DT and AI for Precision Medicine

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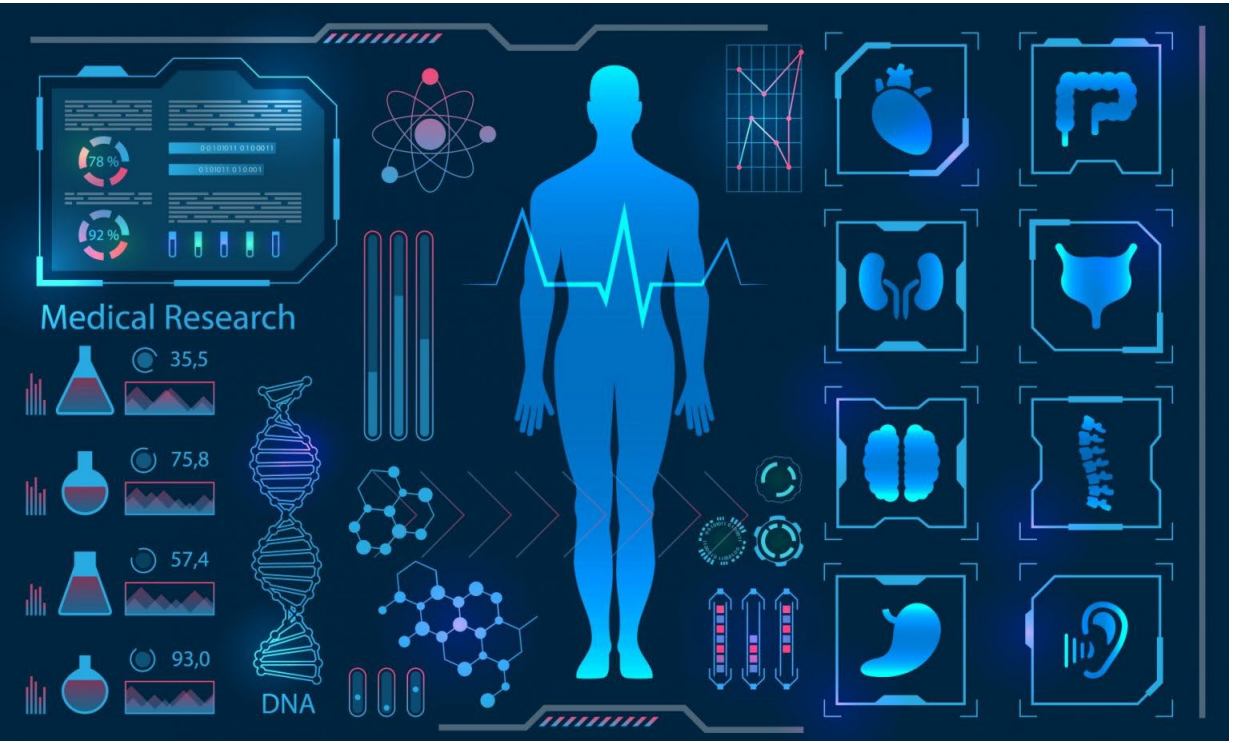
Precision Medicine



- Uses one's genes, proteins, environment, and lifestyle information to prevent, diagnose, or treat disease
- Target the right patients with the right treatments at the right time

How is AI Changing the Future of

Precision Medicine?

Identifying Potential Drug Targets

Identifying Causal Genes

Real-Time Monitoring of Patient Health

Phenotypic & Genetic Heterogeneity

AI-Powered Early Detection of Diseases

Changing Role of Physicians

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
- Human machine interface
- Digital twins for health
- ……

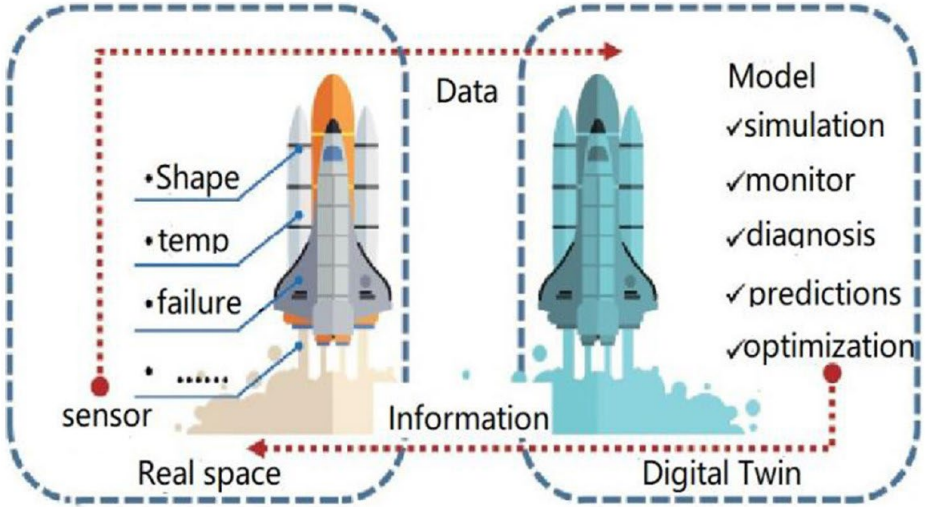
Modern medicine is increasingly becoming a science of information

What is a Digital Twin?

- **A digital representation of a real-world physical system or process** that serves as the effectively indistinguishable digital counterpart of the original for practical purposes such as simulation, integration, testing, monitoring and maintenance

- Used in real time and **regularly synchronized** with the physical system

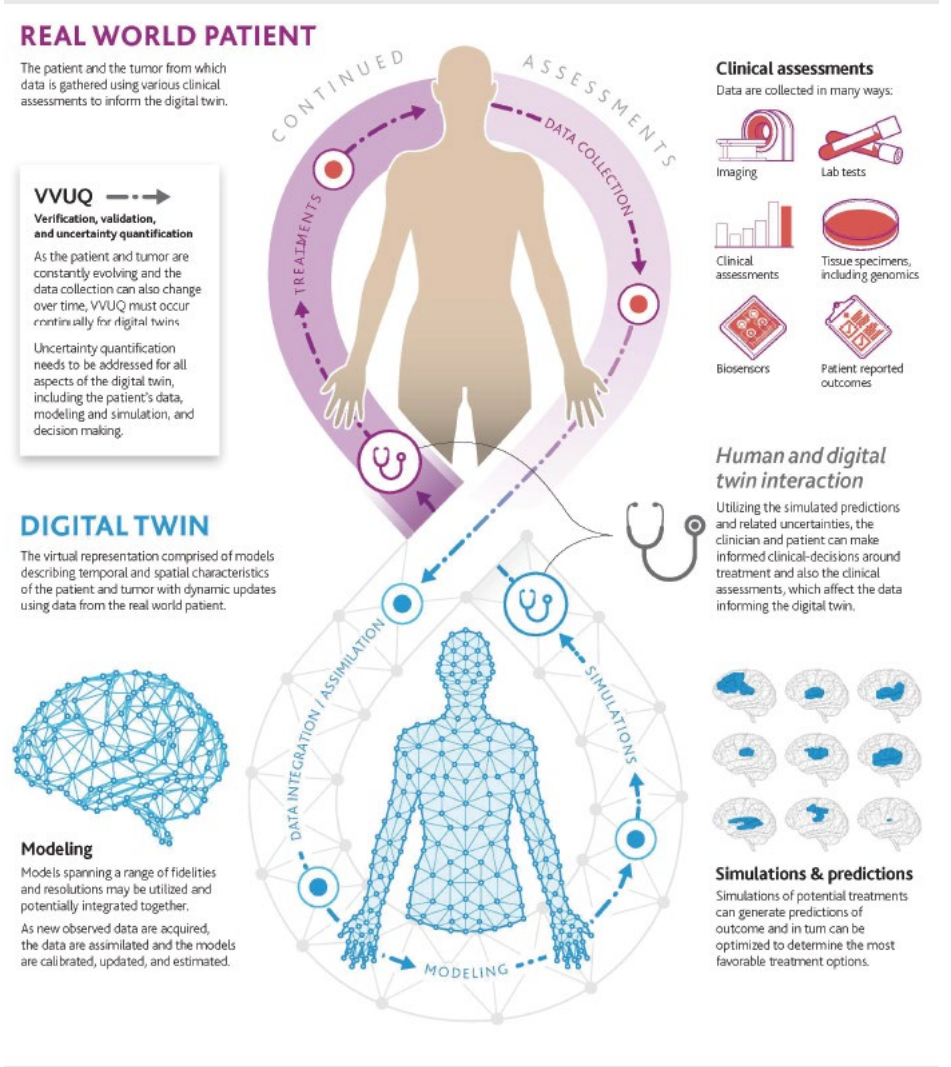
- Originated from NASA in 2010 to improve physical model simulation of spacecraft



