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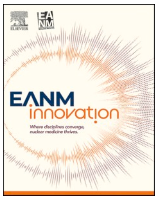

Digital twins in computational medicine with a specific focus on nuclear oncology. Where do we stand?

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ABSTRACT

In medicine, digital twins (DTs) serve as computational models that replicate biological and physiological characteristics of a specific individual — whether a patient, an organ, or even a single cell — and simulate virtual biomedical experiments. DT-based simulations hold the potential to identify the most beneficial intervention at any given moment. A range of technological approaches has been explored across various medical fields, with oncology being one of the most suitable areas of application in view of the necessity of timely and personalized treatment decisions. Medical imaging, and especially nuclear medicine, might have a central role in the development of DTs. In this review we define digital twins, examine current evidence, and discuss opportunities that digital twins can offer in computational nuclear oncology. We also briefly summarize the state-of-the-art of DTs in other fields.

1. Introduction

Digital twin (DT) technology has a long history in engineering and industrial domains, where it has been used for more than a decade to support asset management, manufacturing processes, and aerospace systems [1,2]. Building on these foundations, the concept has increasingly migrated into the biomedical and healthcare fields, where it is undergoing a significant conceptual expansion [3]. While rooted in engineering paradigms, DTs in medicine must account for the unique complexity, variability, and multiscale nature of biological systems, thus requiring a broader interpretive framework that integrates computational modeling, clinical data, and physiological principles.

In biomedicine, traditional population-based approaches rely on representative cohorts that share certain characteristics yet exhibit substantial heterogeneity in genotype, phenotype, and disease progression [4]. However, the shift toward precision and personalized medicine has revealed the limitations of cohort-driven inference and underscored the need for individualized predictive tools. In this context, DTs serve as computational models designed to replicate the biological and physiological characteristics of a specific individual—whether a patient, organ, or even a single cell [5]. Beyond static data-driven analysis, DTs operate as dynamic, mechanistic-informed systems capable of generating biologically realistic synthetic data, simulating virtual biomedical experiments, and forecasting potential clinical trajectories.

A key innovation in medical DTs is the ability to generate digital twin cohorts: ensembles of individualized virtual models that simulate different therapeutic strategies, thereby approximating the outcomes of personalized “in-silico trials” [6]. At a given clinical timepoint, each twin represents a distinct intervention scenario—such as a surgical plan, medication regimen, or radiotherapy protocol—allowing clinicians to evaluate and compare treatment options before implementing them in the real world.

The DT paradigm can be extended into a Digital Twin System (DTS), defined as an adaptive and iterative framework that integrates real-time experimental or clinical data with synthetic data generated by the DT to

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Abbreviations:

artificial intelligence (AI)
Computed tomography (CT)
2-deoxy-2-[^{18}F]fluoroglucose ([^{18}F]FDG)
Digital Twin System (DTS)
Enzyme hexokinase (HK)
electrocardiogram (ECG)
Extended cardiac torso (XCAT)
1-(2Nitro-imidazolyl)-3-[^{18}F]fluoro-2-propanol ([^{18}F]FMISO)
Fibroblast activation protein (FAP)
Flow-limited oxygen-dependent (FLOD)
[^{18}F]fluorothymidine ([^{18}F]FLT)
Gastrin-releasing peptide receptor (GRPR)
Magnetic resonance imaging (MRI)
Positron emission tomography (PET)
Prostate specific membrane antigen (PSMA)
Physiologically based pharmacokinetic (PBPK)
Radioligand therapy (RLT)
Single photon emission computed tomography (SPECT)
Time activity curves (TACs)
Theranostic DTs laboratory (TDTLab)
Virtual Human Twin (VHT)

continuously refine predictions and optimize decision-making [5–8]. As illustrated in Fig. 1, the physical entity (e.g., patient, organ, tissue) generates empirical observations that inform inference models, while the virtual entity simulates prospective outcomes under different interventions. The feedback loop between real and synthetic data distinguishes a DTS from conventional modeling approaches, transforming it into a continuously evolving predictive system.

Within this evolving landscape, the concept of the Virtual Human Twin (VHT) has emerged as a related and more specific application, focusing on multiscale digital representations of human physiology—-from cells to organs to whole-body systems. VHTs aim to replicate biological, behavioral, and environmental factors to support personalized prevention, diagnosis, treatment planning, and medical training. While our manuscript adopts the broader DT terminology to encompass physiological, device-related, and workflow-oriented medical models, VHTs represent a clinically oriented subclass with a patient-centric focus that aligns closely with the goals of precision medicine [7].

Medical imaging demonstrates a central role in the development of DTSs. Indeed, imaging techniques provide high-dimensional, multimodal, and continuously updating data. In the nuclear medicine theranostic paradigm, digital twins might be particularly useful. Combining general knowledge of the physical properties of the isotopes, pharmacokinetics of radiopharmaceuticals, tumor heterogeneity-related biodistribution, and patient-specific variables including systemic immune perturbations, lesion/healthy tissue size, and comorbidities, DT might ultimately overcome the limitations of the current practice and improve treatment outcomes, quality of life, and, ultimately, of the healthcare costs allocation [8–11].

This review provides an overview of medical DT applications, with a particular focus on AI-driven, imaging-based DT models and their role in supporting clinical decision-making and improving patient outcomes in oncology.

2. Methods

Given the evolving and interdisciplinary nature of DT research in healthcare, this work adopts a narrative review approach rather than a formal systematic review format. The objective of this section is not to exhaustively catalogue all publications but to provide a conceptual synthesis of the evolution and current landscape of DTs in medicine, with emphasis on imaging-based and oncology-related applications.

Relevant studies were identified through targeted searches using key terms associated with digital twins and computational nuclear medicine across major biomedical databases, with no start-date restrictions and coverage through December 31st, 2024. Initial exploratory searches employed broad terms (e.g., “digital twin”), which provided an overview of the conceptual landscape but also retrieved many non-imaging and non-clinical applications. To refine the scope and ensure balanced and relevant coverage, additional focused queries were implemented by combining digital-twin terminology with imaging-specific terms such as PET, SPECT, nuclear medicine, theranostics, and dosimetry. Titles and abstracts were screened independently by multiple reviewers, followed by full-text evaluation for eligible articles. Studies outside the scope of medical DTs, non-original publications (e.g., reviews, commentaries, conference abstracts), and non-English articles were excluded. Reference lists of included articles were examined to identify additional pertinent work. Included studies were analyzed based on clinical domain, imaging modality, radiopharmaceutical use, methodological approach, and primary objectives, and subsequently grouped into thematic categories (oncology, cardiovascular, neuroscience, and surgery), with multidisciplinary studies reviewed separately.

