Digital Twins and AI for Precision Medicine

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AI Applications in Medicine

- Disease diagnosis, screening, monitoring, and treatment
- Large language models (LLMs)
- Clinical decision support
- Virtual reality and augmented reality
- New drug discovery
- Virtual clinical trials
- Telemedicine

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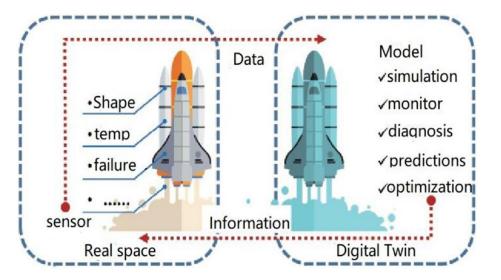
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- Human machine interface
- Digital twins for health

Modern medicine is increasingly becoming a science of information

What is a Digital Twin?

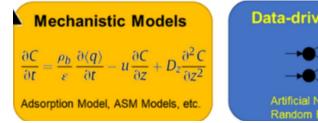
- A digital representation of a real-world physical system that serves as the effectively indistinguishable digital counterpart of the original for simulation, integration, testing, monitoring and maintenance
- Used in real time and regularly synchronized with the physical system
- Originated from NASA in 2010 to improve physical model simulation of spacecraft

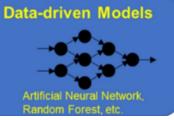


Three Catalysts

• Multimodal data

• Mechanistic & data-driven modeling





• High-performance computing



Clinical Demographics, EHR Data,

Lab Test Results, Diagnoses,

Procedures, Pathology/

Histology Data, Radiology

nages, Microbiology Data,

Discharge and Progress

Provider Notes Admission

Medication

Medication Orders.

Administration

Dose, Route, NDC/RxNorm

codes) Concomitant

Therapies,

Point of Sale Data,

(Prescription & OTC)

Claims

Medical Claims,

Prescription Drug Claims.

Other Drug and Treatment

Use Data

Molecular Profiling

Genomic and Genetic

Testing Data (SNPs/Panels)

Multi-Omics Data

(Proteomics

Transcriptomics,

Metabonomics,

Lipidomics). Other

Family History

Historical Data on

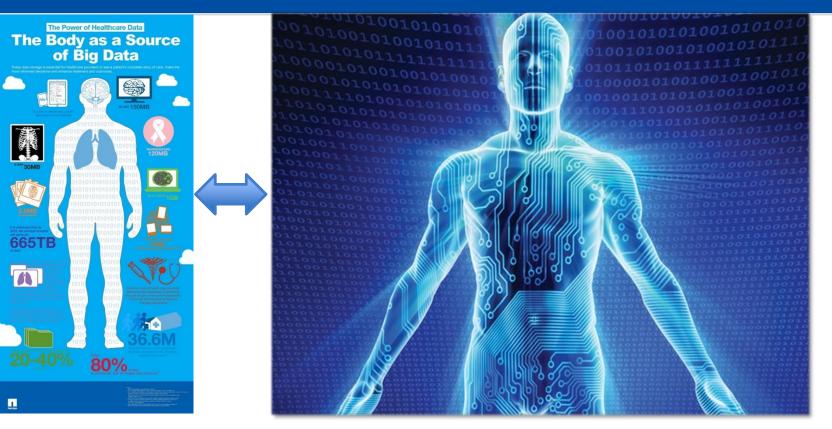
Health Conditions and

Allergies Relating to

Patient and Extended

Family, Smoking

Our Big Idea



NATIONAL ACADEMIES Sciences Engineering Medicine

Foundational Research Gaps and **Future Directions** for Digital Twins

REAL WORLD PATIENT

The patient and the tumor from which data is gathered using various clinical assessments to inform the digital twin.

VVUO ---> Verification, validation, and uncertainty quantification

As the patient and tumor are constantly evolving and the data collection can also change over time, VVUQ must occur continually for digital twins

Uncertainty guantification needs to be addressed for all aspects of the digital twin, including the patient's data, modeling and simulation, and decision making.

DIGITALTWIN

The virtual representation comprised of models describing temporal and spatial characteristics of the patient and turnor with dynamic updates using data from the real world patient.



