/1234> a fhir:CarePlan;
  fhir:status [ fhir:v "active"] ;
  fhir:intent [ fhir:v "order"] ;
  fhir:subject <patient/1234> ;
  fhir:addresses ( [ fhir:reference
      <condition/cd1234> ] ) ;
  fhir:activity ([
      # the planned Treatment
      fhir:plannedActivityReference
          <request/md1234>;
      fhir:performedActivity (
        # and links to record administrations
      [ fhir:reference <encounter/ec1> ]
        [ fhir:reference <administration/adm1> ]
      );
    ]).

# the Treatment Resource
<request/md1234> a fhir:MedicationRequest;
  fhir:status [ fhir:v "active"] ;
  fhir:intent [ fhir:v "order"] ;
  fhir:subject <patient/1234> ;
  # the drug to be administered
  fhir:medication [ fhir:reference
      <medication/med345> ];
  fhir:dosageInstruction (
    fhir:timing [
      #repeated once every three months
      fhir:repeat [
        fhir:frequency [ fhir:v 1 ] ;
        fhir:period [ fhir:v 3] ;
        fhir:periodUnit [ fhir:v "mo" ];
      ];
      # until the end of the year
      fhir:bounds [
        fhir:start  [ fhir:v "2023-01-15"];
        fhir:end  [ fhir:v "2023-12-31" ];
      ];
    ]).

# the request for production and distribution
# of the treatment
<request/sp1234> a fhir:SupplyRequest;
    fhir:status [fhir:v "active"];
    fhir:basedOn <request/md1234>.
```

such as aggregated descriptive statistics and predictions based on machine learning models trained on top of these data. In particular, in this paper, we are interested in exploring if the DT model we built can support the optimisation of the administration procedure, predicting the suitability of the next iteration of a therapy and thus minimising the number of patients whose scheduled treatment administration is delayed due to the negative result of blood tests in the planned date.

The dataset encompasses 12,045 patients, described with features that include age, sex, codification of tumour site, active ingredients of the therapy, number of previous administrations and days from the (eventual) previous administration as well as data concerning the last blood sample. We trained, using a 70-30% split, 3 machine learning algorithms: Support Vector Machine, Random Forest (RF) and an ensemble method, AdaBoost. The problem is configured as a binary classification task, specifically devoted to identifying if a patient will result in a positive or negative blood test. The idea is to embed in each Patient DT, the best-performing model with the goal of predicting in advance if the patient will, or not, be ready for the treatment at the scheduled time. Such information is key to reducing waste of material used for blood tests, optimising the number of operators involved, avoiding inconvenient waiting time for patients and their families, reducing transport, optimising warehouse management and drug preparation and, accordingly, defining an efficient and optimal planning of the whole PSC.

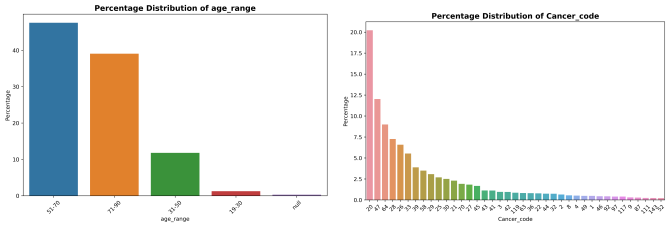

Fig. 2. Patient population characteristics: age distribution (left) and type of cancer identified by its code (right). This shows that the centre deals with a big diversity of patients, each needing individual treatments.

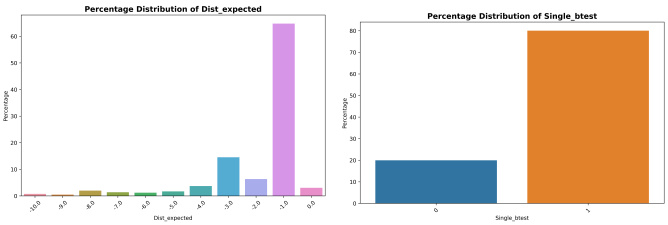

Fig. 3. Analysis of the blood testing process: days between administration of treatment and test (left) and percentage of successful tests on the scheduled date (right). Most patients receive their treatment the day after the test (-1) but some outliers can wait up to ten days (-10). 80% of the tests are positive on the planned appointment.

A. *Preliminary results*

On data acquired and stored in the Patient DT, we can perform descriptive statistics to analyse and reason on aggregate properties of the sample, and on the characteristics of the process. As an example, in Figure 2 we can observe the distribution of treated patients based on their age and cancer type, while in Figure 3 we can have an insight into when blood tests are executed with respect to the scheduled day for treatment administration (-1: the day before, etc) and how many of these tests are positive (patient ready) or not. Stratified statistics are of course also possible but, for the sake of space, we here show only some examples as a demonstration of how the DT approach can be exploited.

TABLE I
PERFORMANCE ON THE TEST SET.

Model	Sensitivity	Specificity	Precision	Accuracy	AUC
RF	**0.988**	0.396	0.867	0.869	0.620
SVM	0.938	0.389	0.859	0.828	0.663
AdaBoost	0.987	**0.418**	**0.871**	**0.872**	0.702

More than that, the DT approach enables more advanced analyses. In this paper, we present the results of the prediction analysis conducted with data-driven models based on trained machine learning algorithms. The performances of the three algorithms on the test set (30% not used during training), are reported in Table I. Even though no algorithm properly outperforms the others, AdaBoost provides the best performance overall (0.987 sensitivity – 0.418 specificity – 0.872 accuracy). It is worth noting that training is strongly affected by an imbalance between the two classes, as demonstrated by the two indicators of sensitivity and specificity. The former is very high meaning that the positive class is recognised with high accuracy, whereas the latter is unacceptably low meaning almost half of the negative records are classified as positive. These results suggest for further investigations, for instance by applying resampling techniques to balance the training set.

VI. CONCLUSION

In this paper, we analysed the problem of supply chain management in oncologic settings taking as reference an Italian research and care centre for oncologic patients. We identified an abstract model of a typical treatment cycle and derived requirements for a tracking system to collect data on the production and distribution process. We then proposed a DTs-based solution for the problem, highlighting how DTs can seamlessly model the diverse range of involved entities, generate high-quality representations of the data using standard interoperable formats and finally how such data can serve as a source to train machine learning models which can be later embed in the DTs to offer prediction services.

We showed preliminary results on the analysis of available patient data to predict suitability for new treatments and optimise appointment planning. The performances of the models are still not sufficient to justify their adoption in the decision-making process. However, they can be improved by training models on new data continuously acquired through the DT ecosystem and by applying more advanced techniques for data preprocessing and analysis. Moreover, knowledge-based models can be envisioned as the basis for a simulation framework on top of which data and domain knowledge can be integrated to perform a wider set of analyses, for instance by defining diverse *what-if* scenarios.

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