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Digital twins for chronic lung diseases

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Abstract

Digital twins have recently emerged in healthcare. They combine advances in cyber-physical systems, modelling and computation techniques, and enable a bidirectional flow of information between the physical and virtual entities. In respiratory medicine, progress in connected devices and artificial intelligence make it technically possible to obtain digital twins that allow real-time visualisation of a patient's respiratory health. Advances in respiratory system modelling also enable the development of digital twins that could be used to predict the effectiveness of different therapeutic approaches for a patient. For researchers, digital twins could lead to a better understanding of the gene-environment-time interactions involved in the development of chronic respiratory diseases. For clinicians and patients, they could facilitate personalised and timely medicine, by enabling therapeutic adaptations specific to each patient, and early detection of disease progression. The objective of this review is to allow the reader to explore the concept of digital twins, their feasibility in respiratory medicine, their potential benefits, and the challenges to their implementation.

Take home message

Digital twins, integrating cyber-physical systems and simulation, are becoming technically feasible in respiratory medicine. They could improve understanding of chronic diseases, enable personalised and timely interventions, and support patient-centred care.

Points for clinical practice:

- Digital twins combining real-time monitoring and simulation have the potential to enable personalised and timely interventions for patients with chronic respiratory diseases.
- Involving patients in the development of their digital twins and setting shared goals between patients, parents, and clinicians will be key for patient-centred care.
- Integrating digital twins into clinical workflows will require addressing issues of data privacy, algorithm bias, and liability for automated recommendations.

Questions for future research:

- How can monitoring and simulation digital twins be optimally combined to leverage their complementary strengths for respiratory medicine applications?
- What are the most meaningful and engaging ways to visually represent a patient's respiratory health status through their digital twin?
- How can the risk of exacerbating health inequities with digital twin technologies be mitigated, particularly for disadvantaged and elderly populations?
- What study designs and endpoints should be used to rigorously evaluate the clinical efficacy, safety, cost-effectiveness and environmental impact of digital twins?

Digital twins for chronic lung diseases

The term 'digital twin' has recently emerged in the healthcare field. Although this term may initially be perceived as a mere buzzword, it actually refers to an innovative technological product that integrates technical advances from various domains. This technology could offer significant benefits for patients with respiratory diseases. The objective of this review is to allow the reader to explore, first, the concept of digital twins and its origins; second, the feasibility of digital twins in respiratory medicine; third, their potential benefits for patients, healthcare professionals, and researchers; and finally, the current challenges and future directions for the development and implementation of digital twins in respiratory care.

1. The concept of digital twins

1.1 From engineering and industry...

The digital twin concept was first introduced at the University of Michigan in 2002 during a product lifecycle management course[1]. On one of his slides, Michael Grieves laid out the notions of real space, virtual space, and a bidirectional flow of information between the two spaces. The first use of the term "digital twin" dates back to 2012 in a report by the National Aeronautics and Space Administration (NASA)[2]. The digital twin was defined as "an integrated multiphysics, multiscale, probabilistic simulation of an as-built vehicle or system that uses the best available physical models, sensor updates, fleet history, etc., to mirror the life of its corresponding flying twin".

While M. Grieves' concept emphasises the three elements of the system - the physical twin, the digital twin, and the bidirectional flow between the two, NASA's approach focuses on the digital twin itself as a highly advanced simulation system. This is related to the fact that the concept of digital twins integrates advances in two different fields: cyber-physical systems and simulation.

Cyber-physical systems are systems where computational elements collaborate for the control and command of physical entities[3]. They represent a new stage in the industrial revolution: after the first industrial revolution and the steam engine, the second industrial revolution and the machine tool, the third (digital) industrial revolution and the automated machine, some authors consider that we have entered the fourth industrial revolution of the intelligent machine[4, 5]. This "intelligence" is made possible thanks to (i) the numerous sensors integrated into machines that allow a real-time representation of its state; (ii) networks that can integrate data from multiple sensors and multiple machines; (iii) machine learning techniques that enable the processing of this data; (iv) actuators that implement changes to the physical system based on insights derived from machine learning algorithms. A typical example of a cyber-physical system is the autonomous car[6]: based on data collected by multiple sensors, transmitted via different networks and processed via various algorithms, the direction and speed of the car is modified in real-time. The concept of digital twins was born partly from the developments of these cyber-physical systems, i.e., from these bi-directional information exchanges between physical entities and virtual entities.