NATIONAL ACADEMIES *Sciences Engineering Medicine*

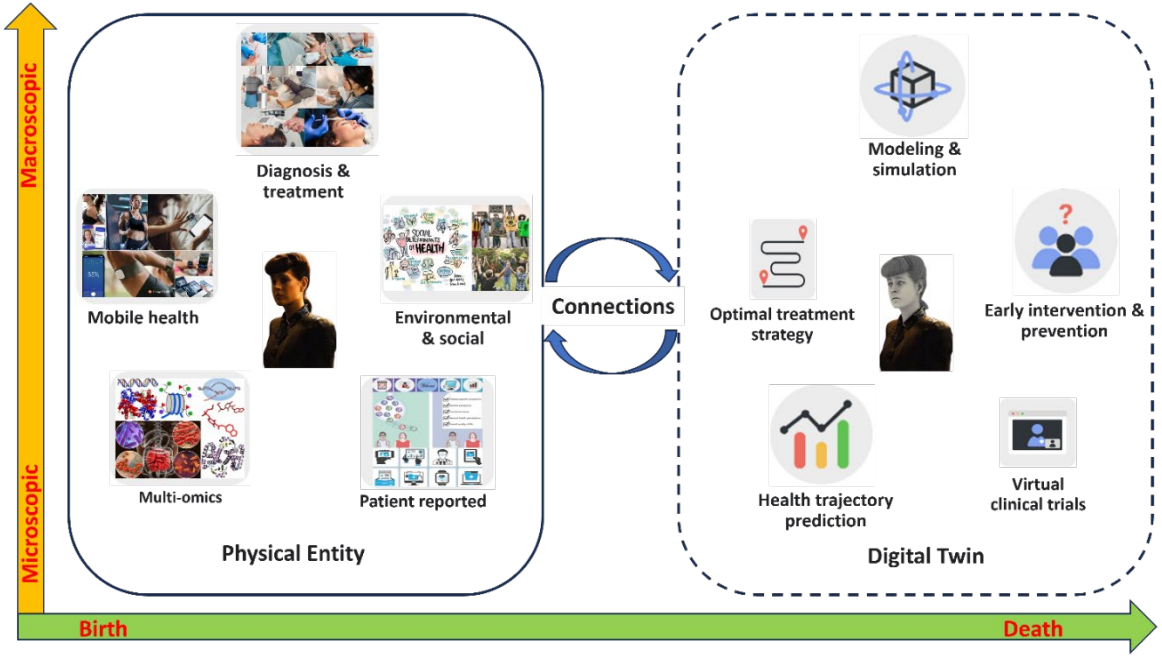
Foundational Research Gaps and Future Directions for Digital Twins

Consensus Study Report



A Human Digital Twin

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

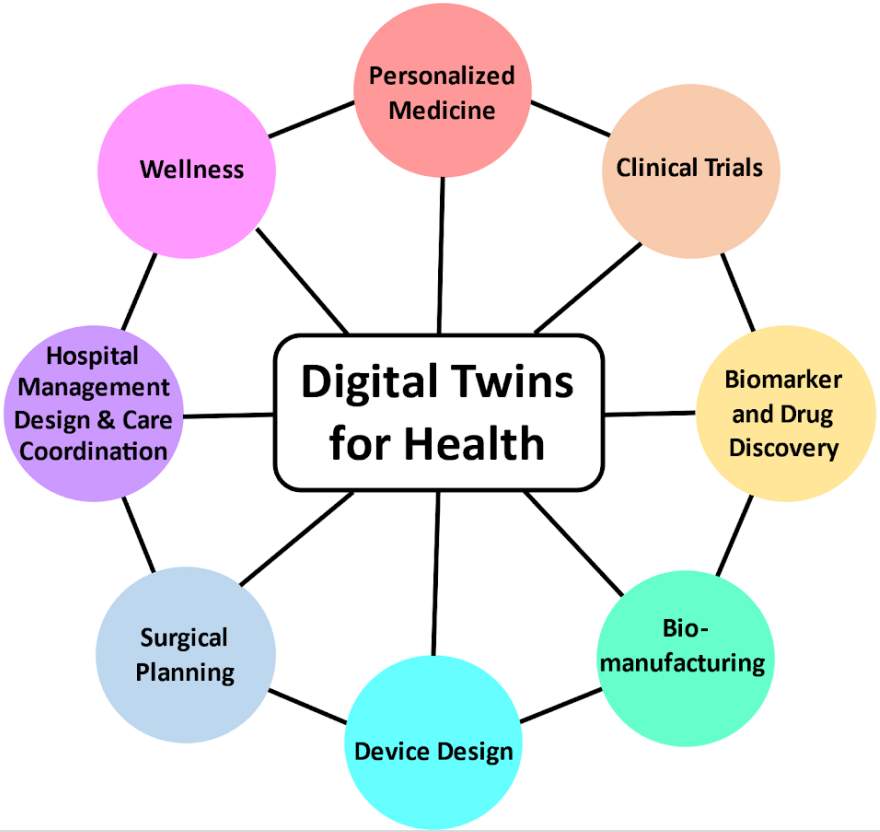


Katsoulakis et al, npj Digital Medicine, 7, 77 (2024)

DT vs AI/ML vs Computational Models

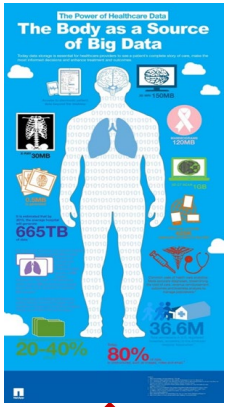
- While they form an important approach toward virtual replica of a physical entity, neither computational modeling nor AI/ML algorithm is the totality of DT
- A DT must have the three components: a physical entity, a virtual replica, and a connection between the two
- A DT should be **individualized, interconnected, interactive, informative, and impactful (5Is)**