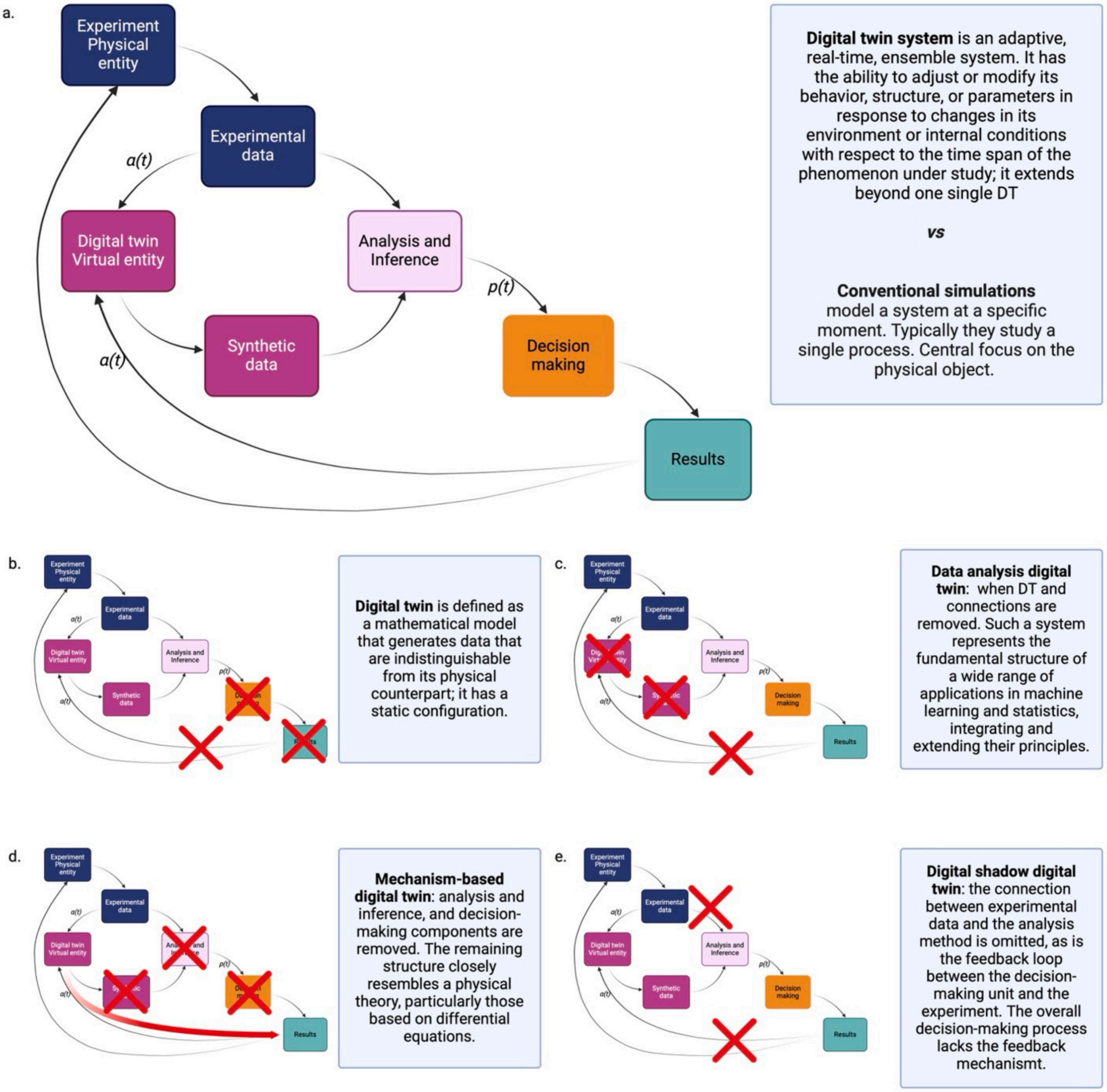
Our selection and interpretation of the literature were additionally informed by the authors’ experience in the development and application of DT-related modeling frameworks in healthcare research, including work in imaging-based modeling, computational oncology, and theranostics-driven precision medicine. This perspective allowed us to critically interpret the terminology variability and conceptual fragmentation still present in the field, and to highlight methodological and translational challenges relevant to future clinical deployment.

The resulting synthesis provides a structured narrative on.

(i) the concept of DT in medical imaging with focus on
(ii) cardiovascular applications
(iii) neuroscience applications
(iv) surgical applications
(v) the concept of DT in computational nuclear oncology with focus on
(vi) diagnosis and staging
(vii) theranostic and dosimetry

3. Digital twin and medical imaging

DTs have been proposed to address problems in a wide variety of diseases. They can make use of non-imaging data, which include clinical history, laboratory test results, or data collected via wearable devices reporting on, for example, blood pressure, temperature, physical activity, and oxygen saturation. These DTs have been proposed, for instance, for diabetes, infection, and inflammation management, as well as neuroscience [12–17]. DTs can also integrate data obtained from imaging modalities, like computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT), which can provide (semi-) quantitative biomarkers. They can capture the underlying physiological and pathological molecular characteristics of cells, tissues, and organs. Vascular perfusion and permeability can be assessed by contrast-enhanced CT and MRI [18]. The motion of water in tissue and cellularity can be evaluated by diffusion-weighted MRI [19]. In PET, metabolism of glucose, amino acids, and lipids can be assessed using 2-deoxy-2-[^{18}F]fluoroglucose ([^{18}F]FDG), [^{18}F]F-tyrosine or [^{11}C] methionine, and ^{11}C- or ^{18}F-labelled choline, respectively. Expression of



Digital twin system is an adaptive, real-time, ensemble system. It has the ability to adjust or modify its behavior, structure, or parameters in response to changes in its environment or internal conditions with respect to the time span of the phenomenon under study; it extends beyond one single DT

vs

Conventional simulations model a system at a specific moment. Typically they study a single process. Central focus on the physical object.

Digital twin is defined as a mathematical model that generates data that are indistinguishable from its physical counterpart; it has a static configuration.

Data analysis digital twin: when DT and connections are removed. Such a system represents the fundamental structure of a wide range of applications in machine learning and statistics, integrating and extending their principles.

Mechanism-based digital twin: analysis and inference, and decision-making components are removed. The remaining structure closely resembles a physical theory, particularly those based on differential equations.

Digital shadow digital twin: the connection between experimental data and the analysis method is omitted, as is the feedback loop between the decision-making unit and the experiment. The overall decision-making process lacks the feedback mechanismt.

Fig. 1. Digital Twin System definition. DTS is an integrated framework that combines real-world experimental data with a Digital Twin (DT) through analytical and inference methods, supported by a decision-making component (panel a). The DTS dynamically adapts its parameters, denoted as α(t), based on continuous input from both the physical experiment and decision-making processes. The time dependency (t) highlights the iterative nature of this system, allowing for real-time updates to experimental data and continuous refinement of predictions p(t) generated by analytical models. A key feature of the DTS is its bidirectional feedback loop: data flow not only from the experiment to the DT but also from the decision-making unit back to the experiment. This feedback mechanism enables optimization of the experimental process, guiding which scenarios to test and improving predictive accuracy. The figure illustrates a schematic representation of a DTS, showing how physical entities (experiments) and virtual entities (digital twins) interact. Both experimental and synthetic data are processed through analysis and inference methods, leading to actionable decisions and dynamically updated parameters α(t) for further refinement. This iterative cycle ensures continuous system learning and enhanced predictive insights, as demonstrated in various healthcare and medical applications. Panels b–e illustrate particular cases of DTs.

various cell surface receptors on cancer cells and cancer microenvironment (e.g., somatostatin receptor, prostate specific membrane antigen [PSMA], fibroblast activation protein [FAP]) can be assessed by PET and SPECT [20]. PET radiopharmaceuticals can also be employed to measure hypoxia and apoptosis [21]. Thanks to highly resolved spatial information, anatomical and molecular imaging, based on radiological and nuclear medicine modalities, PET is increasingly used to develop image-aided digital twins. Image-derived quantitative parameters can be used as inputs to mathematical models that describe biological and physical dynamics. Consequently, image-guided digital twins have the inherent feature to provide spatiotemporal characteristics of the tissues and tumors [22], potentially improving the accuracy of diagnosis and prognosis, as well as provide opportunities to personally optimize treatment.