Simulation is one of the major technologies in aerospace. Physical simulators were used very early on by NASA, notably participating in the rescue of the crew of the Apollo 13 mission by allowing different strategies to be tested on the ground[7]. With the digital revolution, these physical simulators gradually evolved into virtual simulators that became increasingly realistic as modelling techniques improved. The next step was to develop a digital replica of each aircraft in the fleet that follows its evolution from construction to destruction. This digital replica makes it possible to monitor the "health" of the aircraft as it is used in order to reduce costs by optimising its maintenance operations[2, 8]. The concept of digital twins was born partly from this evolution of modelling, which has become high-fidelity and system-specific.

As a result of advances in cyber-physical systems and modelling, the concept of digital twins has attracted interest in many fields. Beyond the manufacturing[9] and aerospace industries[10], digital twins are currently being developed for the management of cities[11, 12], transport[13], agriculture[14], hospital management design and care coordination[15].

This growing interest in the concept of digital twins has led the National Academies of Sciences, Engineering and Medicine in the United States to appoint a committee to identify needs and opportunities to advance the mathematical, statistical, and computational foundations of digital twins in applications across science, medicine, engineering, and society. The report of this work, published in 2024, defined a digital twin as "a set of virtual information constructs that mimics the structure, context, and behaviour of a natural, engineered, or social system (or system-of-systems), is dynamically updated with data from its physical twin, has a predictive capability, and informs decisions that realise value. The bidirectional interaction between the virtual and the physical is central to the digital twin"[16]. This definition extends the concept of digital twins to "natural systems", and thus paves the way for digital twins of patients.

1.2 ...To patients

The concept of a patient digital twin is quite intuitive. Most people are familiar with the term "twins" to refer to two siblings born on the same day, and "avatar" for a virtual representation. Thus, the idea of a patient digital twin, corresponding to a digital avatar allowing the visualisation and monitoring of a person's health status, predicting its evolution, and helping to adapt and personalise their care, should be comprehensible and accessible to both patients and healthcare professionals (Figure 1).

However, a real question arises as to the transferability of the concept of the digital twin, born in an engineering context, to healthcare and in particular to the patient. Indeed, there are several difficulties in developing patient digital twins compared to digital twins of engineered systems

such as an aircraft. First, while an aircraft is created from parts whose nature and mechanical, thermal, chemical, and electrical properties are known, physical and biological processes that underline the functioning of different parts of the human body remain incompletely understood[17]. Second, while humans design the assembly plan for aircraft and thus have a multi-scale view of the aircraft from the smallest electrical unit to the entire apparatus, the same cannot be said of cell-tissue, tissue-organ, and organ-organ interactions which remain incompletely elucidated. Third, while it is easy to integrate a growing number of sensors into an aircraft to obtain an increasingly faithful digital replica, obtaining a data flow from the human body requires the implantation or wearing of sensors with their attendant technical, medical and ethical problems[18]. Fourth, while modifications to the aircraft are easily implemented through actuators, having a human factor in the loop, whether a patient or a healthcare professional, adds a degree of uncertainty to the system. Fifth, unlike aircraft, whose "health" depends solely on mechanical and physical factors, patients' health also includes emotional and spiritual dimensions that must be taken into account[19].

With this in mind, our team conducted a systematic literature review including all peer-reviewed articles that claimed to have developed a digital twin of a patient or part of a patient to provide an overview of what authors claimed as "patient digital twin"[20]. Eighty-six studies corresponding to 80 unique "claimed digital twins" were included up to 2023. Many "claimed digital twins" identified in the scoping review had in fact no characteristics that could make them relate to a digital twin. We therefore proposed that a patient digital twin be defined as "a viewable digital replica of a patient, organ, or biological system that contains multidimensional, patient-specific information and informs decisions". This definition therefore excludes: (i) non-patient-specific systems, such as generic organ and biological system modelling used for drug development[21, 22], or virtual patients generated for in silico trials not linked to a real patient[23, 24]; (ii) purely cyber-physical systems, without patient visualisation such as

artificial pancreas [25]; (iii) models created from a single data source such as images from a scanner[26]. Next, we identified two major trends through an unsupervised analysis of the characteristics of the claimed digital twins using the partitioning around medoids method, guided by silhouette width analysis [20] (Figure 2):

- Digital twins relying mainly on cyber-physical systems, named "monitoring patient digital twins". This type of digital twin is based on a data-driven approach, allowing the representation of all or part of the patients from data collected via connected objects, and informing decisions thanks to analyses carried out by machine learning techniques. These are dynamic systems that allow the patient to be followed over time, sometimes in real-time. To be differentiated from a telemonitoring system, this type of digital twin must rely on multiple data sources, allow visualisation of the patient's organ, system, or body, and integrate data analysis systems that inform decision-making. None of the articles included in this review met all of these requirements, but some advanced systems suggested that this type of digital twin should quickly emerge.