Main Applications of DT in Health



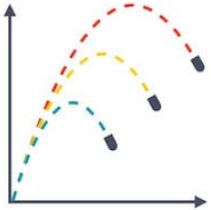
Digital Twins for Precision Medicine

Personal Phenotypes



Digital Twin Simulation Using HPC

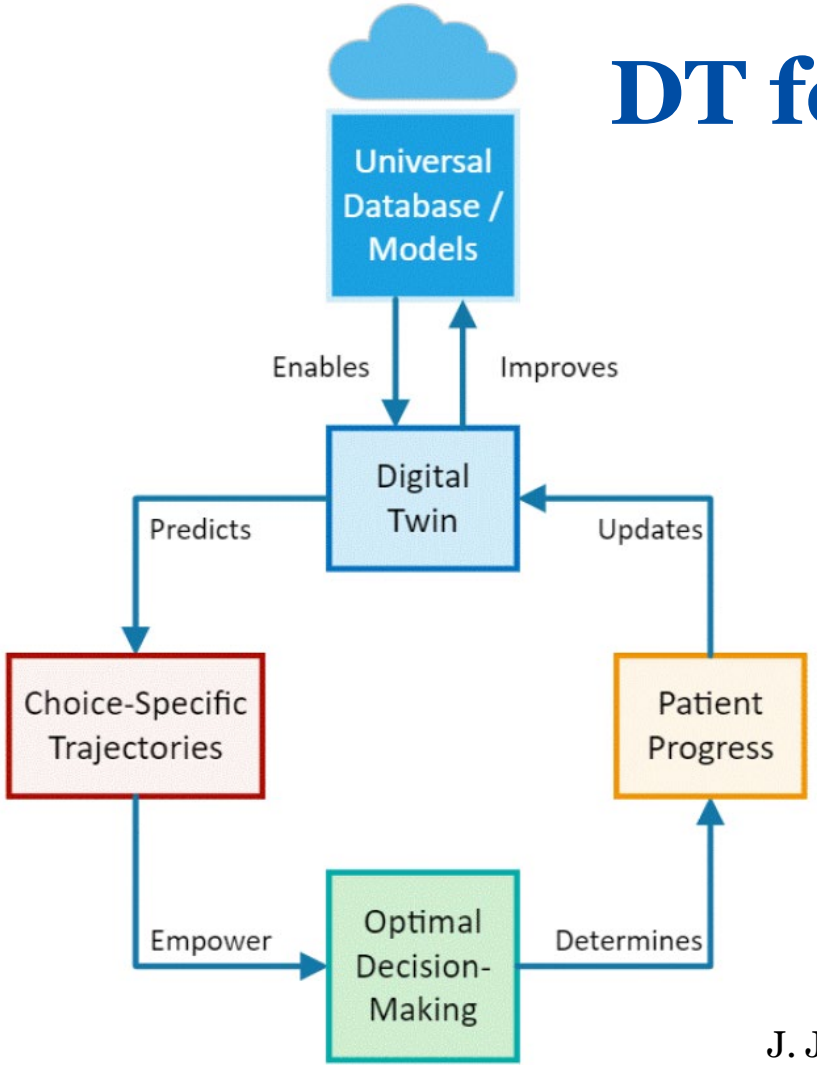
Personalized Care Trajectories



Shared Decision Making

Choose a care path

DT for Radiation Oncology



Components

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

Benefits

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

Barriers

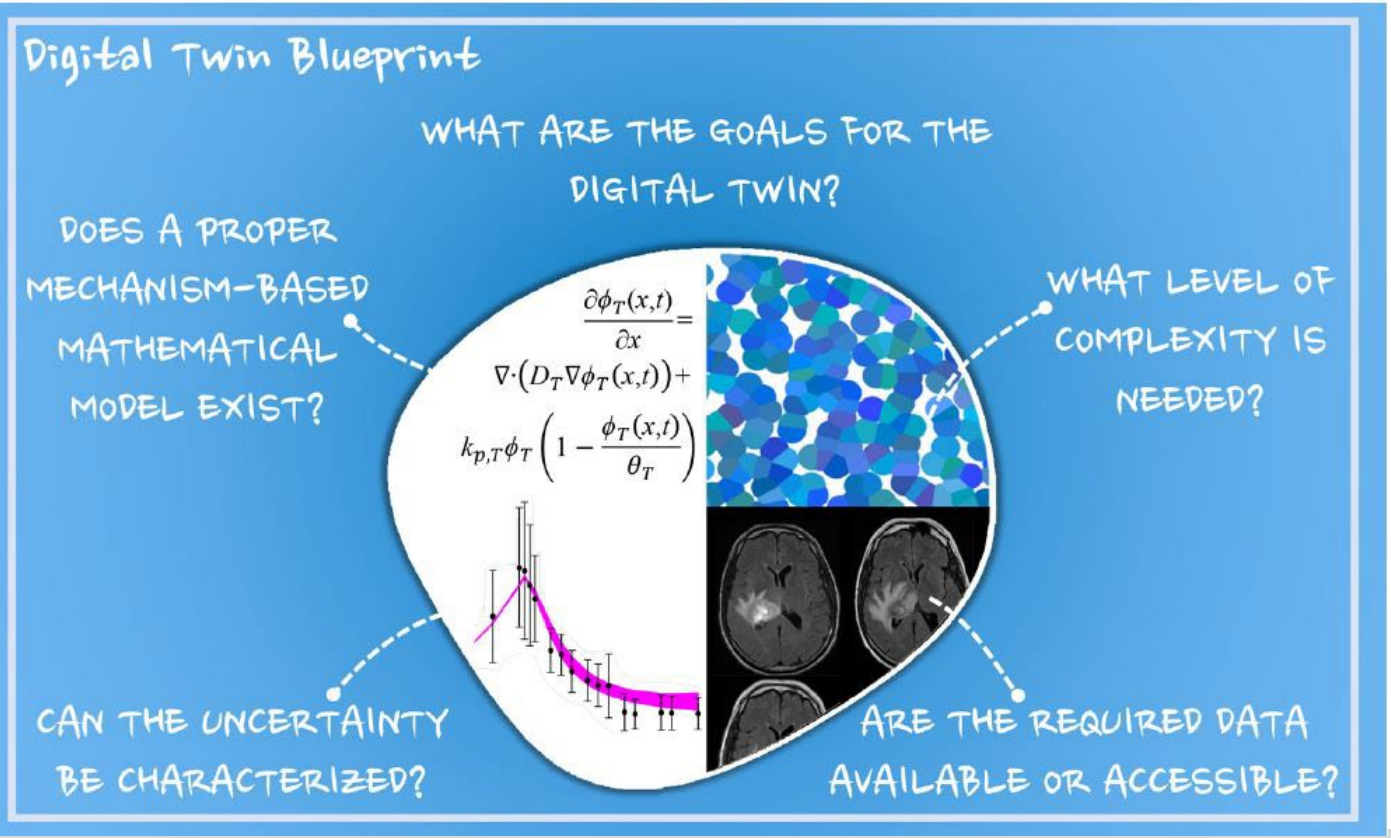
- Centralized data commons
- Patient-specific data assembly
- Multiscale modeling

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

Potential DT Applications in RT

- Real-time monitoring and comprehensive analysis of cancer patient health status undergoing RT
- DT-enabled optimal treatment pathway
- Treatment plan optimization and adaptation based on DT simulations of individual cancer patient, considering their anatomy, treatment history, RT toxicity, treatment goal, and personal preferences
- Virtual clinical trials with DT-enabled patient control
- A linac DT assisted with an agile robot for proactive maintenance and automated QA

Digital Twin Blueprint

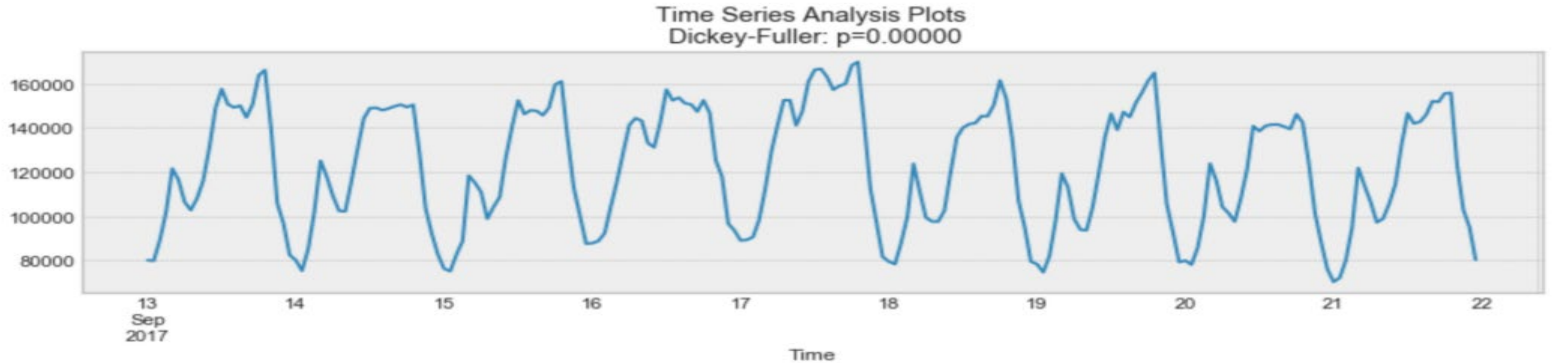


- "All models are wrong but some are useful", George Box
- "Everything should be made as simple as possible, but not simpler", Albert Einstein