3.1. Imaging-based DT applications in cardiovascular system

A recent review summarized literature on cardiovascular system models illustrating various approaches to address specific diseases [23]. The reviewed models include those capturing biomechanical and electrophysiological characteristics of the heart, simulating the start of thrombus formation in the veins, planning of targeted ablation of tachycardia foci, mimicking heart failure, modelling arterial hemodynamics, developing models of the cardiovascular-respiratory system, and replicating the interactions between the cardiovascular and renal systems. In these works, MRI and CT imaging are the most common input data. In Ref. [24], automatic segmentation package for aortic valve stenosis has been proposed to model patient-specific anatomies and, in the long run, to be used to simulate virtual interventional procedures. The authors used CT imaging as input and developed a fully automatic AI tool capable of reconstructing the DT geometry and analyzing the calcification distribution on the aortic valve. Dubs et al. [25] aimed to predict fractional flow reserve in extracranial internal carotid artery using CT angiography as input. Besides good performance in predicting peak systolic velocity, they discussed hyperemic simulations in a physiological range. In Ref. [26], authors estimated key ventricular activation properties, integrating electrocardiography and cardiac MRI as inference method. The results showed successful estimation of the ventricular speeds and earliest activation sites. Furthermore, Azzolin et al. [27] assessed arrhythmia vulnerability via an automated framework, tested on 29 patients on MRI and electro-anatomical maps. The authors demonstrated that the proposed tool generated the fiber orientation and found local conduction velocities. Lastly, Li et al. [28] proposed a platform integrating multi-modal data, such as cardiac MRI and electrocardiogram (ECG), for the inference of tissue properties in myocardial infarction. The authors demonstrated that the model could capture complex relationship between infarct characteristics and electrophysiological features.

3.2. Imaging-based DT applications in neuroscience

DTs in neuroscience might allow the in-silico modeling of functions and pathology. In Ref. [29], a DT application was demonstrated for estimating the age of onset of disease-specific brain atrophy in patients affected by multiple sclerosis using brain MRI. The authors found the onset age of progressive brain tissue loss occurred, on average, 5–6 years earlier than the clinical symptom onset and discovered two patient clusters: earlier vs simultaneous onset of brain atrophy. In Ref. [30], Sampson et al. tested the ability of an algorithm using MR diffusion tensor imaging to predict patient-specific drug distributions by convection-enhanced drug delivery. This simulation algorithm was considered clinically useful in 85 % of cases to select catheter trajectories and thereby improve the efficacy of drugs. To generate DTs and virtual patient cohorts of cerebrovascular anatomy for in-silico studies and trials, Xia et al. [31] proposed an end-to-end generative adversarial network that can produce high-resolution 3D MR angiography using T1, T2, and proton density-weighted MR images. The results showed promise for use of the proposed approach to synthetize DT cohorts of cerebrovascular anatomy at scale.

3.3. Imaging-based DT applications in surgery

In neurosurgery, DTs, including neuronavigational methods, robotics, and image-guided surgical methods, showed great promise in reducing surgical complications and improving outcomes. Image-guided neuronavigation has been applied in the operative treatment of various neurological disorders, such as foraminal stenosis, intra-axial brain lesions, arteriovenous malformations, and spinal stenosis. DTs have shown the potential to be more effective than conventional neurosurgical approaches [32]. Recently, Shu et al. [33] evaluated a DT framework designed specifically for skull base surgeries. The framework combines optical tracking and real-time simulation, making it possible to integrate it into image-guided interventions. The system provided augmented surgical views and, during the drilling process, demonstrated an average error of 1.39 mm. Also, the system updates the virtual model in real time. In Ref. [34], the authors constructed MRI-based 3D biophysical DTs to plan microwave ablation for treatment of primary and secondary liver cancers. The system predicted ablation delivery in the livers (with 5 levels of fat content) in the presence of a tumor. The authors found that the account for patient-specific tumor tissue properties significantly influences the prediction of ablation zone coverage. Moreover, a case study of tibia fracture [35] demonstrated that a patient-specific finite element model approach using a post-operative 3D X-ray image can simulate fracture risk and guide post-surgical management.

4. Imaging-based DT for computational nuclear oncology

In oncology, DT can potentially improve the accuracy of diagnosis and prognosis, as well as provide opportunities to optimize treatment. Medical imaging, which is widely used for the purpose of screening, diagnosing, staging, therapy guiding, monitoring, and assessing response, represents one of the main sources of patient-specific information on tumor progression and response. Moreover, medical imaging provides serial assessments of the physical state of the patient and characteristics of the tumor. These can be used as the observational update data for a DT.

4.1. Imaging-based DT applications in diagnosis and staging

Initial experiences have demonstrated that mathematical models can estimate tumor-specific parameters of proliferation and invasion in patients with glioblastoma [36], identify patient-specific and spatially varying net-proliferation rates and tumor cell diffusion in breast cancer patients [37], and identify alternative therapeutic regimens that were hypothesized to outperform the standard-of-care for each individual patient affected by breast cancer [38].

Nuclear medicine offers the advantage to explore different biological mechanisms, pathways, and targets, using specific radiopharmaceuticals. However, the selection of the most appropriate radiopharmaceutical is dictated by guidelines and availability [20], with logistics frequently playing a significant role in decision-making. DTs provide an alternative characterization approach at patient-level (i.e. physiology-based pharmacokinetic modeling). In the context of solid tumors, Wang et al. [39] have established a framework to model the pathways of glucose metabolism and lactate oxidation in order to establish the quantitative relationship between the expression of several transporters (GLUT, MCT1, and MCT4), the expression of the enzyme hexokinase (HK), the microvasculature and the metabolism of glucose or lactate, and extracellular pH distribution. Based on this in silico modeling, they simulated the spatiotemporal uptake of [^{18}F]FDG during PET imaging [40]. Similarly, Shi et al. [41] used experimental data to optimize the reaction-diffusion modeling of 1-(2Nitro-imidazolyl)-3-[^{18}F]fluoro-2-propanol ([^{18}F]FMISO) PET imaging to highlight hypoxia. Based on the comparison between the simulated dynamic uptake of tracer and the actual dynamic PET scan of nude mice with xenograft tumor models, a flow-limited oxygen-dependent (FLOD) model [42] was developed to improve the matching between measurements and simulations as an extension to the Kelly & Brady model [43]. For the development of precise physiological quantification to improve dosimetry-guided treatment planning for radioligand therapy, Segars et al. [44] developed a computational simulation work of virtual patient based on 4D extended cardiac torso (XCAT) human phantoms and physiologically based pharmacokinetic (PBPK)-based reaction-diffusion modelling. A recent study [45] extended the histology-driven simulation framework to consider the opposing effects of fibrosis on tracer delivery, by considering the different diffusivity properties in the tissue. For proof of concept, they simulated the [^{18}F]fluorothymidine ([^{18}F]FLT) time activity curves (TACs) of lesions from patients with pancreatic ductal adenocarcinoma and intraductal papillary mucinous neoplasm. The preliminary results confirmed that the simulation can capture the phenotype differences and generate different characteristic TACs reflecting the underlying delivery and uptake situations. This simulation further enhanced the investigation of the detection on 4D imaging approach, suggesting the prognostic power of time-varying biomarkers. Towards the exploitation of DT for early diagnosis, Cavinato et al. [46]

