EDITORIAL

Digital Twins for Personalized Healthcare: Application to Radiopharmaceutical Therapies

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Received: 03 December 2022 / Accepted: 07 December 2022

Abstract

There is significant interest and value in utilizing Digital Twins (DTs) to extend healthcare from 'one-size-fits-all' to personalized therapies. Radiopharmaceutical Therapies (RPTs), which represent very powerful developments in the battle against cancer, are no exceptions to this. In fact, Theranostic Digital Twins (TDTs), which we elaborate in this work, present viable and feasible approaches to personalize RPTs. TDTs are computational representations of the human body that, unlike images, are operable; i.e. virtual trials can be conducted on them to propose optimal therapies for individual patients. TDTs can be built using Physiologically Based Pharmacokinetic (PBPK) models. This work elaborates that TDTs can be developed in static, dynamic and interactive modes towards routine use in future clinical settings. TDTs will open a new area of theranostics research and development in terms of new radiopharmaceutical designs, synthesis and enabling of more optimal therapies.

Keywords: Digital Twins; Radiopharmaceutical Therapies; Theranostics; Personalized Therapy; Physiologically Based Pharmacokinetic Models.

DOI: https://doi.org/10.18502/fbt.v10i1.11505

Frontiers in BIOMEDICAL TECHNOLOGIES

1. Introduction

Radiopharmaceutical Therapies (RPTs) have shown very promising results in management of several cancers, providing powerful options for patients with systemic metastatic cancer [1,2]. In RPTs, radiopharmaceuticals deliver targeted radiation doses in the body, systematically or locally, and destroy cancer cells. However, the success of RPTs depends on several physical, biological, physiological, pharmacological, and radiobiological factors which should be considered in RPT planning [3,4]. Furthermore, to personalize RPTs, patient-specific dose prescriptions in terms of predictive dosimetry would play a critical role [5]. Although recent efforts have been directed toward improvement in these areas, further research should be undertaken.

Digital Twins (DTs) provide powerful frameworks founded on realistic simulations, and are being investigated as promising technologies for personalized medicine [6]. They have been mostly investigated in industrial applications as virtual representation of physical objects based on mathematical and computational models to predict future behaviors of the studied subjects and to improve them [7]. In medical settings, DTs have been suggested as data-driven or mechanistic computational models to be utilized as simulation platforms to improve diagnosis, prognosis, and therapies [8]. For example, DTs are studied in cancer therapies [9], cardiovascular diseases [10], immunological diseases [11], neurological disorders [12], and pharmacological research and development [13]. Meanwhile, DTs for RPTs remain to be fully explored, and this is an area of significant interest, which we describe next.

2. Theranostic Digital Twins

Theranostic DTs (TDTs) hold significant potential to move from "one-size-fits-all" to personalized RPT models [14]. An important point is that TDTs are operable: they are not mere data banks or collections of image, but models on which virtual clinical trial can be conducted towards optimization for application to patients [15]. In the personalized RPT model, therapeutic profiles such as injected radioactivity, the number of injection cycles, and injection profiles can be individualized based on TDTs. Meanwhile, to develop TDTs, a number of clinical and pre-clinical data are needed. In Figure 1, we show data obtained from different sources such as imaging, omics-based (e.g. genomics, proteomics, etc.), laboratory tests (e.g., blood markers), clinical documents (or medical literature), and preclinical (animal or in-vitro) tests that can be used as main inputs for fitting the TDT models. Theranostic images (e.g. pre-therapy PET scans) are expected to play a significant role. Advanced molecular imaging systems such as Long Axial Field Of View (LAFOV) Positron Emission Tomography (PET) scanners [16] are expected to act as rich sources of biological information towards accurate TDTs. Further, single-cell sequencing concerning genomics and transcriptomics data that decode cancer cell complexities, including heterogeneity, can provide several biological parameters to develop and personalize TDT models [17].

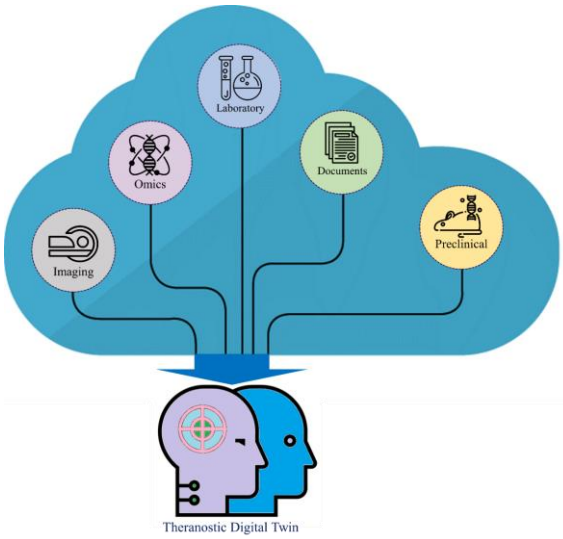

Figure 1. Various data can be utilized to develop TDTs, including imaging, omics, laboratory, documentation, and preclinical data