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

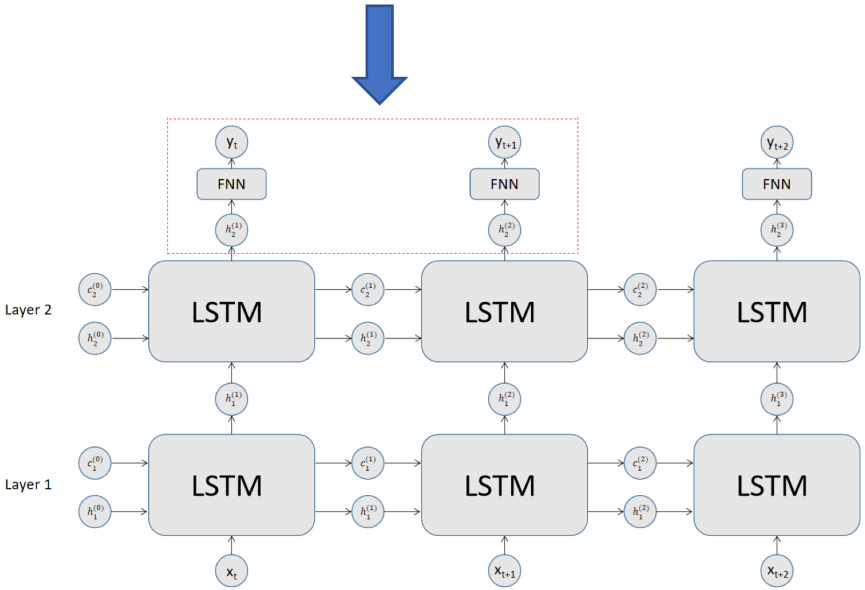
Modeling of Time-Series Patient Data

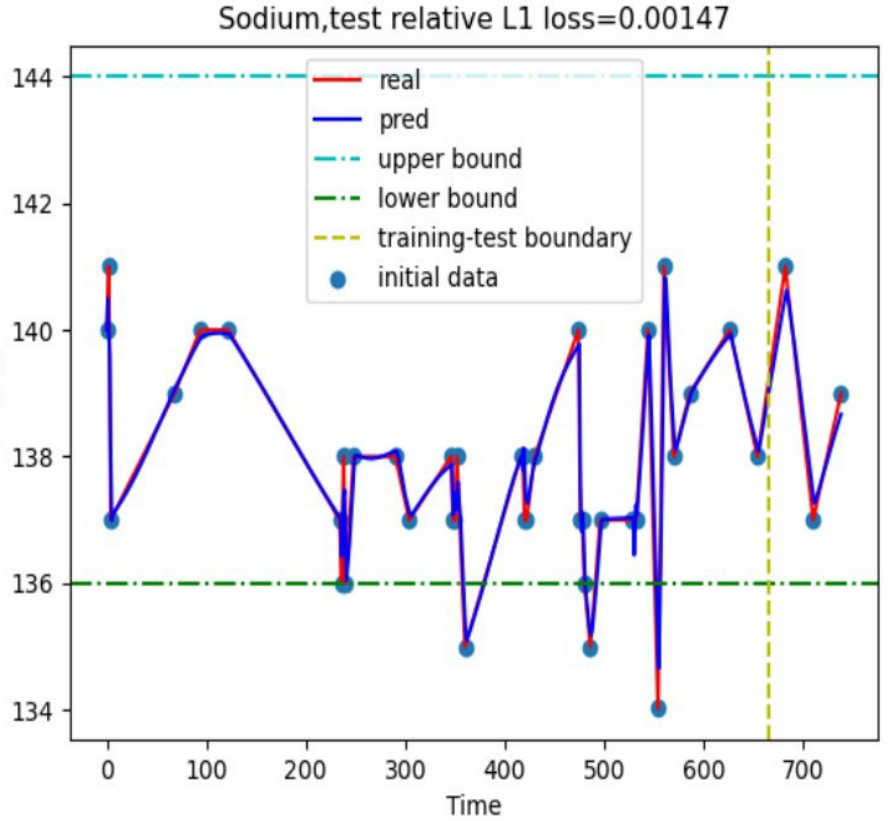
- Collected at multiple time points before, during, and after cancer treatments
- Δtime-series data correlate with treatment outcomes, QoL
- More precise and effective treatments and interventions and faster responses to mitigate adverse effects



Forecasting Metabolic Indices Using LSTM

Our concatenated LSTM model

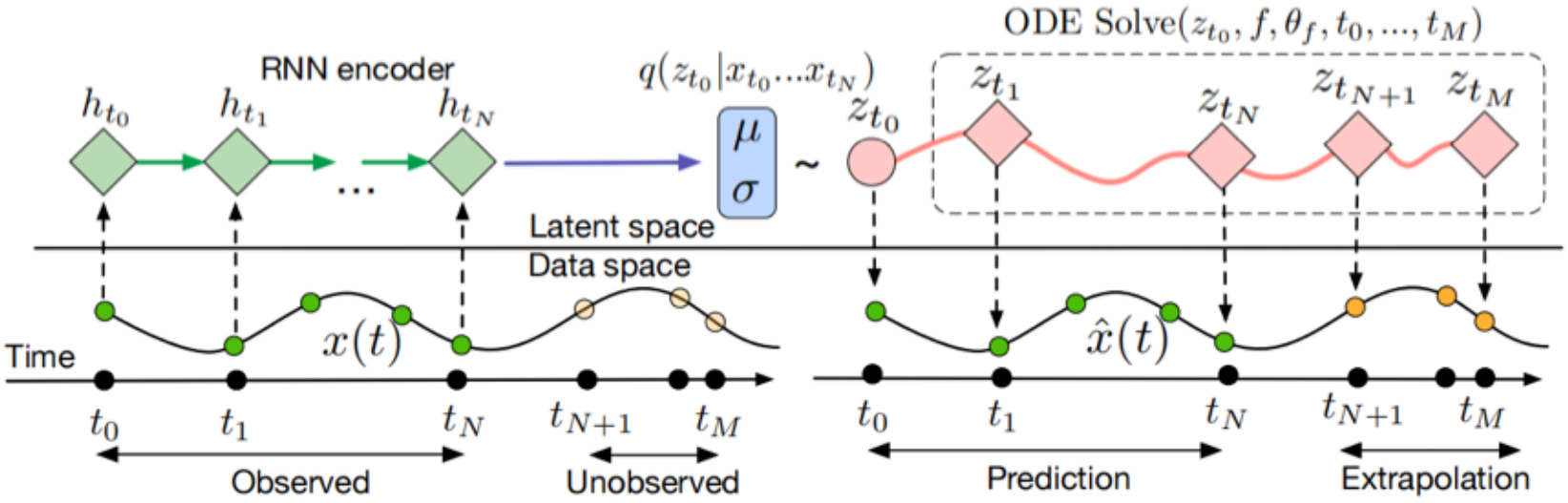




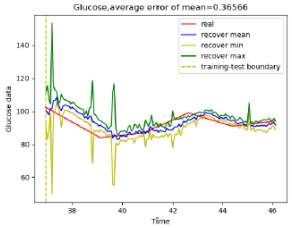
Hou et al. 2022. https://doi.org/10.3390/jpm12050742