- Patient digital twins relying mainly on simulation, named "simulation patient digital twins". This type of digital twin is based on a mechanistic approach, allowing the representation of all or part of the patients from anatomical (3D) and/or physiological modelling of their organ or biological system. These models allow simulations to be carried out to predict the evolution of the disease or the effectiveness of different therapeutic approaches. These are generally static systems, for one-time assessments, due to the need to acquire data in-hospital (CT scan, MRI). An emblematic example is that of digital twins of the heart, which start from the patient's imaging data to obtain a 3D model of their heart, and integrate electrophysiology models and the patient's specific electrocardiograms[27]. Such digital twins allow, for example, the prediction of the effectiveness of different ablation strategies in patients with atrial fibrillation[28].

2. Towards digital twins in respiratory medicine

Among the 80 claimed digital twins identified in the systematic review, only six (8%) claimed digital twins were related to respiratory medicine compared to 20 (25%) and 10 (13%) related to cardiovascular and musculoskeletal systems, respectively[20]. Among these six claimed digital twins, three did not meet the definition of a patient digital twin because they were limited to personalised prediction models without a viewable representation of the patient or their lungs. The other three corresponded to "simulation patient digital twins". This small number of digital twins in respiratory medicine raises the question of their feasibility, whether for monitoring or simulation digital twins.

2.1 From sensors to monitoring digital twins in respiratory medicine

Monitoring digital twins rely on the combination of multiple sensors, visualisation and decision systems, and actuators (Figure 2). In respiratory medicine, each of these elements has undergone technical advances over the past ten years.

First, sensors are becoming more numerous, reliable, and acceptable[29–31]. The first types of monitoring were "active", meaning that the sensors required the active participation of the patient. A typical example is connected spirometers, used at home by patients. Whether in asthma, chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), cystic fibrosis, or lung transplantation, home spirometry gives reliable results, with values often slightly below those collected in pulmonary function testing laboratories, but allowing longitudinal monitoring of patients at home[32–35]. Less well validated, the numerous commercially available oximeters are also widely used by patients with chronic respiratory diseases[36]. More recently, wearable stethoscopes associated with artificial intelligence algorithms can be used by patients to monitor their lung sounds[37, 38]. The major limitation

of this type of sensor for a digital twin is that they require the active participation of the patient. In most pathologies, daily recording of spirometry or SpO₂ increases the burden of care without changing medical outcomes, resulting in a rapid decrease in compliance[39]. Passive monitoring, on the other hand, uses sensors that require very little investment from the patient and are better suited to a continuous or near-continuous flow of data to the digital twin. Smart inhalers and nebulisers that record patients' use of treatments, and sometimes their inhalation technique, provide information on adherence to inhaled treatments and/or deterioration of asthma in the event of recourse to emergency treatment[40, 41]; smart watches or bracelets provide data on patients' level of physical activity, heart rate and SpO₂ values[42, 43]; passive recording of cough using smartphone-based acoustic artificial intelligence software is also promising with applications in all respiratory diseases[44, 45]; finally, as respiratory diseases are strongly impacted by air quality, geolocation associated with environmental databases and wearable air quality sensors represent an indispensable data source for most digital twins[46].

Data from different sensors can be integrated into a single database. To meet the sus-mentioned definition of a digital twin, this data must be presented in a meaningful way with a visible representation of the patient. At a time when it is possible to create one's avatar from a picture on the internet[47], the problem lies less in technical feasibility but in finding a consensual definition of what meaningful representations is in respiratory medicine between healthcare professionals, patients, and engineers.

The data must also give rise to automated processing by algorithms to inform decision-making. Advances in machine learning, both supervised and unsupervised, are becoming increasingly effective in predicting patient trajectories and risks of exacerbation, with several examples in asthma and COPD [48–51]. Rather, the challenge is to address the ethical and legal implications of using these algorithms for clinical decision-making, as well as the practical barriers to

seamlessly integrating these advanced tools into everyday clinical workflows and decision-making processes[18].

Finally, actuators allowing feedback to the patient can be in automated form or in the form of recommendations. Automated feedback concerns feedback that passes through machines such as automated adjustments of oxygen flow by the concentrator[52]. Recommendation feedback can be made directly to the patient, or via the healthcare professional. Large language models could here directly transform an algorithm output into an understandable and justified recommendation to the patient.

Thus, progress in digital health makes possible monitoring digital twins in respiratory medicine that would allow real-time monitoring of reliable virtual representations of the health status of patients with respiratory diseases.

2.2 From models to simulation digital twins in respiratory medicine

Simulation digital twins are based on a mechanistic approach, primarily focused on physics in the context of respiratory care.