Modeling

Models spanning a range of fidelities and resolutions may be utilized and potentially integrated together.

As new observed data are acquired, the data are assimilated and the models are calibrated, updated, and estimated.

CONTINUED DATA COLLECTION TREALMENTS 0 MODELING

Clinical assessments

Data are collected in many ways:







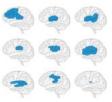


assessments



Human and digital twin interaction

Utilizing the simulated predictions and related uncertainties, the clinician and patient can make informed clinical-decisions around treatment and also the clinical assessments, which affect the data informing the digital twin.

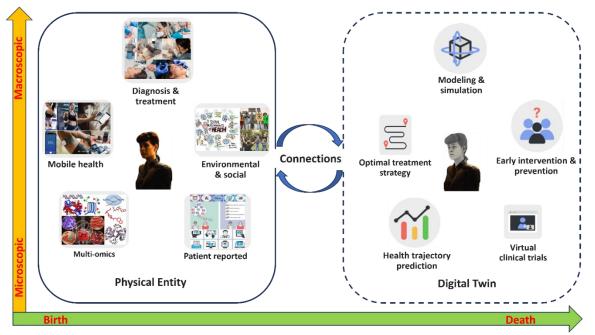


Simulations & predictions

Simulations of potential treatments can generate predictions of outcome and in turn can be optimized to determine the most favorable treatment options.

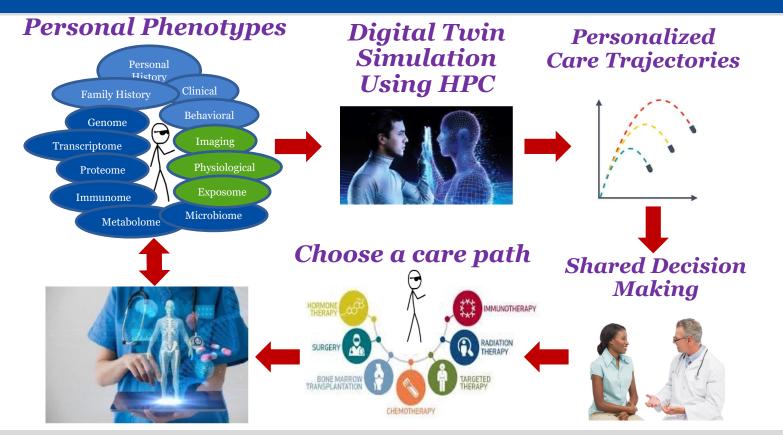
A Human Digital Twin

• A dynamic virtual representation of an individual, an organ, or an organ system based on multiscale modeling of multimodal data



Yale SCHOOL OF MEDICINE Katsoulakis et al, npj Digital Medicine, 7, 77 (2024)

The Big Picture

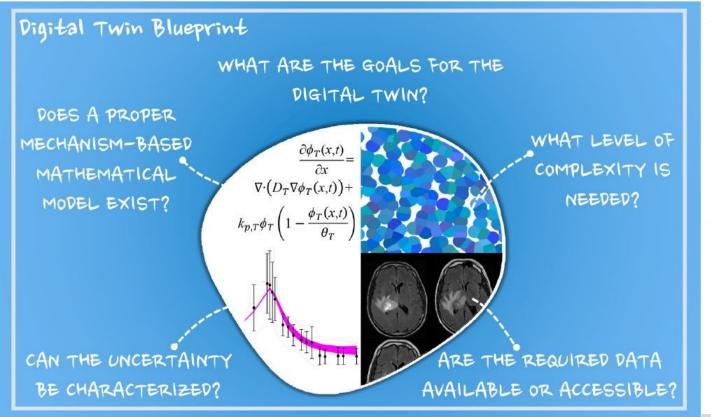


What Would DT Enable?