Latent Ordinary Differential Equations

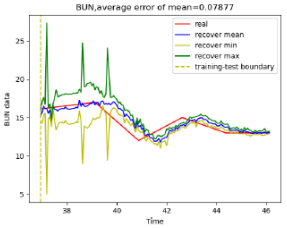
- Reduced-order methods can be used to “smooth” noisy data and produce more robust Neural Ordinary Differential Equations in the latent variable space



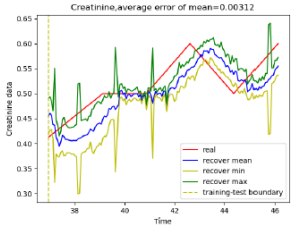
Forecasting Metabolic Indices Using LODE



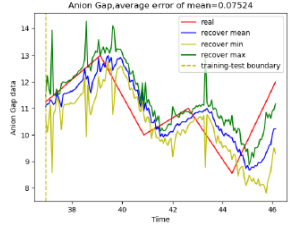
(a) Glucose,



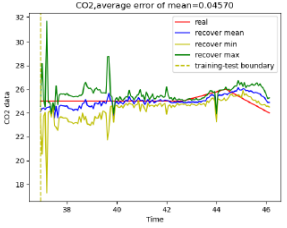
(b) BUN,



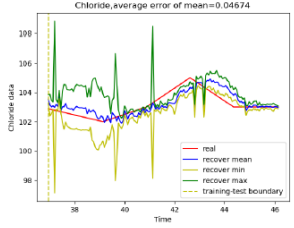
(c) Creatinine,



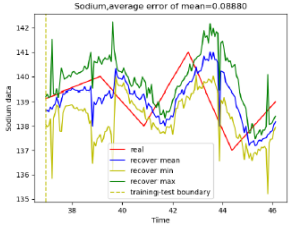
(d) Anion Gap,



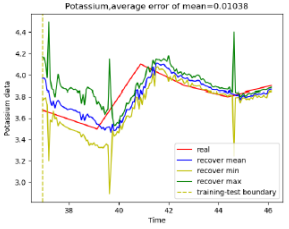
(e) CO2,



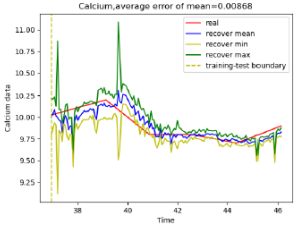
(f) Chloride,



(g) Sodium,

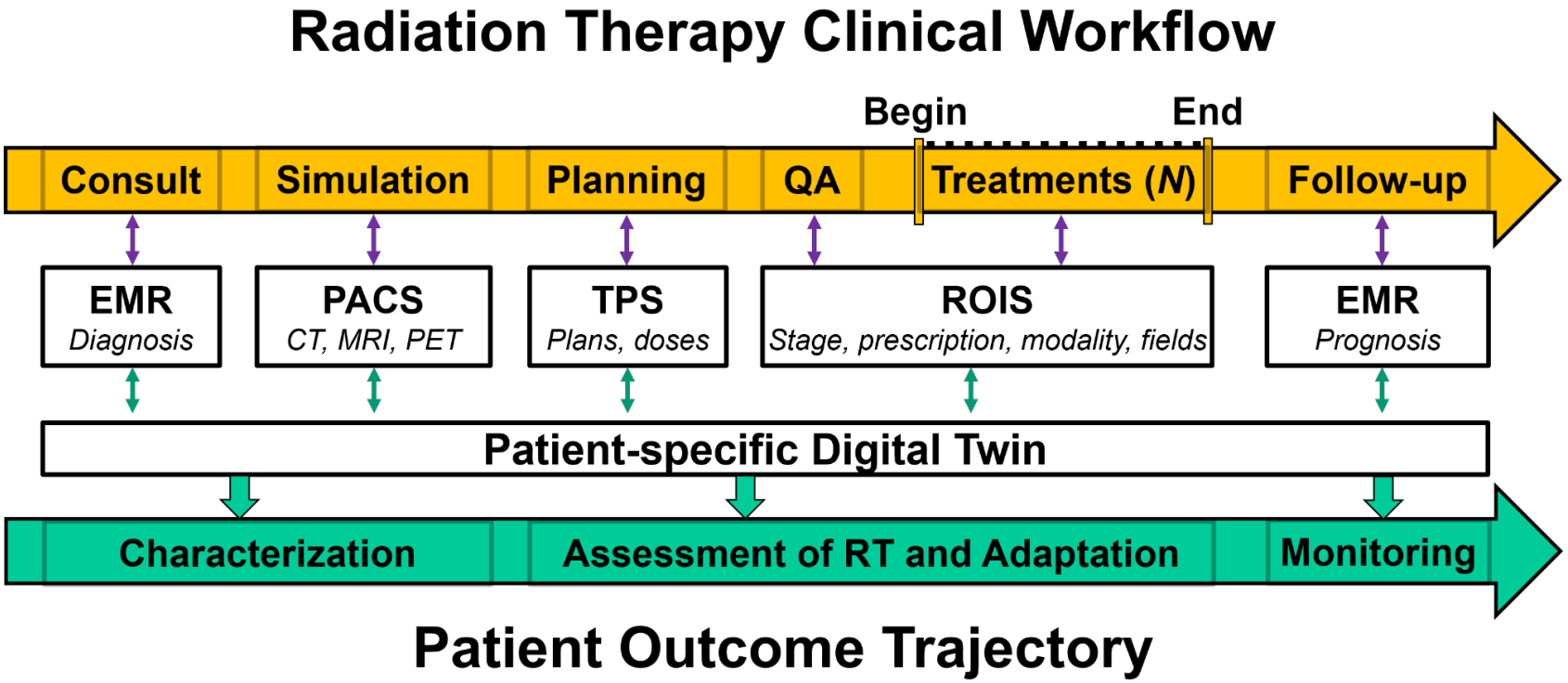


(h) Potassium,



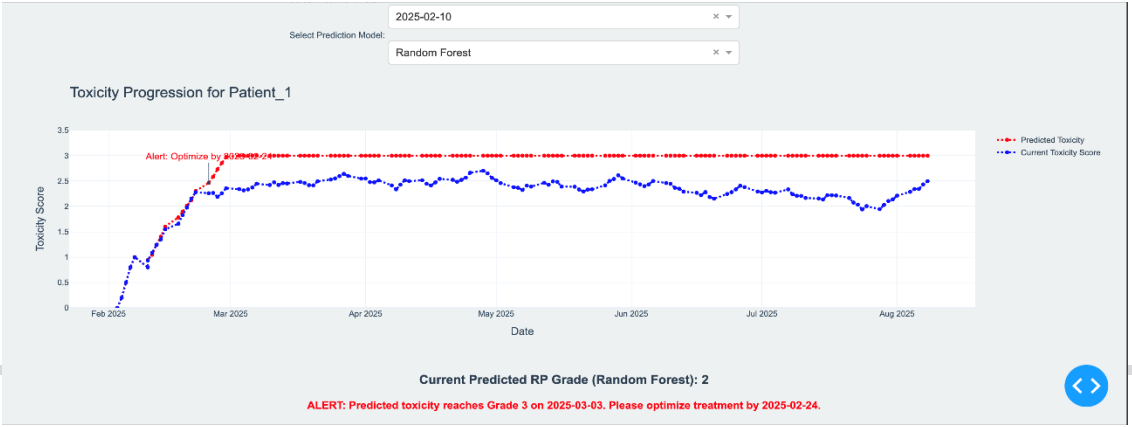
(i) Calcium,

Radiotherapy Workflow

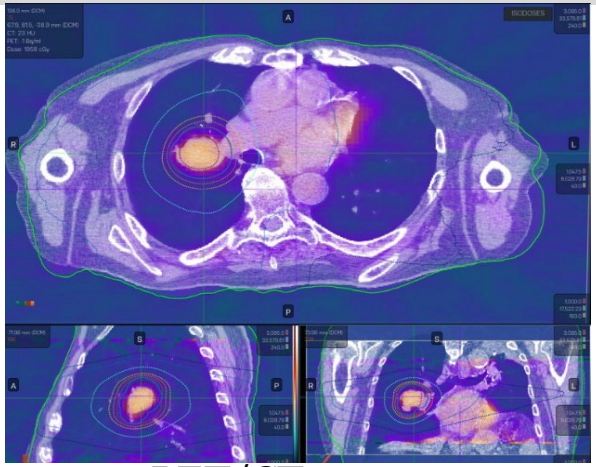


Cancer Patient Digital Twin

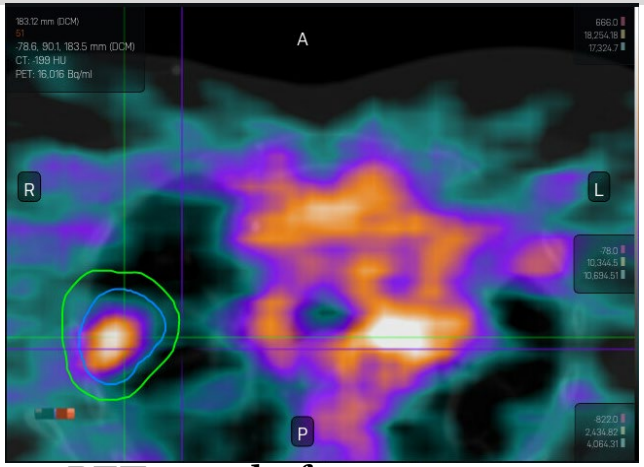
- **Patient health prediction**
- **Treatment outcome trajectory**
- **Shared decision making with patient engagement**
- **An early warning system for whole body all organ monitoring of toxicity induced by RT**



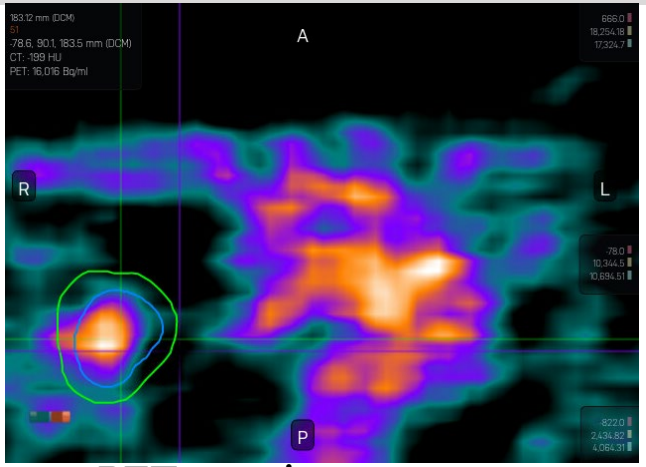
Biology-Guided Radiotherapy



PET/CT merge



PET scan before treatment



PET scan in treatment

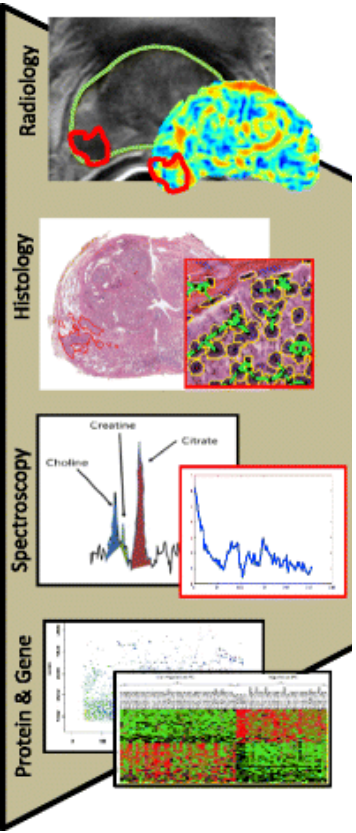