2.2.1 General considerations on physical modelling toward digital twins

Many models have been proposed for the lungs, and it is important to recall the famous aphorism “all models are wrong, but some are useful”—in that sense, models should not be compared in terms of “which one best describes the lungs?”, but instead in terms of “which one best addresses the investigated question?”.

In the following sections, we chose to classify the different models based on the physical processes they represent in the pulmonary context, such as airflow and ventilation, blood flow, gas exchange, tissue motion and deformation, and tissue remodelling (Figure 3). However, this choice is somewhat arbitrary; we could have alternatively classified these models based on

spatial scales, ranging from molecular and cellular to organ levels, or based on temporal scales, such as the short timescales of chemical reactions to the longer timescales of tissue remodelling.

An aspect to consider is the data that the model can assimilate. Some data (that correspond to model input or output, e.g., pressure-volume curves) can be used directly for model personalisation (i.e., adapting model parameters using optimisation techniques to minimise the distance between observed data and model predictions), while other data require data processing steps. This is especially true for images, which might require segmentation to extract geometries [53, 54], registration to extract motion [55, 56], etc.

Another aspect to consider when comparing models is the associated computational cost. Indeed, if some of the models discussed later can be solved in real time on a standard computer, other require dedicated computer codes and hours of computing time on super computers. The development of digital twins can make this computational cost issue especially critical.

In summary, the art of modelling in the context of digital twins consists in finding the “right” (with respect to the question to address) trade-off between physiology, modelling complexity, computational cost and available data.

2.2.2 Reduced respiratory models

Global respiratory models, often called "reduced" or "lumped", aim to represent the lungs' main functions (ventilation and gas exchange) by modelling relationships between global variables rather than explicitly representing each mechanism. The simplest “single-compartment” models basically represent the global pressure-volume relationship of the lung together with some basic O₂/CO₂ diffusion models [57, 58], while the most complex models can have hundreds of compartments that can exchange air and diffuse O₂/CO₂ [59–61], some even including blood “compartments” to take into account hemodynamics [62, 63].

Such models can integrate breathing and air/blood composition data, such as inspired/expired oxygen fraction, blood partial pressure of O₂/CO₂ and pH, cardiac output, etc. They have already been applied to various clinically relevant questions, including better understand how COPD [64] or Covid [65] affect breathing, how various manoeuvres affect alveoli recruitment [66, 67], the role of PEEP in ARDS patients [68], etc. Interesting reviews can be found in [69, 70].

If these models are good at representing the global function of the lungs, they are intrinsically limited at representing finer or more complex phenomena. That is why refined models of specific phenomena have been developed. Depending on the objective, these fine models can be designed autonomously, or in interaction with a reduced model of the rest of the system [71, 72].

2.2.3 Refined air flow models

To better represent the complex flow of air within the airway tree, 3D flow models have been developed [73–75]. Since only the larger airways can be represented while keeping a reasonable computational cost, one very important question is the coupling with the smaller airways represented in a lumped manner [76, 77]. Another distinction between approaches comes from the airway walls, which can be fixed [78] or moving [73, 79] to represent the breathing motion. Such models can be based on idealised [80] or personalised [81] geometries, which are then extracted from clinical images through segmentation. Once personalised, such digital twins can notably be used to study aerosols penetration and drug deposition [82, 83].

2.2.4 Refined gas exchange models

Gas exchanges in the lungs have been the subject of an extensive literature since a long time [84, 85]. However, well established models are still being debated, and novel relations proposed [86, 87]. 3D models of blood perfusion and gas exchanges within alveolar walls have been

proposed [88, 89], though such detailed models have not yet been coupled to global respiratory models.

2.2.5 Refined tissue motion/deformation models

The lung parenchyma has also attracted many contributions from the solid mechanics community. If original work aimed at describing how the alveolar structure generates the tissue-scale mechanical properties (i.e., stiffness/compliance) based on idealised microstructures [90–92], more recent work used realistic acinar microstructures (obtained from micro-CT images though image segmentation, cf. [93, 94] for instance) to study the complex deformation patterns of such structures [95, 96], potentially including surface tensions at the air-wall interface and the effect of surfactant [82, 97, 98].

At the organ scale, the lung has been modelled as a compressible solid [99], or as a poroelastic solid (i.e., a mixture of solid, which can deform, and fluid, which can flow in, out & within the solid) [100–102]. In terms of boundary conditions (i.e., forces and pressures applied onto the lung body and boundary that drive the deformation), many proposals have been made, including simple pressure fields representing the pleural pressure [99, 102], complex pressure fields that depend on gravity and the lung shape [103], contact conditions with the thoracic cage [101], etc.

