

Towards Developing an AI-powered Digital Twin Modeling Framework for Personalized Radiotherapy

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University of Nebraska
Medical Center™



1. What is digital twin?

- “Digital twin” are software replicas of the dynamic function and failure of engineered products and process.
- Patient-specific digital twins could integrate known human physiology and immunology with real-time patient patient-specific clinical data to predict computer simulations of tumor response after radiation treatment.
- Such digital twin can be powerful
 - Obtain best patient-specific customized treatment
 - Combine mechanistic knowledge and experimental observation data
 - Integrate mathematical and computational techniques and the power of artificial intelligence



2. Research trajectory and context



In silico medicine

1 language

Article Talk

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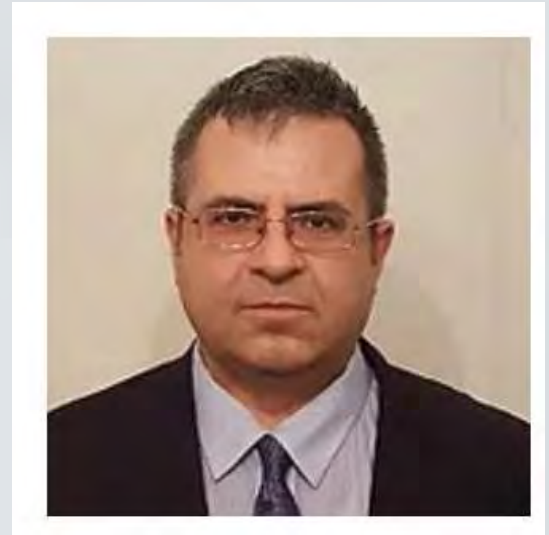
From Wikipedia, the free encyclopedia

Not to be confused with [Insilico Medicine](#).

***In silico* medicine** (also known as "**computational medicine**") is the application of *in silico* research to problems involving health and medicine. It is the direct use of [computer simulation](#) in the [diagnosis](#), [treatment](#), or [prevention](#) of [a disease](#). More specifically, *in silico* medicine is characterized by [modeling](#), [simulation](#), and visualization of biological and medical processes in computers with the goal of simulating real biological processes in a virtual environment.^[1]

History [[edit](#)]

The term *in silico* was first used in 1989 at a workshop "Cellular Automata: Theory and Applications" by a mathematician from National Autonomous University of Mexico (UNAM).^[2] The term *in silico radiation oncology*, a precursor of generic *in silico* medicine was coined and first introduced by G. Stamatakos in Proceedings of the IEEE in 2002.^[3] The same researcher coined and introduced the more generic term *in silico oncology*.^[4] *In silico* medicine is considered an extension of previous work using mathematical models of biological systems.^[4] It became apparent that the techniques used to model biological systems has utility to explain and predict dynamics in the medical field. The first fields in medicine to use *in silico* modeling were genetics, physiology and biochemistry. The field saw a dramatic influx of data when the human genome was sequenced in the 1980s and 1990s. Concurrently the increase in available computational power allowed for modeling of complex systems that were previously impractical.^[5]



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Modeling Tumor Growth and Irradiation Response *in vitro*—A Combination of High-Performance Computing and Web-Based Technologies Including VRML Visualization

Georgios S. Stamatakos, Evangelia I. Zacharaki, Mersini I. Makropoulou, Nikolaos A. Mouravliansky, *Student Member, IEEE*, Andy Marsh, Konstantina S. Nikita, *Senior Member, IEEE*, and Nikolaos K. Uzunoglu, *Senior Member, IEEE*

2002 paper for in silico oncology

Computational oncology



The University of Texas at Austin
Biomedical Engineering
Cockrell School of Engineering

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ABOUT THE DIRECTOR



The Center for Computational Oncology is directed by **Thomas Yankeelov**, a distinguished senior cancer researcher in computational biology, advanced imaging and mathematical modeling. He is a professor biomedical engineering in the Cockrell School of Engineering and of diagnostic medicine in the Dell Medical School. He holds the W.A. "Tex" Moncrief Jr., Simulation-Based Engineering and Sciences Professorship II in Computational Oncology.

Mathematical oncology



JCO® Clinical Cancer Informatics

An American Society of Clinical Oncology Journal

[JCO Clin Cancer Inform.](#) 2019; 3: CCI.19.00357.

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NIHMSID: [NIHMS1050188](#)

PMID: [31026176](#)

Introduction to Mathematical Oncology

[Russell C. Rockne](#), PhD¹ and [Jacob G. Scott](#), MD, DPhil²

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Mathematical oncology—the use of mathematics, modeling, and simulation to study cancer—is at once both an old and a new field of research.¹⁻⁸ Its roots date back hundreds of years, to the earliest days of the study of calculus. The principles of rates of change and differential equations have been used to model and predict the uncontrolled proliferation of cancer cells and the effects of treatment for decades. Today, with the dawning of the era of routine cancer genome sequencing and the resulting surge of data that have necessitated new mathematical methods and modeling approaches, these principles have been given new life and found new applications.