recently proposed an innovative end-to-end in-silico framework linking [^{18}F]FLT PET-derived biomarkers to biological tissue properties in healthy pancreas, pancreatic intraductal papillary mucinous neoplasm, and pancreatic adenocarcinoma. Their in-silico framework modeled patient-specific PET images by simulating tissue parameters like fibrosis and perfusion and allowed to extract biomarkers to be validated against simulated biological properties to evaluate their predictive value. High-resolution tissue maps of each sample revealed distinct tissue characteristics, with corresponding differences in [^{18}F]FLT uptake patterns. This approach underscored the significant impact of individual biological properties on PET imaging findings. It allowed identifying biological underpinnings of radiomics features, paving the way for better patient stratification and personalized treatment oncology, particularly in cancers with complex microenvironments like pancreatic ductal adenocarcinoma.

4.2. *Imaging-based DT applications in theranostics and dosimetry*

Nuclear medicine therapy relies on the administration of pharmaceuticals labelled with radionuclides (radiopharmaceuticals) that, targeting specific molecules, deliver radiation to cells expressing the target. In recent years, theranostics, which combines diagnostic imaging and therapy employing paired radiopharmaceuticals (i.e., the same biochemical core labelled to a radionuclide, respectively, for imaging and for treatment), has been proved effective and well tolerated. Pretreatment imaging assesses tumor burden and confirms treatment eligibility demonstrating in-vivo expression of the target. Despite the efforts to develop treatment response prediction or prognostication models, the lack of ready-to-use tools has hindered the implementation of quantitative assessment and personalization prior to therapeutic radiopharmaceutical administration. Individualized dosimetry conversion through Monte Carlo simulation factors of radioactive emission counts of therapeutic radiotracer in a region of interest imaged at different time points, integrated with pharmacokinetic modeling, to absorbed dose at the tissue/lesion [47] has been proposed to tailor patient treatment; however, it is not standard practice.

Challenges commonly associated with modeling radiation dosimetry include, among others, variability in calculation methodology, assumptions based on historical data, possible inconsistency between the biodistribution and kinetics of therapeutic and diagnostic radiopharmaceuticals, and limited knowledge on radiobiology [11]. Indeed, significant differences in absorbed dose results have been reported when stylized and voxel-based models (i.e., models containing simplified-geometries organs and anatomically realistic voxel-based models obtained from tomographic or digital cryosections, respectively) [48–51].

Preclinical dosimetry using small animals has become increasingly common for developing new theranostic agents and linking absorbed doses to biological effects in preclinical theranostic models [52,53]. The generation of digital animal models, optimizing the calculation of organ-absorbed doses, has significantly enhanced the accuracy and utility of preclinical applications of dosimetry in the theranostic setting [54].

The ability of DT to quantitatively assess and monitor variations in the nonuniform distribution of radiopharmaceuticals, absorbed doses, and radiobiology might predict treatment response and toxicity at the patient level. To this aim, the theranostic DTs laboratory (TDTLab), an open-source, user-friendly software platform has been developed and released [55]. TDTLab allows users to access ready-to-use published models or implement new custom models. It also includes a library of realistic parameters from the literature and patient data, streamlining the model development and analysis process. Abdollahi et al. [56,57] recently proposed a DTs theranostic multi-steps model. It included three main components: i) a radiopharmacokinetic engine (to predict the physical dose and secondary risk, and also control the pharmacokinetic and injection profile through analyzing patient data, including imaging, lab tests, and other clinical measurements), ii) a radiobiological optimizer (this module with improved biological dose and clinical outcomes prediction adding radiobiological data such as radiosensitivity, repair, and proliferation capacities using lab tests or other measurements), and iii) an immunological modulator (considering immune factors derived from lab tests and other measurements aimed at evaluating tumor microenvironment characteristics, immunological cell death, antigen, and cytokine expression to improve and personalize the model). The simulations revealed that Lutetium-177 provides more uniform dose distributions than Actinium225 due to the broader range of β particles with respect to α particles. However, the dose distribution for both α and β emitters in poorly vascularized domains is heterogeneous and the resulting dose delivered to the hypoxic tissues is suboptimal for both [^{177}Lu]-PSMA-ligands and [^{225}Ac]-PSMA-ligands. For both α and β emitters, a higher degree of oxygenation corresponds to a lower cell survival probability, being the efficacy of the [^{225}Ac]-PSMA-ligands therapy higher than that of [^{177}Lu]-PSMA-ligands. The findings highlight that tumor vascularization significantly impacts the dose distribution and effectiveness of PSMA radioligand therapy (RLT), particularly in hypoxic areas. Very recently, Hong et al. [58] tackled a similar problem and described their in-silico experience with spatial transcriptomics, modeling—at the cellular level—a method for dosimetry and biological effects of RLT in prostate cancer. They applied spatial transcriptomics to prostate cancer tissue samples to map the expression of hypoxia-related genes, malignant and endothelial cells, as well as key targets for RLT, including PSMA, FAP, and gastrin-releasing peptide receptor (GRPR). These data were used to model the spatiotemporal biodistribution of radiopharmaceuticals, generate absorbed dose maps, and analyze dose-volume histograms, ultimately estimating cell survival probabilities while accounting for dose and hypoxia information. In this study, [^{225}Ac]-PSMA RLT demonstrated greater efficacy than [^{177}Lu]-PSMA, highlighting its potential to overcome hypoxic microenvironments. The strong negative correlation between PSMA density and cell survival rate, particularly pronounced with Actinium-225, underscores the complexity of RLT and the need to consider ligand-specific responses for optimal therapeutic outcomes. When the in-silico PSMA-based RLT model was compared with those targeting FAP and GRPR, Actinium-225 consistently outperformed Lutetium-177 across targets, though FAP and GRPR displayed distinct spatial response patterns. Notably, tumor cell-rich regions exhibited lower FAP expression, leading to resistance to RLT in those areas. Overall, PSMA-targeted RLT showed superior therapeutic efficacy compared to those targeting FAP and GRPR. These findings highlight the diverse responses to radionuclides and targets, emphasizing the importance of tailored strategies in theranostics.

5. Discussion

Applications of DTs span over all medical fields in cardiovascular diseases, neuroscience, surgery, and nuclear medicine. DTs enable modeling various scenarios, such as drug administration or surgical procedures, or simulation of hypothetical molecular, cellular, and clinical states over time. Multiple simulations can explore different conditions, resulting in a DT cohort in which each twin represents a specific experimental condition. These simulations provide a powerful means to predict outcomes and improve personalized medicine, by exploring all possible solutions in silico [59]. A key application of DTS emerges in oncological treatments, where patient-specific decision making is critical to optimize therapy selection and improve outcomes.