- Incorporate genetic, molecular, clinical, environmental, and social factors to predict individual trajectories
 - Identify optimal treatment strategy
- Predict outcomes and side effects throughout one's health trajectory

 Improve quality of life
- Benchmark clinical performance via virtual control
 - Enable virtual clinical trial
- Early intervention and prevention for general public

Digital Twin Blueprint



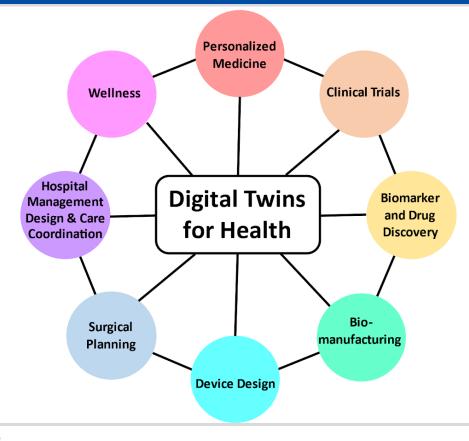
 "All models are wrong but some are useful", George Box

• "Everything should be made as simple as possible, but not simpler", Albert Einstein

Yale school of medicine

Wu et al., Biophysics Rev. 3, 021304 (2022)

Main Applications of DT in Health



Virtual Clinical Trials

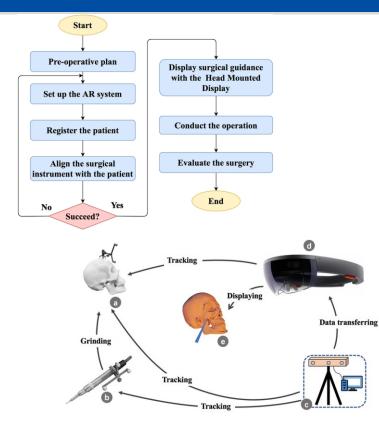
- Increase the statistical power
- Enhance patient recruitment
 - Targeted selection of right patients and in silico simulation for estimated outcomes
 - Increase the likelihood of success for the proposed trial
- Help physicians in making adaptive and personalized clinical decision for their patients

Virtual Drug Testing

- Testing various candidate drugs against a target protein can be done through computational models
- Candidates can be ranked according to their ability to interact with the target their binding affinity
- Best candidates then chosen for the patient specific target

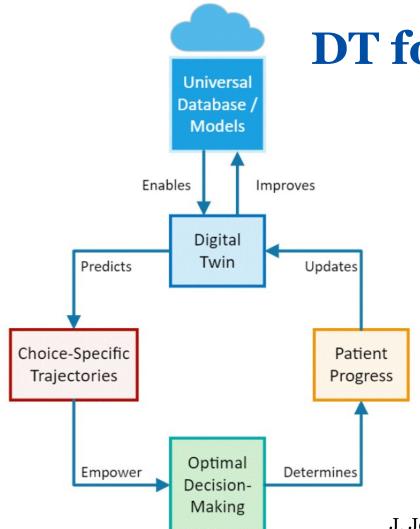


DT of a Surgical Patient





Liu et al. Sci Rep 11, 10043 (2021)



DT for Radiation Oncology

Components

- Multimodal patient data
- Multiscale modeling
- High-performance computing

<u>Benefits</u>

- Predicting patient outcomes
- Treatment plan optimization
- Innovative research tools

Barriers

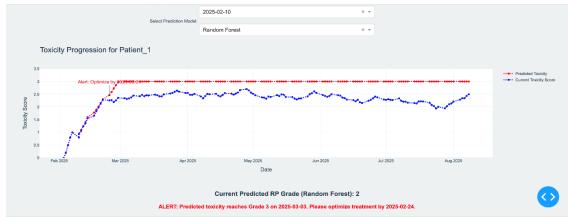
- Centralized data commons
- Patient-specific data assembly
- Multiscale modeling

J. Jensen and J. Deng, https://doi.org/10.1145/3543873.3587688

Cancer Patient Digital Twin

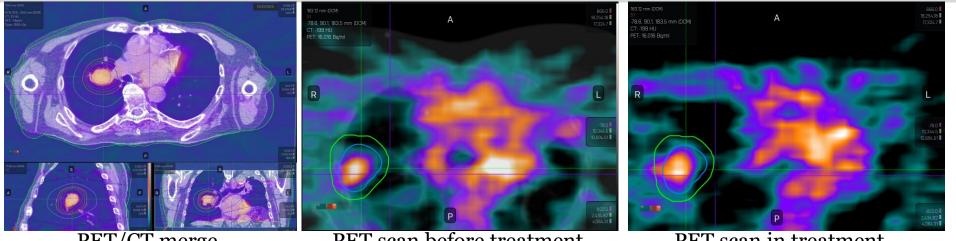


- Patient health prediction
- Treatment outcome trajectory
- Shared decision-making involving patients
- Whole body all organ tracking and monitoring