A reaction diffusion model including RT-induced cell death

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

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

PET scans courtesy of Huixiao Chen, PhD

Multiscale Modeling



Clinical

Sputum

Blood

Imaging (X-ray, CT, MRI, Bonescan)

Cellular analysis (flow cytometry, cell counting, etc.)

Biochemical (Gene/protein) markers

Biopsy

Immunohistochemical markers

Cancer staging

Chemotherapy

Immunotherapy

Radiation therapy

Physiological model (Patient level)

Phase field model based on flow cytometry (CTM) (Dynamical cell model)

Protein dynamical model, gene regulatory networks

Phase field model based on imaging (Dynamic cancer model)

Drug toxicity model (PKPD model)

Dosage planning model

Multimodal fusion

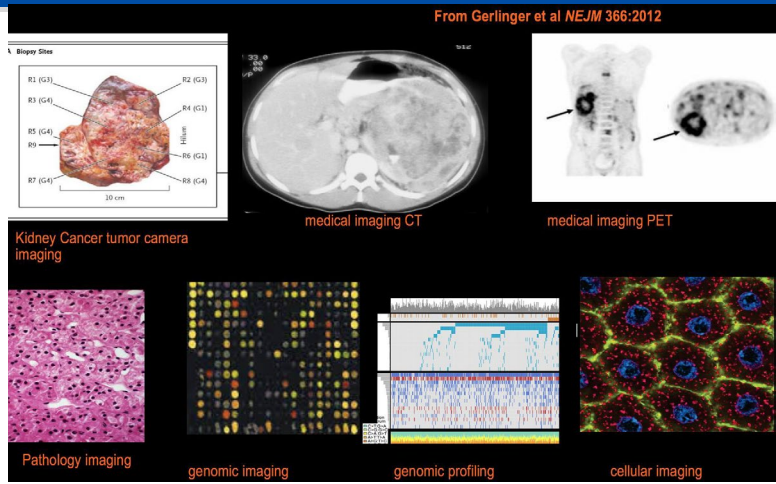
Multiscale Digital Twin Model

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

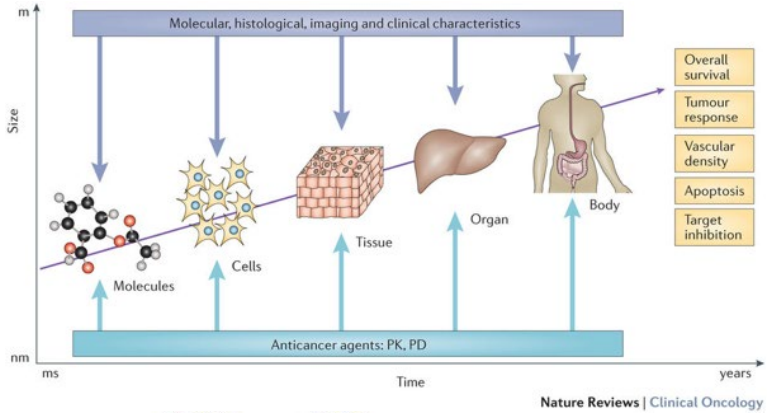
- Functional and molecular imaging
- Radiomics (deep learning-augmented analysis of radiology)
- Liquid biopsies (e.g., circulating tumor cells)
- Whole-slide, highly-multiplexed digital pathology
- Genomic profiling
- Single-cell profiling (e.g., scRNA-seq)
- Patient-derived cell cultures, organoids,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