From the literature review, numerous gaps in knowledge, methodological limitations, and barriers to clinical translation emerge. Many of the DTs described in the literature adopt a structure without the connection between the experimental data and the analysis method, or without the feedback loop between the decision-making unit and the experiment. In this streamlined form, the DTS functions as a linear sequence: starting with the experiment, progressing through the DT and the analysis method, and culminating in decision-making. The absence of feedback is often attributed to factors such as the prolonged timescales required for data collection, which can be challenging to access, or the high costs of managing huge unstructured datasets, leading to partial observations. These structures should be referred to as digital shadows rather than digital twins.

Unlike conventional simulations, the interactions between the components of a DTS are necessary to enable iterative data integration for informed decision-making, positioning the DTS as a system fundamentally designed for decision-making. In this context, feedback loops—i.e., bidirectional integration of real-world clinical or experimental data into the DT—are essential to refine predictions and ensure the twin evolves in synchrony with the patient's status. Moreover, an often overlooked but equally important aspect is the quantification of uncertainty in the outputs of the DTS, particularly when these are derived from data-rich but variable sources such as imaging modalities. Given the heterogeneity in image acquisition protocols, resolution, and segmentation algorithms, it becomes crucial to explicitly model and communicate the uncertainty associated with imaging-derived inputs and inferences. Doing so not only enhances the reliability and robustness of the DTS but also increases clinical trust in the system's recommendations.

Due to limitations in biological knowledge, DTs are not perfect replicas; however, they hold the promise to progressively approach a real system as we integrate data from different and multi-scale sources. Indeed, a DTS has the potential to integrate population-level oncology data with patient-specific dynamic data to refine treatment strategies over time. Population-level data, including genomics, histopathology, imaging, and survival models, serve as a digital template to build the DT of an individual patient. The patient's dynamic clinical data, such as molecular biomarkers, imaging findings, and treatment responses, are continuously fed into the DT model. The DTS runs iterative inference cycles, using updated patient data to simulate different treatment scenarios. These simulations help predict tumor progression, response to therapy, and potential side effects. At each clinical decision point, the DTS supports informed decision-making, helping oncologists personalize treatment plans by selecting the most effective interventions based on predicted patient-specific outcomes. This workflow is illustrated in Fig. 2. This dynamic and adaptive approach ensures that oncological treatments are continuously optimized as new data become available, allowing for a more personalized and precise path in cancer care. DTS models in oncology hold particular promise in radiotherapy planning, chemotherapy response prediction, and nuclear medicine applications, where imaging-based DT models can provide non-invasive insights into tumor biology and treatment response.

A critical challenge in developing reliable image-based DTs lies in the sparsity of imaging data, both in the longitudinal domain—where imaging is often acquired at irregular intervals or only at key clinical milestones—and in the spatial domain, where resolution limitations or incomplete anatomical coverage may lead to partial observations. This

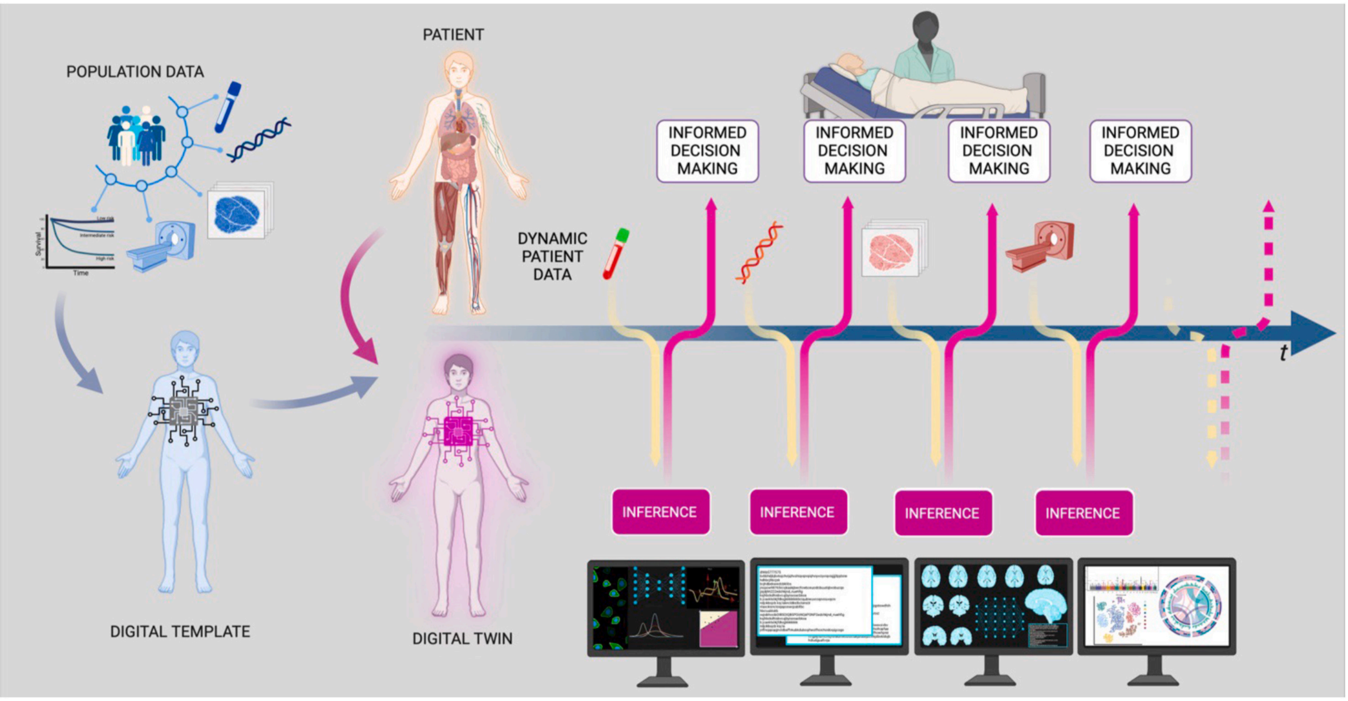


Fig. 2. Conceptual framework of a Digital Twin in computational nuclear oncology for personalized cancer care: this figure illustrates a computational framework leveraging Digital Twin technology to support personalized decision-making throughout the cancer care pathway. The process flows from left to right, beginning with population-level data and culminating in individualized, dynamic clinical decisions. Left Panel – Foundational Data Integration: the pipeline starts with the aggregation of population data, including genomic information, medical imaging, clinical guidelines, molecular diagnostics, and historical treatment outcomes. These diverse data sources inform the construction of a digital template — a generalized, modular model representing anatomical and physiological structures and typical disease progressions. Middle Left – Personalization through Dynamic Patient Data: this digital template is customized with dynamic patient-specific data such as individual imaging, histopathology, omics data (genomics, proteomics), and electronic health records (EHRs). The integration of these data layers results in the generation of a Digital Twin — a virtual replica of the patient that evolves in real-time as new data are acquired. Right Panel – Inference and Clinical Decision Support: the Digital Twin undergoes iterative inference cycles, where advanced computational modeling, machine learning, and data assimilation techniques continuously update predictions regarding disease evolution, therapy response, and toxicity risks. At each key decision point in the cancer care continuum — including diagnosis, treatment planning, therapy monitoring, and follow-up — the model informs informed decision-making, enabling clinicians to simulate interventions and evaluate personalized treatment strategies virtually before applying them in real life. As care progresses, clinical outcomes are fed back into the Digital Twin, enhancing the accuracy of future predictions through continuous learning. This feedback-enabled adaptive system transforms the static standard-of-care approach into a dynamic, patient-specific model that supports precision oncology. The iterative refinement of the Digital Twin ensures that therapeutic interventions are both personalized and optimized over time.

data sparsity can significantly impair the ability of the DT to capture disease progression with sufficient granularity or spatial fidelity, particularly in applications such as tumor growth modeling or treatment response assessment. To address these limitations, machine learning and statistical modeling approaches offer powerful tools for enhancing image-based DTs. For instance, generative models (e.g., variational autoencoders, GANs) can be used to infer missing spatial information or simulate intermediate time points, effectively densifying sparse imaging series. Similarly, probabilistic models can propagate uncertainty and impute unobserved regions or time points while maintaining physiological plausibility. These techniques not only help mitigate the impact of sparse data but also improve the robustness and continuity of the DT's evolution over time [60].