Human body is an all-connected dynamic and open system

Biology-Guided Radiotherapy



PET/CT merge

PET scan before treatment

PET scan in treatment

A reaction diffusion model including RT-induced cell death

$$\frac{\partial c}{\partial t} = \nabla \cdot (D\nabla c) + \rho c \left(1 - \frac{c}{k}\right) - R(x, t, Dose) c \left(1 - \frac{c}{k}\right)$$

Develop digital twins to predict NSCLC response to RT *via* integrating mechanistic modeling with patient-specific longitudinal PET scans

Challenges

Data Acquisition, Integration, Standard, and Quality

- Multimodal data acquisition, integration and curation
- Data standards, quality and accuracy

Multiscale Modeling and Simulations

- Complex human behaviors with vast dynamic impacting factors and sophisticated causal relations
- Dynamic biological phenomena at multiscale in space-time

Responsible AI

- Fairness, transparency (explainability), accountability, robustness, safety, privacy, and security

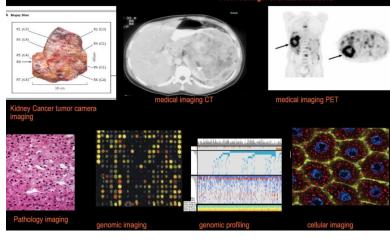
Computing Infrastructure

- HPCs, quantum computing, and their access

Multimodal Data Fusion

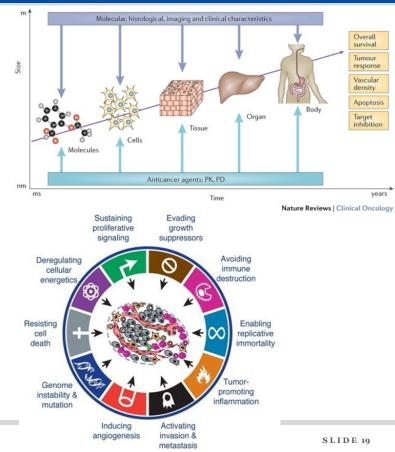
- Functional and molecular imaging
- Radiomics (deep learning-augmented analysis of radiology)
- Liquid biopsies (e.g., circulating tumor cells)
- Whole-slide, highly-multiplexed digital pathology
- Genomic profiling
- Single-cell profiling (e.g., scRNA-seq)
- Patient-derived cell cultures, organoids, & assays
- Intravital imaging (live microscopy within a patient)
- Fitness trackers & wearables
- Implantable sensors

Each technology gives new light on a patient's health state, but it is challenging to coherently <u>fuse</u> these together

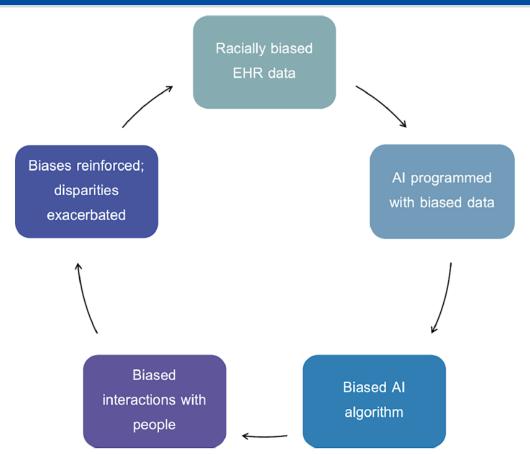


Complex Human Body

- Individual cell processes and dynamics
- Interactions between heterogeneous cells
- Physical constraints (e.g., oxygen diffusion, mechanical barriers)
- Procedures can cause toxicity, resistance, and long-term adverse effects
- Constant interactions with environment
- Social determinants influence one's health and wellbeing across life course
- Many factors involved (e.g., lifestyle, dietary, family history, medication)