Such organ-scale models can be personalised to a given patient by extracting geometry (cf. [53, 104] for instance), texture (as in [105]) and motion (at least two images, e.g., end-expiration and end-inspiration, are necessary for this) and identifying model parameters that make the model as close as possible to the data.. For instance, in the case of pulmonary fibrosis, it was hypothesised that regional compliance estimated through such digital twins could represent objective and quantitative biomarkers for early diagnosis and treatment monitoring [106, 107]

2.2.6 Tissue remodelling modelling

All models discussed until now are located at the breathing temporal scale. However, taking into account in the models the long-term remodelling mechanisms that take place in health and disease could help better understand disease evolution, and allow digital twins to make prognosis—maybe someday treatment optimisation. If general continuum models of remodelling have been proposed for living tissues [108, 109], discrete models are usually easier to formulate and implement. Various remodelling models have been proposed specifically for the lungs, notably continuum models of inflammation [110] and of growth-induced obstruction [111] in airways, as well as discrete models of fibrosis in the alveolar wall [112, 113].

In summary, significant progress has been made in the last few decades to develop physics-based modelling of the respiratory system that could be used for the development of multi-physics, multi-scale digital twins of patient lungs.

3. Expected benefits of digital twins in chronic respiratory diseases

Advances in cyber-physical systems and modelling have brought the development of digital twins for chronic respiratory diseases closer to technical feasibility. Future investments in research and development to further refine and implement this technology are justified in view of the expected benefits for the population, the three main ones being a better understanding of the development of chronic respiratory diseases, personalised and timely medicine, and patient-centred medicine (Figure 4).

3.1 A better understanding of the development of chronic respiratory diseases

The most common respiratory diseases in children and adults, i.e., asthma and COPD, are not monogenic diseases, but syndromes that cover different pathophysiology[114]. While some susceptibility genes have been identified, many environmental factors are also involved, making these diseases examples of gene (G)-environment (E) interaction. As the impact of these environmental factors is not the same depending on the time of the individual's life, Augusti et

al. proposed the principle of G x E x T (time) and thus of GETomics to better understand and act on the development of chronic respiratory diseases[115, 116]. It should be noted that the time dimension includes the age of the individual at which a GxE interaction takes place, but also the cumulative history of all previous interactions resulting in the current state of the lung. This is particularly important for the evolution of FEV1 over the course of life, which in adulthood is a predictor of all-cause mortality[117].

Digital twins embody this principle of GETomics: they integrate data from multiple sources, whether the patient's genomic data (G), data from their environment collected via multiple sensors (E), and the time factor by being dynamic representations of these patients over time (T). Thus, this type of information system could allow a better understanding of the development of the main chronic respiratory diseases through the ages.

3.2 Personalised and timely respiratory medicine

Digital twins allow us to take a further step towards personalised medicine. Simulation digital twins, by combining anatomical and physiological approaches make therapeutic adaptations specific to each patient possible. In radiology, Zhu et al. developed a personalised and dynamic 3D digital model of a patient's lungs, created from their CT scan images and electrical impedance tomography (EIT) measurements, thus integrating the patient's lung mechanical and electrical properties with anatomical data[118]. In intensive care, Förster et al. presented a high-resolution, patient-specific digital lung model of a premature newborn, based on their imaging and functional tests, allowing simulation and 3D visualisation of the regional distribution of oxygen in the patient's lung and optimisation of their high-frequency ventilation settings[119]. Finally, in surgery, Tai et al. developed a personalised and dynamic 3D digital model of the lungs of 90 patients based on their imaging and clinical data. These virtual lungs were viewable via a mixed reality system allowing the surgeon to visualise, interact, and thus test different surgical procedures[120]. These examples of patient simulation digital twins were the only three

identified in the systematic review presented above but already show the potential applications of simulation digital twins.

Digital monitoring twins have the potential to add personalisation to the timing of diagnosis and management. Chronic respiratory diseases alternate between periods of stability, progressive worsening, and exacerbations. The current system of scheduled consultations at fixed intervals has the consequence that the doctor is faced with a *fait accompli* when they find that a child with asthma has experienced multiple severe attacks requiring oral corticosteroid therapy since the last visit, or that an adult with ILD has had a substantial decline in their FEV1. Early detection of progression and worsening is a major challenge that digital twins could contribute to not only through connected sensors but also through their integration of the patient's cumulative history. For example, the detection of an abnormally high level of pollen and pollution in the environment of a patient who has already had an asthma attack under these conditions could lead the digital twin to recommend that the patient not engage in outdoor sports and/or wear a mask.