Although current medical DTs primarily function as high-fidelity predictive models calibrated to individual patients, the field is rapidly evolving toward systems with more autonomous and proactive capabilities. As digital twins become increasingly integrated with real-time clinical data streams, multimodal imaging, and advanced AI architectures, they are expected to transition from passive simulators into interactive and agentic digital companions that support medical decision-making [61].

Emerging developments such as VHTs exemplify this shift, emphasizing multiscale physiological representation, patient-specific learning, and integration across biological, behavioral, and environmental layers. Parallel advances in agentic AI and clinical decision-support systems indicate that future DTs may not only anticipate disease trajectories, but also evaluate treatment strategies, propose optimized interventions, and engage in continuous dialogue with clinicians and patients. This reflects a broader paradigm transition in medicine—from AI as a diagnostic tool to AI as a co-adaptive clinical partner.

Realizing this vision will require rigorous validation, transparency in algorithmic reasoning, and ethical frameworks that ensure safety, explainability, accountability, and patient trust. Nonetheless, these emerging directions underscore the transformative potential of DTs and VHTs to evolve into dynamic and intelligent entities capable of supporting high-precision, personalized, and anticipatory healthcare.

The success of digital twin technology depends on a robust data infrastructure, advanced computational models, clinical validation, and regulatory compliance. Multi-modal data — including genomics, imaging, health records, histopathology, biomarkers, and liquid biopsy — must be collected in a structured and standardized manner to ensure interoperability and scalability. To reliably approximate biophysical processes, gaps in knowledge regarding tumor growth, evolution models, and cellular and molecular pathways must be addressed. Additionally, pharmacokinetic and pharmacodynamic models need to be further elucidated to build robust and accurate predictions for drug response. The processing power required for large-scale simulations may emerge as a key challenge. Consequently, its impact on energy sustainability could become a critical concern in the future. Therefore, joint efforts among all stakeholders —including policymakers, industry leaders, academia, patients, and regulatory bodies — must be coordinated to ensure technological competitiveness and long-term societal well-being. As AI and computing technologies continue to evolve, DTs will play a crucial role in the future of precision oncology.

CRediT authorship contribution statement

Lara Cavinato: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Martina Sollini:** Writing – review & editing, Writing – original draft, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Laszlo Papp:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Kuangyu Shi:** Writing – review & editing, Data curation. **Dimitris Visvikis:** Writing – review & editing, Data curation. **Arturo Chiti:** Writing – review & editing, Data curation. **Margarita Kirienko:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Martina Sollini reports financial support was provided by Italian Association for Cancer Research. MK declares speaker honoraria from United Imaging and Novartis. L Papp is a consultant of Telix Pharmaceuticals (Melbourne, Australia). MS declares speaker honoraria and travel reimbursement from General Electric. Kuangyu Shi reports a relationship with Novartis AG that includes: funding grants, speaking and lecture fees, and travel reimbursement; with Boston Scientific Corporation that includes: funding grants and speaking and lecture fees; with Siemens Healthineers AG that includes: funding grants; with Hermes Medical Solutions AB that includes: funding grants; with DOSIsoft that includes: funding grants; with Varian Medical Systems Inc that includes: funding grants; with THQ Medical Products that includes: funding grants; with QDose that includes: funding grants; with PMOD that includes: funding grants; with Sirtex Medical Inc that includes: funding grants; with MIM Software Inc that includes: funding grants; with ICPO Foundation that includes: funding grants. AC reports consulting role for Blue Earth Diagnostics, Telix Pharmaceuticals and InnovaRadi Therapeutic. AC declares speaker honoraria from Bracco Diagnostics, General Electric, Novartis, Telix Pharmaceuticals and United Imaging. DV and LC declare no conflicts of interest.

MK and MS are Associate Editors of Cancer Imaging for the “Artificial intelligence, machine learning and radiomics” section. AC is Editor-in-Chief of the EANM journal. DV is the Editor-in-Chief of the IEEE TRPMS. **All Authors had no involvement in the peer review of this article and had no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to another journal editor.**

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Data availability

No data was used for the research described in the article.

References

[1] Appendix N: TA11 modeling, simulation, and information technology and processing | NASA space technology roadmaps and priorities: restoring NASA's technological edge and paving the way for a new era in space | The National Academies Press n.d. https://nap.nationalacademies.org/read/13354/chapter/21 (accessed November 7, 2025).

[2] Digital twin: manufacturing excellence through virtual factory replication. https://doi.org/10.5281/ZENODO.1493930; 2018.

[3] Aghamiri SS, Amin R, Isavand P, Vahdati S, Zeinoddini A, Kitamura FC, et al. Digital twin technology in radiology. Journal of Imaging Informatics in Medicine 2025;1–18:2025. https://doi.org/10.1007/S10278-025-01597-1.

[4] Drummond D, Gonsard A. Patient digital twins: an introduction based on a scoping review. medRxiv 2024. https://doi.org/10.1101/2024.02.20.24303096. 2024.02.20.24303096.

[5] Wickramasinghe N, Jayaraman PP, Forkan ARM, Ulapane N, Kaul R, Vaughan S, et al. A vision for leveraging the concept of digital twins to support the provision of personalized cancer care. IEEE Internet Comput 2022;26:17–24. https://doi.org/10.1109/MIC.2021.3065381.

[6] Dong Y, Lal A, Niven AS, Zhong X. Evolution of simulation and digital twin in health care: from discovery to design and integration. 2024. p. 249–66. https://doi.org/10.1007/978-3-031-69107-2_11.

[7] 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 2023:491–501. https://doi.org/10.1109/JBHI.2023.3323688.

[8] Liu G, Gu Y, Sollini M, Lazar A, Besson FL, Li S, et al. Expert consensus on workflow of PET/CT with long axial field-of-view. Eur J Nucl Med Mol Imaging 2025;52:1038–49. https://doi.org/10.1007/S00259-024-06968-4.

[9] Rahmim A, Brosch-Lenz J, Fele-Paranj A, Yousefirizi F, Soltani M, Uribe C, et al. Theranostic digital twins for personalized radiopharmaceutical therapies: reimagining theranostics via computational nuclear oncology. Front Oncol 2022;12. https://doi.org/10.3389/FONC.2022.1062592.

[10] Currie GM, Hawk KE, Rohren EM. The potential role of artificial intelligence in sustainability of nuclear medicine. Radiography 2024;30:119–24. https://doi.org/10.1016/J.RADI.2024.03.005.

[11] Currie GM, Rohren EM. Radiation dosimetry, artificial intelligence and digital twins: old dog, new tricks. Semin Nucl Med 2023;53:457–66. https://doi.org/10.1053/J.SEMNUCLMED.2022.10.007.