Physiologically Based Pharmacokinetic (PBPK) models can act as key engines in TDTs. The PBPK models are compartment-based models connected through ordinary differential equations involving anatomical, physiological, and drug-specific parameters [18]. PBPK models have been utilized in the past as feasible approaches to analyzing and predicting the pharmacokinetics of new drugs and evaluating the effects of intrinsic and extrinsic factors on drug exposure [19]. In the realm of RPTs, they have been applied to describe the organ distribution of radiopharmaceuticals such as 177Lu-PSMA [20] and 177Lu-DOTATATE [21] in cancer patients or in preclinical studies. They have also proposed as treatment planning algorithms for RPTs [22].

We depict a TDT model in Figure 2, involving a whole-body PBPK model that can simulate real patients by

defining normal and tumor organs as main compartments and predicting time-activity curves for each organ. In the real world, Single-Photon Emission Computed Tomography (SPECT) and/or planar theranostic imaging can be used for retrospective dosimetry, while a PBPK-based TDT model aims to enable predictive dosimetry. However, since PBPK models have several patient- and drug-specific parameters, a number of experimental and clinical analyses are needed to personalize them. Existing PBPK models are developed based on the literature, including pre-clinical and clinical studies, and suffer from limitations such as uncertainty and lack of clinical validation [23] which ongoing research aims to tackle. As such, approaches including parameter estimation, bias reduction, and uncertainty analyses are critical during PBPK modeling. Artificial Intelligence (AI) approaches can be used to enable reliable identifiability and uncertainty analyses, and to better personalize such models [24].

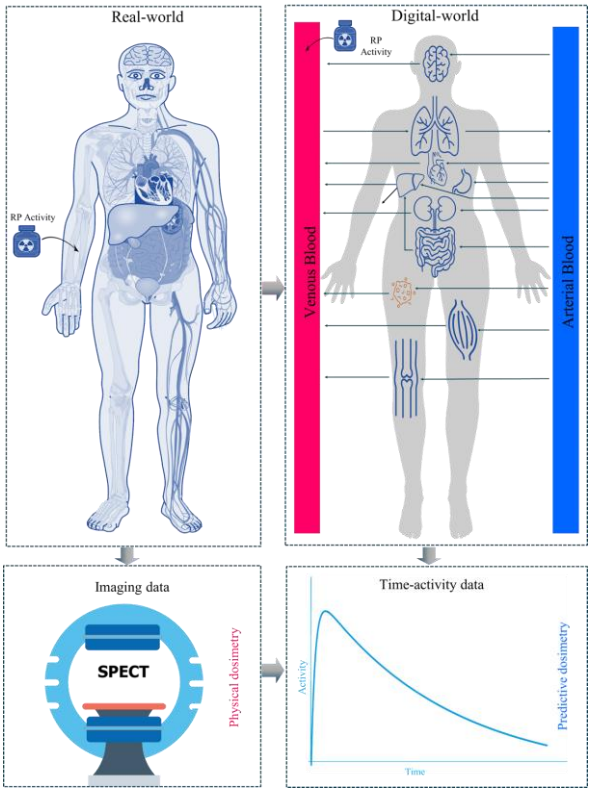

Figure 2. Towards TDTs: A real patient is shown in the left panel, and on the right, a digital twin involving a whole-body PBPK is depicted. In the real world, physical dosimetry including SPECT imaging is used for retrospective dosimetry, while in the digital realm, PBPK produces time activity curves that can be utilized in predictive dosimetry. PBPK can help better predict the time-activity curves for all normal and tumor organs

3. Modes of Action for Theranostic Digital Twins

One of the main aims of proposed TDTs is to personalize RPTs via prediction of radiobiological outcomes including Biological Effective Dose (BED), Tumor Control Probability (TCP), and Normal Tissue Complication Probability (NTCP). To reach these aims, several TDT modes of action need to be invoked. As shown in Figure 3, we propose three modes of action including static, dynamic and interactive modes. Static TDTs are models which can be constructed using initial patient data. They are models developed using currently available data, and are utilized for prediction of future cycles of RPTs by using such early data. In dynamic mode, TDTs are updated based on changes in patients due to new cycles of therapy. The updated models predict future cycles of therapy. This process can be repeated and iterated with new data obtained intra- or post-therapy.