3.3 A patient-centred approach to respiratory medicine

In addition to its personalised nature, the viewable aspect of the digital twin is a central element for patient-centred medicine[121]. The ability for the patient to visualise the state of their lungs and environment in real-time at any moment should allow them to better understand their disease and the interaction of environmental factors on their respiratory system, and encourage them to take care of their digital twin and thus their respiratory health. This is particularly important in diseases such as asthma where patients may stop their maintenance treatment, thinking they are "cured" in the absence of symptoms, while their bronchial inflammation persists and puts them at risk of a severe attack. The digital twin should also enrich discussions between doctor and patient and lead to a more collaborative approach around optimising the health of the digital twin.

On the clinician side, visualisation of the digital twin is also crucial. Just as the first computer systems only displayed lines of code before being replaced by graphical interfaces, digital twins must replace dashboards and allow the patient's state of health to be visualised at a glance to facilitate decision-making or the interpretation of the digital twin's recommendations. This is all the more necessary as the amount of data relating to a patient has only grown exponentially over the last hundred years. In anaesthesia and intensive care, presenting the different data from the monitor in the form of an avatar helps to reduce the perceived workload of clinicians[122]. Finally, the fact that the digital twin is an avatar of the patient is important for quality care, firstly because the clinician can immediately see which patient it is and relate their previous knowledge of the patient to the current problem of their digital twin, and secondly because it adds a human dimension to the care by reminding the doctor that they are treating patients and not numbers, which could reduce the risk of burnout.

4. Challenges and future research directions

Digital twins share the technical issues related to all systems using artificial intelligence, whether they concern the quality of the data collected, their transfer speed, their integration, their security, the risk of bias in algorithms, and the liability issues of the recommendations made [123].

Data quality and accuracy are crucial for reliable digital twins. Inaccurate or incomplete data can result in flawed representations and unreliable insights. Digital twins also require longitudinal data, which increases the risk of incomplete datasets and presents significant challenges to model accuracy. Maintaining data integrity across different sources over time necessitates robust data management, interoperability standards, and continuous quality validation to ensure the safe and effective use of digital twins in healthcare[124].

Data interoperability is a key challenge for digital twins in managing chronic lung diseases. Healthcare data comes from diverse sources such as electronic health records, laboratory results, and wearable devices, each using different formats and terminologies. This creates significant barriers to data integration, which is essential for constructing accurate and functional digital twins. Common data models (CDMs), like the Observational Medical Outcomes Partnership, are crucial in addressing these challenges by standardising data across different sources[125]. By harmonising data structures and vocabularies, CDMs enable the integration of complex datasets, making them more useful for digital twin applications[126]. In addition, Health Level 7 (HL7) Fast Healthcare Interoperability Resources (FHIR) is a widely adopted standard specifically designed to enable the seamless exchange of healthcare information across different systems in real time. FHIR ensures that data from various sources—whether electronic health records, wearable devices, or monitoring systems—can be integrated and communicated efficiently[127]. Within the European Respiratory Society, the CRC (clinical research collaboration) CONNECT (Moving multiple digital innovations towards connected respiratory care: Addressing the over-arching challenges of whole systems implementation) launched in 2023 is advancing the field towards an interoperable connected digital ecosystem that should help to achieve digital twins for patients with respiratory disease[128].

From a legislative perspective, current regulations such as the Health Insurance Portability and Accountability Act (HIPAA), the General Data Protection Regulation (GDPR), and the European Union Artificial Intelligence Act (EU AI Act) provide effective frameworks for ensuring data privacy, security, and algorithmic transparency. This is particularly important for digital twins, which rely on the aggregation of extensive personal health information and the generation of automated recommendations. Such sensitive data makes digital twins especially vulnerable to misuse if accessed by unauthorised parties.

However, despite these regulations, digital twins present unique challenges that extend beyond the scope of current legislative frameworks. Indeed, unlike traditional medical data collection, digital twins require an ongoing data stream to maintain an accurate virtual representation of a patient's condition. This need for constant updates raises significant regulatory concerns, particularly regarding how and when patient consent should be renewed or updated. The continuous nature of these updates also impacts decision-making authority, as digital twins may support or even drive clinical decisions based on dynamic, evolving data. Current regulations do not adequately address how such ongoing data collection, consent renewal, or automated decision-making processes should be managed, underscoring the need for specific regulatory frameworks tailored to the complexities of digital twins in healthcare[129].

The concept of a patient digital twin integrating patients and doctors as "humans in the loop" means that human factors must also be taken into account. First, the acceptability of such a system deserves to be studied. Two studies conducted in France revealed that among 295 parents of children with asthma surveyed in 2019 before the Covid pandemic, 55% would agree to use such a digital twin system combining sensors and automated recommendations[130], while among 95 parents surveyed in 2022 after the pandemic, 69% were ready to use the same type of system for managing their child's asthma[131]. The two factors associated with refusal of the system were, on the one hand, the importance attached to the human doctor-patient relationship and, on the other hand, a disadvantaged socio-economic level.