[12] Shamanna P, Saboo B, Damodharan S, Mohammed J, Mohamed M, Poon T, et al. Reducing HbA1c in type 2 diabetes using digital twin technology-enabled precision nutrition: a retrospective analysis. Diabetes Ther 2020;11:2703–14. https://doi.org/10.1007/S13300-020-00931-W.

[13] Ribeiro HAL, Vieira LS, Scindia Y, Adhikari B, Wheeler M, Knapp A, et al. Multi-scale mechanistic modelling of the host defence in invasive aspergillosis reveals leucocyte activation and iron acquisition as drivers of infection outcome. J R Soc Interface 2022;19. https://doi.org/10.1098/RSIF.2021.0806.

[14] Laubenbacher R, Adler F, An G, Castiglione F, Eubank S, Fonseca LL, et al. Toward mechanistic medical digital twins: some use cases in immunology. Front Digit Health 2024;6. https://doi.org/10.3389/FDGTH.2024.1349595.

[15] Castiglione F, Celada F. Immune system modelling and simulation. Immune System Modelling and Simulation 2015. https://doi.org/10.1201/B18274.

[16] Schürmann F, Courcol JD, Ramaswamy S. Computational concepts for reconstructing and simulating brain tissue. Adv Exp Med Biol 2022;1359:237–59. https://doi.org/10.1007/978-3-030-89439-9_10/FIGURES/7.

[17] Zhang S, Qin Y, Wang J, Yu Y, Wu L, Zhang T. Noninvasive electrical stimulation neuromodulation and digital brain technology: a review. Biomedicines 2023;11. https://doi.org/10.3390/BIOMEDICINES11061513.

[18] Wu C, Pineda F, Hormuth DA, Karczmar GS, Yankeelov TE. Quantitative analysis of vascular properties derived from ultrafast DCE-MRI to discriminate malignant and benign breast tumors. Magn Reson Med 2019;81:2147–60. https://doi.org/10.1002/MRM.27529.

[19] Partridge SC, Nissan N, Rahbar H, Kitsch AE, Sigmund EE. Diffusion-weighted breast MRI: clinical applications and emerging techniques. J Magn Reson Imaging 2017;45:337–55. https://doi.org/10.1002/JMRI.25479.

[20] Kirienko M, Gelardi F, Fiz F, Bauckneht M, Ninatti G, Pini C, et al. Personalised PET imaging in oncology: an umbrella review of meta-analyses to guide the appropriate radiopharmaceutical choice and indication. Eur J Nucl Med Mol Imaging 2024;52:208–24. https://doi.org/10.1007/S00259-024-06882-9.

[21] Sharma S. PET radiopharmaceuticals for personalized medicine. Curr Drug Targets 2016;17:1894–907. https://doi.org/10.2174/1389450117666160720091233.

[22] Wu C, Lorenzo G, Hormuth DA, Lima EABF, Slavkova KP, DiCarlo JC, et al. Integrating mechanism-based modeling with biomedical imaging to build practical digital twins for clinical oncology. Biophys Rev 2022;3. https://doi.org/10.1063/5.0086789.

[23] Sel K, Osman D, Zare F, Shahrbabak SM, Brattain L, Hahn JO, et al. Building digital twins for cardiovascular health: from principles to clinical impact. J Am Heart Assoc 2024;13. https://doi.org/10.1161/JAHA.123.031981.

[24] Rouhollahi A, Willi JN, Haltmeier S, Mehrtash A, Straughan R, Javadikasgari H, et al. CardioVision: a fully automated deep learning package for medical image segmentation and reconstruction generating digital twins for patients with aortic stenosis. Comput Med Imaging Graph 2023;109. https://doi.org/10.1016/J.COMPMEDIMAG.2023.102289.

[25] Dubs L, Charitatos V, Buoso S, Wegener S, Winklhofer S, Alkadhi H, et al. Assessment of extracranial carotid artery disease using digital twins - a pilot study. Neuroimage Clin 2023;38. https://doi.org/10.1016/J.NICL.2023.103435.

[26] Camps J, Lawson B, Drovandi C, Minchole A, Wang ZJ, Grau V, et al. Inference of ventricular activation properties from non-invasive electrocardiography. Med Image Anal 2021;73:102143. https://doi.org/10.1016/J.MEDIA.2021.102143.

[27] Azzolin L, Eichenlaub M, Nagel C, Nairn D, Sánchez J, Unger L, et al. AugmentA: patient-specific augmented atrial model generation tool. Comput Med Imaging Graph 2023;108. https://doi.org/10.1016/J.COMPMEDIMAG.2023.102265.

[28] Li L, Camps J, Jenny Wang Z, Beetz M, Banerjee A, Rodriguez B, et al. Toward enabling cardiac digital twins of myocardial infarction using deep computational models for inverse inference. IEEE Trans Med Imaging 2024;43:2466–78. https://doi.org/10.1109/TMI.2024.3367409.

[29] Cen S, Gebregziabher M, Moazami S, Azevedo CJ, Pelletier D. Toward precision medicine using a “digital twin” approach: modeling the onset of disease-specific brain atrophy in individuals with multiple sclerosis. Sci Rep 2023;13:1–14. https://doi.org/10.1038/s41598-023-43618-5. 2023 13:1.

[30] Sampson JH, Raghavan R, Brady ML, Provenzale JM, Herndon JE, Croteau D, et al. Clinical utility of a patient-specific algorithm for simulating intracerebral drug infusions. Neuro Oncol 2007;9:343–53. https://doi.org/10.1215/15228517-2007-007.

[31] Xia Y, Ravikumar N, Lassila T, Frangi AF. Virtual high-resolution MR angiography from non-angiographic multi-contrast MRIs: synthetic vascular model populations for in-silico trials. Med Image Anal 2023;87. https://doi.org/10.1016/J.MEDIA.2023.102814.

[32] Chumnanvej S, Chumnanvej S, Tripathi S. Assessing the benefits of digital twins in neurosurgery: a systematic review. Neurosurg Rev 2024;47. https://doi.org/10.1007/S10143-023-02260-5.

[33] Shu H, Liang R, Li Z, Goodridge A, Zhang X, Ding H, et al. Twin-S: a digital twin for skull base surgery. Int J Comput Assist Radiol Surg 2023;18:1077–84. https://doi.org/10.1007/S11548-023-02863-9.

[34] Servin F, Collins JA, Heiselman JS, Frederick-Dyer KC, Planz VB, Geevarghese SK, et al. Simulation of image-guided microwave ablation therapy using a digital twin computational model. IEEE Open J Eng Med Biol 2024;5:107–24. https://doi.org/10.1109/OJEMB.2023.3345733.

[35] Aubert K, Germaneau A, Rochette M, Ye W, Severyns M, Billot M, et al. Development of digital twins to optimize trauma surgery and postoperative management. A case study focusing on tibial Plateau fracture. Front Bioeng Biotechnol 2021;9. https://doi.org/10.3389/FBIOE.2021.722275.

[36] Swanson KR, Alvord J, Murray JD. A quantitative model for differential motility of gliomas in grey and white matter. Cell Prolif 2000;33:317–29. https://doi.org/10.1046/J.1365-2184.2000.00177.X.