The interactive mode of action is a dynamic model which does not merely predict dose deliveries in future cycles, but also models the radiobiological interactions of radiopharmaceuticals with the patient's body in those cycles and thus predicts the patient's response and is able to predict future TDTs; i.e. not only does it predict delivered doses but also the body's response to them. Such models would be more mechanistic in comparison to static and dynamic models and consider multiscale radiobiological effects, and enable even more effective prescriptions of therapies. In the process of TDT modelling, AI can be used in any of these modes of action. For example, it can be utilized to solve inverse problems for parameter estimation. On the other hand, TDT models would be flexible, modular and upgradable, to optimize different clinical RPT scenarios.

4. Discussion and Conclusion

Digital twins represent an important future component of personalized healthcare [6]. In RPTs, TDTs can be developed based on PBPK models, incorporating and personalizing anatomical, physiological, and radiopharmaceutical parameters. This requires improved integration of biological models, and utilizing methodologies for parameter estimation and bias reduction.

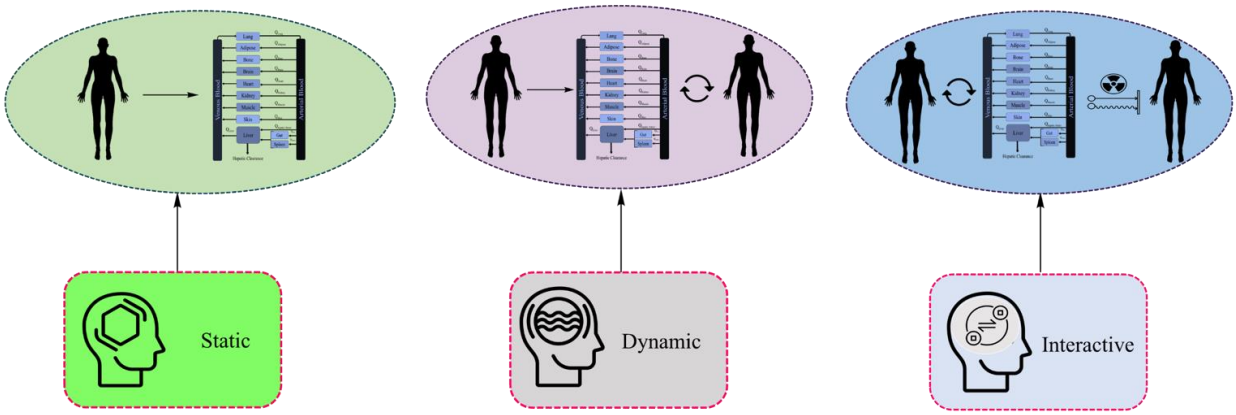

Figure 3. TDT modes of action are shown, namely static, dynamic, and interactive. In the static mode, the model is developed based on early data. The dynamic mode, by contrast, is updated based on changes in data from cycles of therapy, thus iteratively updated. Interactive mode of action performs modeling of biological interactions of radiopharmaceuticals with the patient's body, and thus predicts not only the delivered doses but also the patient's response to them, predicting future TDTs, and enabling even more optimal therapies

As RPTs are creating significant waves in cancer therapy, it is incumbent upon the community to not be satisfied with current practice of injecting fixed radioactivities to patients (e.g. 200mCi for Lu-177-PSMA and Lu-177-DOTATATE). In fact, existing paradigm results in very significant variabilities in delivered doses to tumors and Organs-At-Risk (OARs) [25,26]. TDTs provide a viable solution to move beyond the existing paradigm. Utilizing such computational platforms will reduce costs, and clinical trials using TDTs would need to be conducted to prove their value. Meanwhile, advanced radiobiological phenomena in RPTs can be better and better modeled, e.g. including dose rate and dose heterogeneities, to better optimized tumor treatments vs. OAR toxicities.

TDTs provide a paradigm shift from "one-size-fits-all" to personalized RPTs. This shift is an important move from purely empirical RPT approaches to integrate advanced computational platforms, integrating patient- and radiopharmaceutical-specific data. Overall, TDTs are expected to pave the way to improved RPTs and will open a new area of theranostics research and development enabling new optimal therapies, and filling important gaps between existing empirical vs. optimal therapies.

Acknowledgments

We gratefully acknowledge funding from the Canadian Institutes of Health Research (CIHR) Project Grant PJT-162216 as well as Networking Health Ltd.

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