Concerning the doctor-patient relationship, it is common to anticipate that digital twins will reduce interactions. However, a systematic literature review led by the CRC CONNECT and the DRAGON project[132] on the impact of digital health interventions on the patient-provider relationship in respiratory medicine showed that telemonitoring systems were associated with easier patient access to their healthcare professional and a pleasant feeling of being cared for

constantly, or a "guardian angel" effect. Moreover, creating a patient's digital twin requires working with the patient on the goals that the digital twin's algorithms should seek to achieve. In paediatric asthma, a study revealed that children attach the most importance to reducing their symptoms during exercise, their parents to preserving their child's respiratory function, and their doctors to avoiding severe asthma attacks[133]. Within the same triad, correlations were very low, and only in-depth discussions between the three parties would allow coordination of the digital twin's objectives. Thus, this study supported the idea that the more digital there is, the more humanity is needed.

Finally, the risk of exacerbating inequalities is a genuine concern due to the cost of the system and the lower digital literacy among certain populations, particularly those from disadvantaged socioeconomic backgrounds and the elderly[134]. Mitigating this risk will depend on the industrialisation of digital twins, which could significantly reduce costs, and on integrating these systems from childhood, ensuring familiarity and acceptance throughout the lifespan[135].

The next steps from a technological perspective are to obtain digital twins that combine simulation and monitoring patient digital twins, i.e., digital twins based on both mechanistic and data-driven approaches, as is already emerging in cardiology[136]. From a medical perspective, digital twins in respiratory medicine will only truly be established once clinical research studies have demonstrated their clinical efficacy, safety, cost-effectiveness, and environmental impact.

In conclusion, while the term 'digital twin' may appear to be a buzzword, it actually covers the evolution and integration of two technologies: cyber-physical systems and simulation. Although many challenges remain, digital twins represent a real opportunity to improve the management of patients with chronic respiratory diseases.

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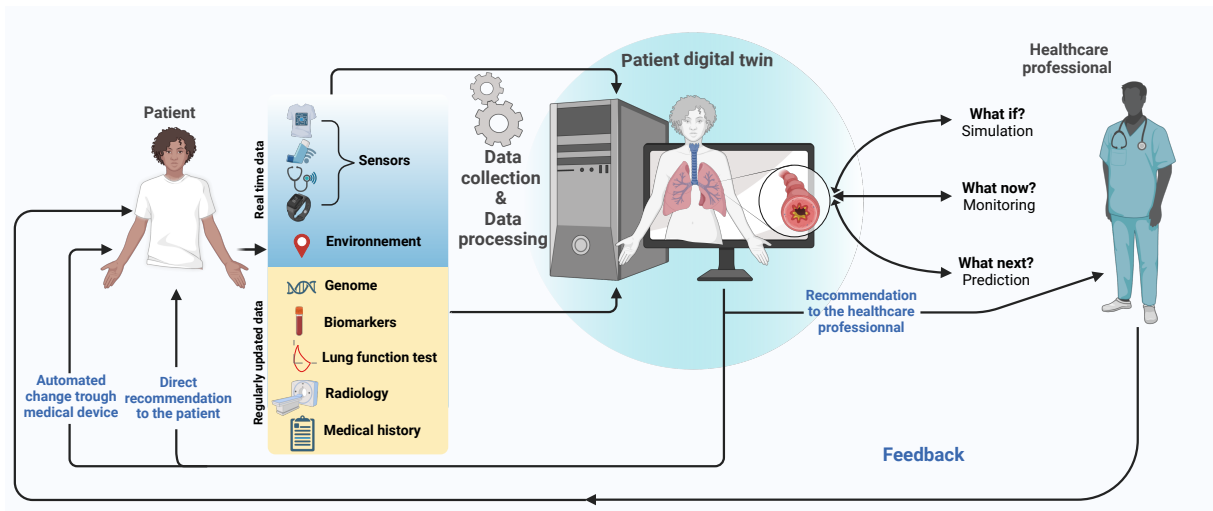
Figure legends

Figure 1: Components a patient digital twin system for respiratory diseases.