[37] Weis JA, Miga MI, Arlinghaus LR, Li X, Chakravarthy AB, Abramson V, et al. A mechanically coupled reaction-diffusion model for predicting the response of breast tumors to neoadjuvant chemotherapy. Phys Med Biol 2013;58:5851–66. https://doi.org/10.1088/0031-9155/58/17/5851.

[38] Jarrett AM, Hormuth DA, Wu C, Kazerouni AS, Ekrut DA, Virostko J, et al. Evaluating patient-specific neoadjuvant regimens for breast cancer via a mathematical model constrained by quantitative magnetic resonance imaging data. Neoplasia 2020;22:820–30. https://doi.org/10.1016/J.NEO.2020.10.011.

[39] Wang Q, Vaupel P, Ziegler SI, Shi K. Exploring the quantitative relationship between metabolism and enzymatic phenotype by physiological modeling of glucose metabolism and lactate oxidation in solid tumors. Phys Med Biol 2015;60:2547–71. https://doi.org/10.1088/0031-9155/60/6/2547.

[40] Wang Q, Liu Z, Ziegler SI, Shi K. A Reaction-Diffusion Simulation Model of [$$ˆ{18}$$ F]FDG PET Imaging for the Quantitative Interpretation of Tumor Glucose Metabolism. Lecture Notes in Computational Vision and Biomechanics 2015;22:123–37. https://doi.org/10.1007/978-3-319-18431-9_13.

[41] Shi K, Bayer C, Gaertner FC, Astner ST, Wilkens JJ, Nüsslin F, et al. Matching the reaction-diffusion simulation to dynamic [18F]FMISO PET measurements in tumors: extension to a flow-limited oxygen-dependent model. Physiol Meas 2017;38:188–204. https://doi.org/10.1088/1361-6579/AA5071.

[42] Birindelli G, Drobnjakovic M, Morath V, Steiger K, D’alessandria C, Gourni E, et al. Is hypoxia a factor influencing PSMA-directed radioligand therapy?—an in silico study on the role of chronic hypoxia in prostate cancer. Cancers 2021;13:3429. https://doi.org/10.3390/CANCERS13143429. 2021;13:3429.

[43] Kelly CJ, Brady M. A model to simulate tumour oxygenation and dynamic [18F]-Fmiso PET data. Phys Med Biol 2006;51:5859–73. https://doi.org/10.1088/0031-9155/51/22/009.

[44] Segars WP, Sturgeon G, Mendonca S, Grimes J, Tsui BMW. 4D XCAT phantom for multimodality imaging research. Med Phys 2010;37:4902–15. https://doi.org/10.1118/1.3480985.

[45] Cavinato L, Hong J, Reinhard S, Wartenberg M, Zunino P, Manzoni A, et al. A tissue-aware simulation framework for [18F]FLT spatiotemporal uptake in pancreatic ductal adenocarcinoma. CIBCB 2023 - 20th IEEE conference on computational intelligence in bioinformatics and computational biology. 2023. https://doi.org/10.1109/CIBCB56990.2023.10264884.

[46] Cavinato L, Hong J, Wartenberg M, Reinhard S, Seifert R, Zunino P, et al. Unveiling the biological side of PET-derived biomarkers: a simulation-based approach applied to PDAC assessment. Eur J Nucl Med Mol Imaging 2025;52:1708–22. https://doi.org/10.1007/S00259-024-06958-6.

[47] Parach AA, Rajabi H, Askari MA. Assessment of MIRD data for internal dosimetry using the GATE monte carlo code. Radiat Environ Biophys 2011;50:441–50. https://doi.org/10.1007/S00411-011-0370-0.

[48] Stabin MG, Peterson TE, Holburn GE, Emmons MA. Voxel-based mouse and rat models for internal dose calculations. J Nucl Med 2006;47.

[49] Dogdas B, Stout D, Chatziioannou AF, Leahy RM. Digimouse: a 3D whole body mouse atlas from CT and cryosection data. Phys Med Biol 2007;52:577. https://doi.org/10.1088/0031-9155/52/3/003.

[50] Bitar A, Lisbona A, Thedrez P, Sai Maurel C, Le Forestier D, Barbet J, et al. A voxel-based mouse for internal dose calculations using monte carlo simulations (MCNP). Phys Med Biol 2007;52. https://doi.org/10.1088/0031-9155/52/4/010.

[51] Bitar A, Lisbona A, Bardiès M. S-factor calculations for mouse models using Monte-Carlo simulations. Q J Nucl Med Mol Imag 2007;51.

[52] Bednarz B, Grudzinski J, Marsh I, Besemer A, Baiu D, Weichert J, et al. Murine-specific internal dosimetry for preclinical investigations of imaging and therapeutic agents. Health Phys 2018;114. https://doi.org/10.1097/HP.0000000000000789.

[53] Mauxion T, Barbet J, Suhard J, Pouget JP, Poirot M, Bardiès M. Improved realism of hybrid mouse models may not be sufficient to generate reference dosimetric data. Med Phys 2013;40. https://doi.org/10.1118/1.4800801.

[54] Gupta A, Lee MS, Kim JH, Lee DS, Lee JS. Preclinical voxel-based dosimetry in theranostics: a review. Nucl Med Mol Imaging 2020;54. https://doi.org/10.1007/s13139-020-00640-z.

[55] Fele Paranj A, Uribe C, Saboury B, Rahmim A. Theranostic digital twins laboratory (TDTLab): a platform for Numerical experimentation with PBPK models for optimization of radiopharmaceutical therapies. J Nucl Med 2023;64:P1419. P1419.

[56] Abdollahi H, Saboury B, Soltani M, Shi K, Uribe C, Rahmim A. Radiopharmaceutical therapy on-a-chip: a perspective on microfluidic-driven digital twins towards personalized cancer therapies. Sci Bull (Beijing) 2023;68:1983–8. https://doi.org/10.1016/J.SCIB.2023.08.009.

[57] Abdollahi H, Yousefirizi F, Shiri I, Brosch-Lenz J, Mollaheydar E, Fele-Paranj A, et al. Theranostic digital twins: concept, framework and roadmap towards personalized radiopharmaceutical therapies. Theranostics 2024;14:3404–22. https://doi.org/10.7150/THNO.93973.

[58] Hong J, Bae S, Cavinato L, Seifert R, Ryhiner M, Rominger A, et al. Deciphering the effects of radiopharmaceutical therapy in the tumor microenvironment of prostate cancer: an in-silico exploration with spatial transcriptomics. Theranostics 2024;14: 7122–39. https://doi.org/10.7150/THNO.99516.

[59] Emmert-Streib F, Yli-Harja O. What is a digital twin? Experimental design for a data-centric machine learning perspective in health. Int J Mol Sci 2022;23. https://doi.org/10.3390/IJMS232113149.

[60] Cavinato L, Kirienko M, Papp L, Shi K, Visvikis D, Chiti A, et al. A roadmap for AI-aided digital twins in computational nuclear oncology: a position paper by the EANM. The EANM Journal 2025;1:100007. https://doi.org/10.1016/J.EANMJ.2025.100007.

[61] Ryhiner M, Song Y, Saboury B, Glatting G, Rahmim A, Shi K. Mathematical and computational nuclear oncology: toward optimized radiopharmaceutical therapy via digital twins. Pet Clin 2025. https://doi.org/10.1016/J.CPET.2025.09.005.