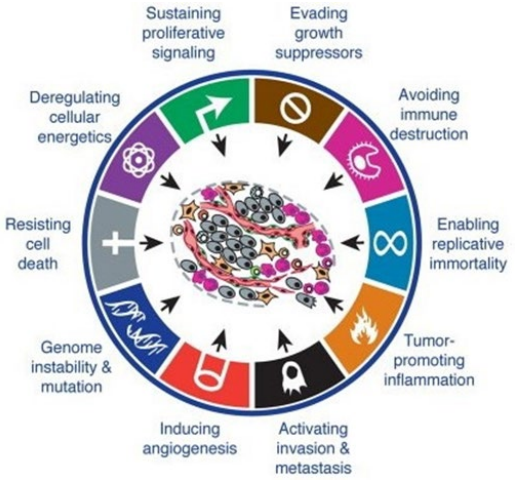


Each technology gives new light on a patient's health state, but it is challenging to coherently *fuse* these together

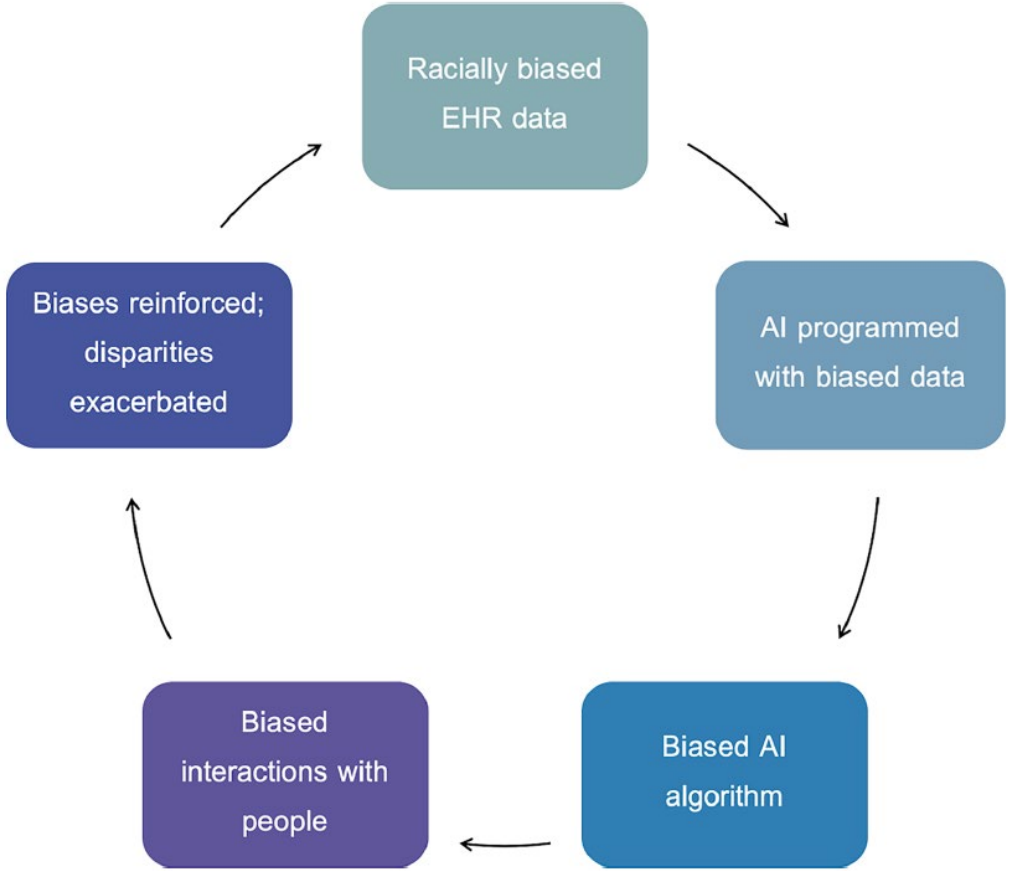
Complex Human Body

- 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)





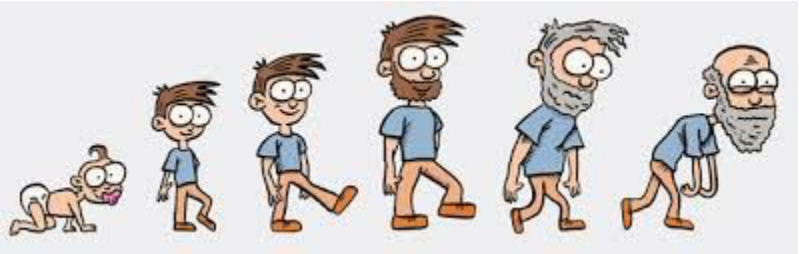
Responsible AI



- 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

Outlook

- Human digital twins fully functional and autonomous as HDT agents
- True companions and safeguards of people's health
- Interact with humans in physical world, with other HDT agents in virtual world
- Human digital twin simulations from birth to death