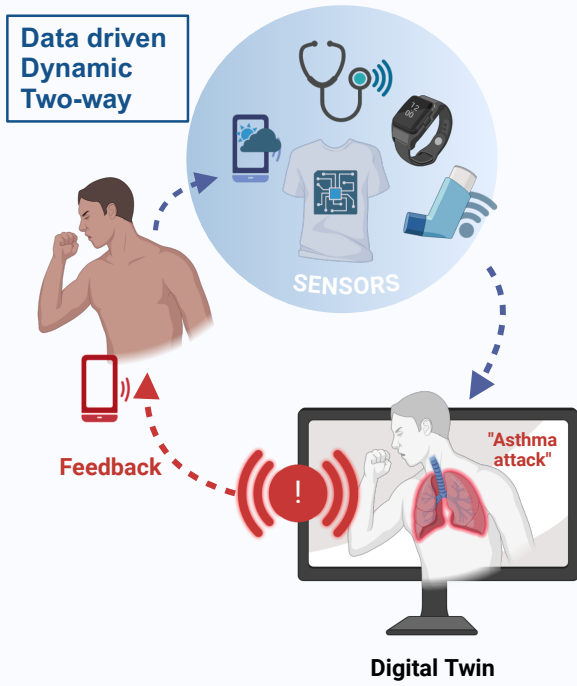
Figure 2: Comparison of monitoring and simulation digital twins for chronic lung diseases.

Figure 3: Multi-physics and multi-scale aspects of lung modelling for simulation digital twins

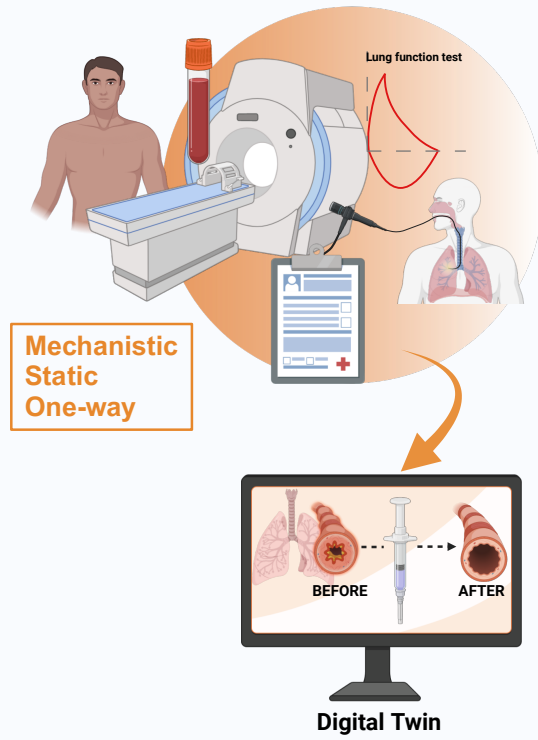
Figure 4: Expected benefits and main challenges of patient digital twins in chronic lung diseases



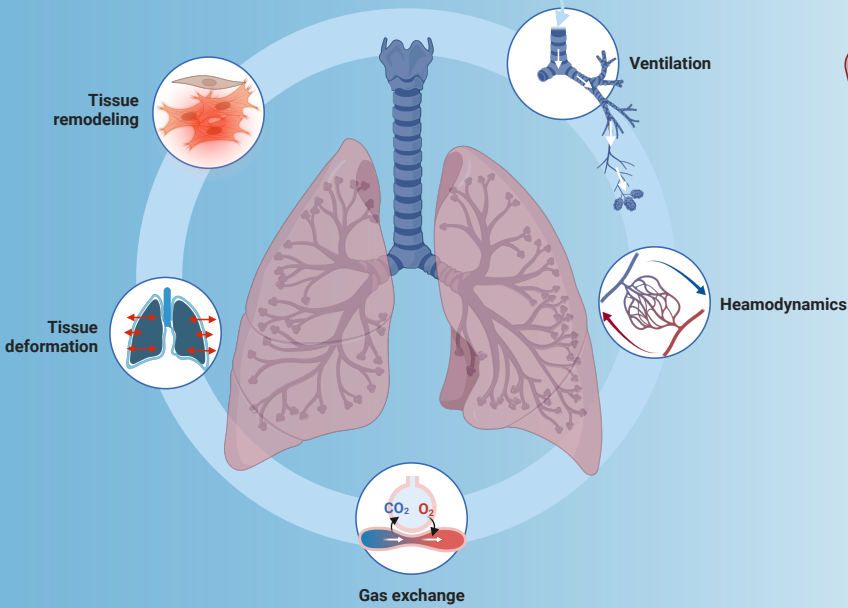
Monitoring Digital Twin



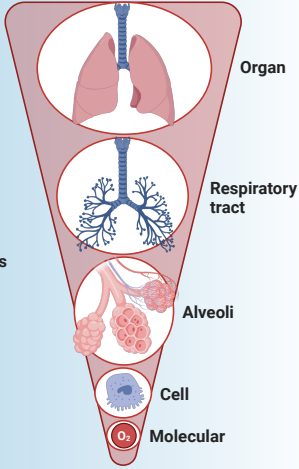
Simulation Digital Twin



Physics in lung modelling



Spatial scale in lung modelling



Temporal scale in lung modelling