Responsible AI



- Require right people, right processes, and right technologies
- Clinical practitioners need to be trained to understand what responsible AI means, what tools and metrics are available to quantify and evaluate responsible AI
- Appropriate technologies need to be used to enforce responsible AI from the beginning to the end for every model, every time

Into the Future

- Artificial General Intelligence (AGI)
 - PhD level intelligent systems/robots (arriving in 2029 or so?)
- Quantum computing
 - > 10⁸ times faster than Frontier HPC
- Physical AI or spatial intelligence
 - AI that can see, talk, and do
- Human digital twin from birth to death
 - Fully autonomous as HDT agents
 - Companion and safeguard of one's health

Ability to simulate the future has been a motive for human intelligence evolution

Take Home Messages

- Digital twins have great potential in precision medicine
- Deep understanding of human biology is the key
- Multimodal data integration and multiscale modeling are challenging
- We must tame AI before the arrival of AGI
- Cross-disciplinary collaborations are essential

Acknowledgement



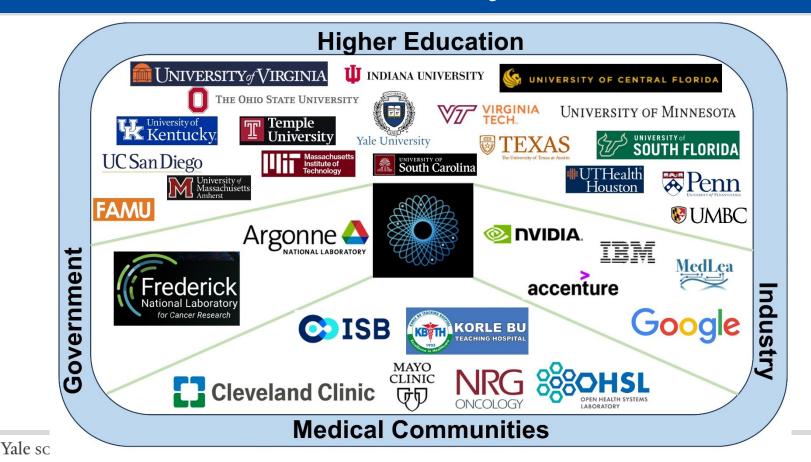
Digital Twins for Health Consortium

Digital Twins for Health Consortium



- Yale
- Florida A&M University
- George Washington University
- Indiana University
- MIT
- Ohio State University
- Temple University
- University of Virginia
- University of Kentucky
- University of Texas Austin
- University of Texas Health
- U of California San Diego
- U of Maryland Baltimore County
- UMass Amherst
- University of South Carolina
- University of Pennsylvania
- University of Central Florida
- University of South Florida
- University of Minnesota
- Virginia Tech
- Mayo Clinic
- IBM
- Accenture

DT4H Ecosystem





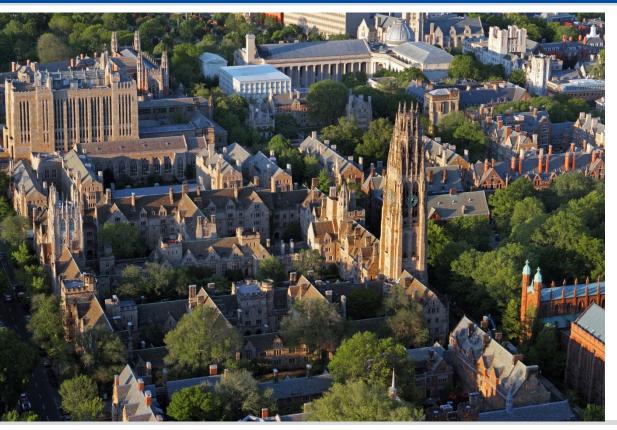
Digital Twins for Health

Digital Twins for Health Consortium

Forging a leading international network in developing and applying digital twins for better health and well-being in collaboration with all the stakeholders in the healthcare spectrum.

https://dt4h.org

Thank You



Yale Smart Medicine Lab

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