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

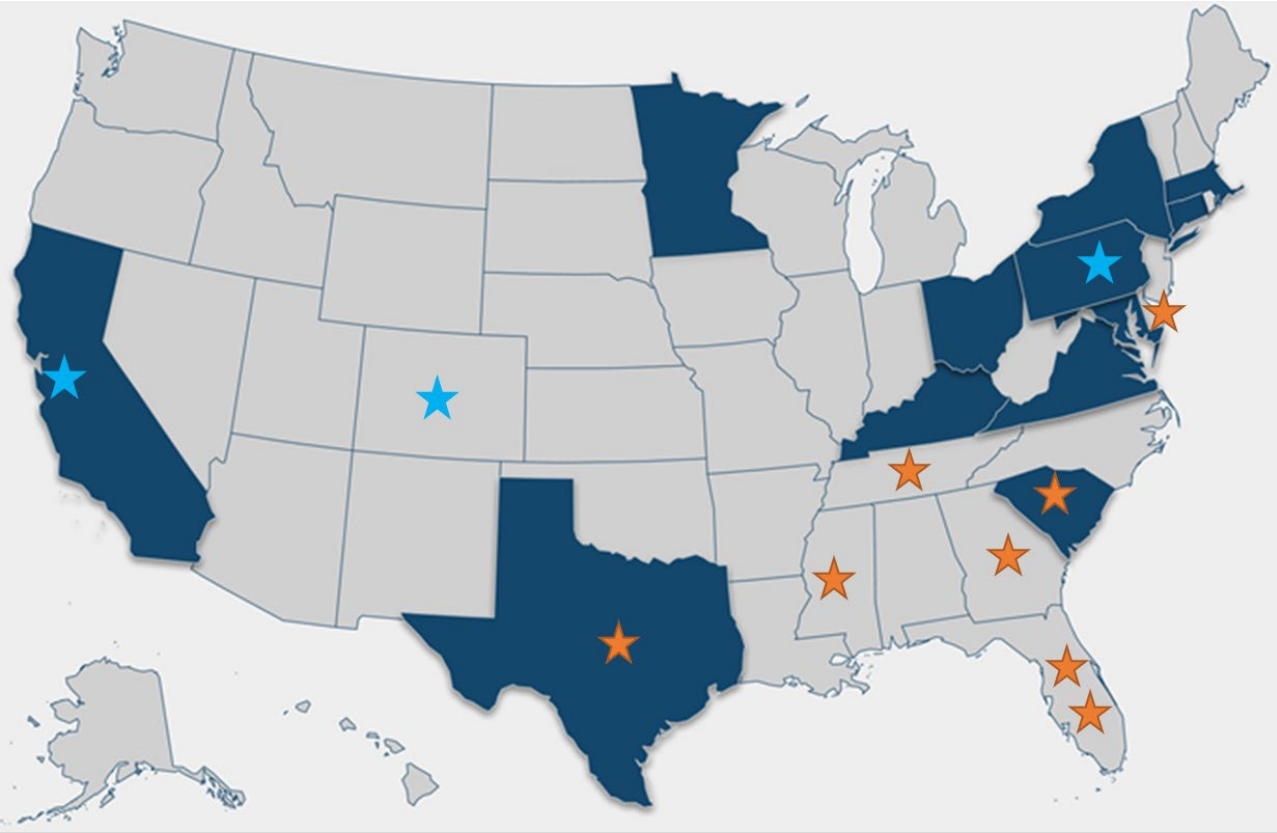
Conclusions

- Human 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
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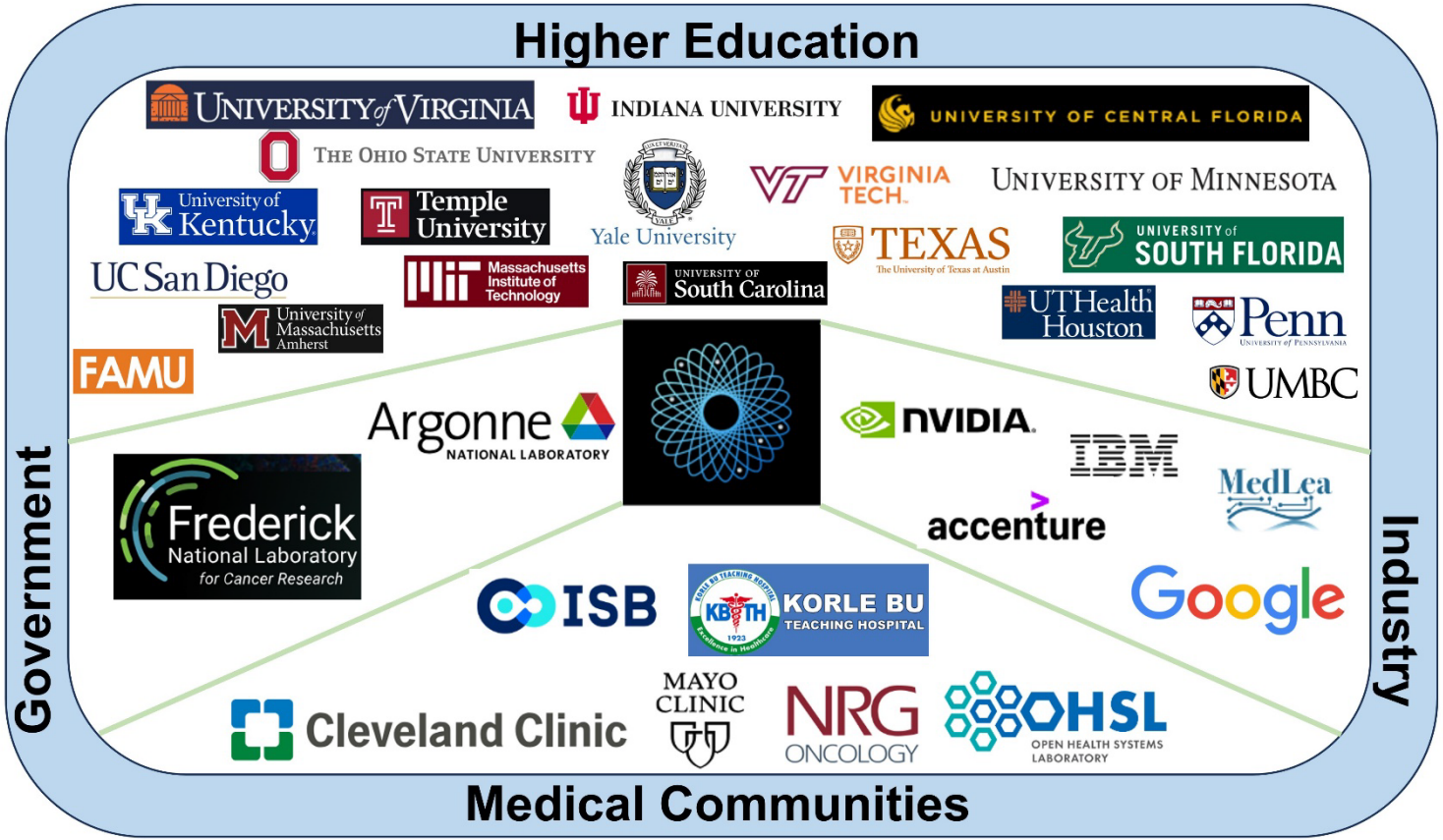
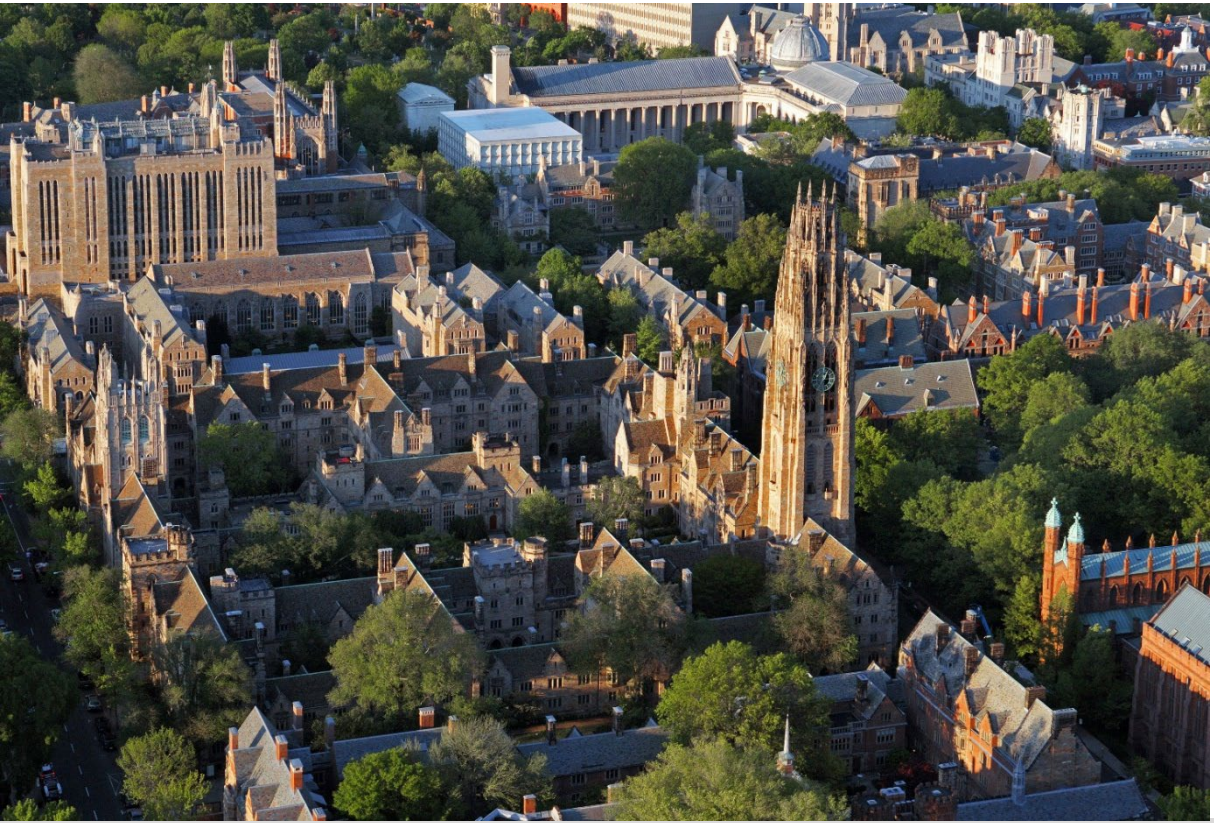
- Mayo Clinic
- IBM
- Accenture

DT4H Ecosystem



https://dt4h.org

Thank You



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