Computational radiation biology

Physics in Medicine & Biology

PAPER

Development of a coupled simulation toolkit for computational radiation biology based on Geant4 and CompuCell3D

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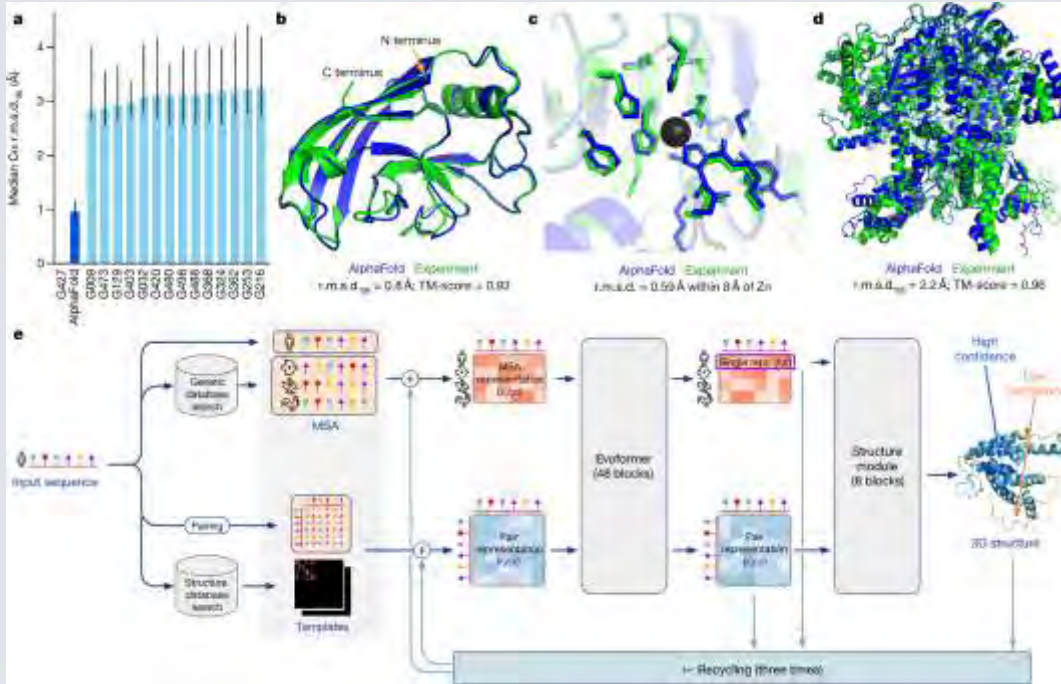
[Physics in Medicine & Biology](#), [Volume 66](#), [Number 4](#)

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DOI [10.1088/1361-6560/abd4f9](https://doi.org/10.1088/1361-6560/abd4f9)



3. Enthusiasm from industry



AlphaFold 3 predicts the structure and interactions of all of life's molecules

Introducing AlphaFold 3, a new AI model developed by Google DeepMind and Isomorphic Labs. By accurately predicting the structure of proteins, DNA, RNA, ligands and more, and how they interact, we hope it will transform our understanding of the biological world and drug discovery.

Google DeepMind AlphaFold team | Isomorphic Labs



Nature

<https://www.nature.com/articles> · 翻译此页

Highly accurate protein structure prediction with AlphaFold

作者: J Jumper · 2021 · 被引用次数: 25523 — The AlphaFold network directly predicts the 3D coordinates of all heavy atoms for a given protein using the primary amino acid sequence and ...





Mark Zuckerberg and Priscilla Chan announced they're building a computing system to help eliminate human disease by 2100, but costs may be hefty

Maaya Eochi Sep 22, 2023, 2:40 PM CDT

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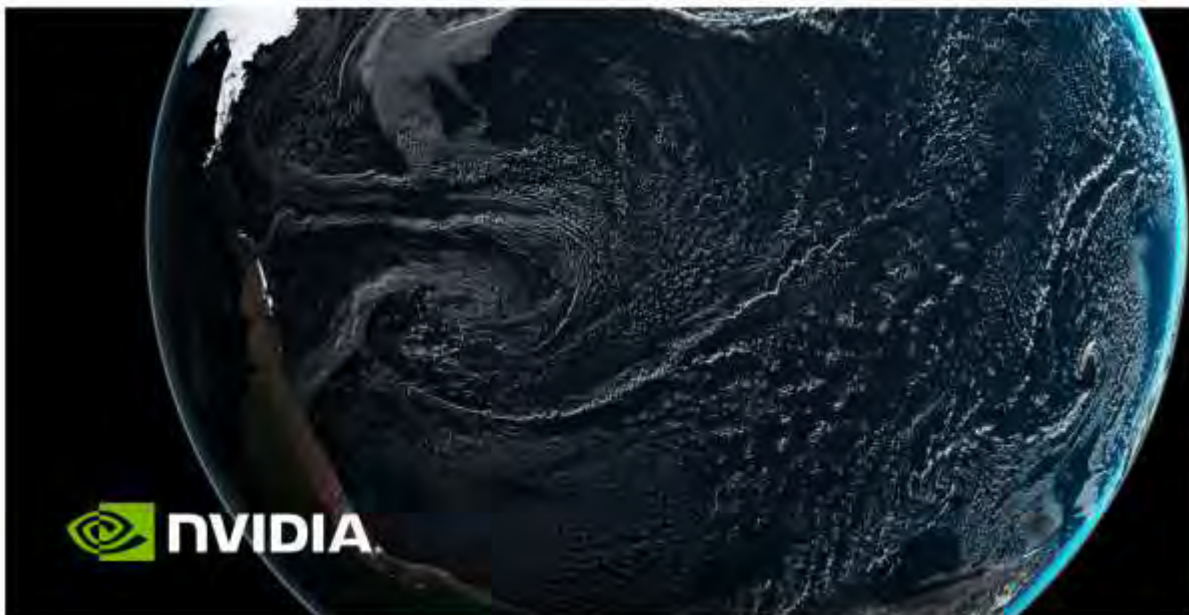


How will they eradicate all diseases by 2100?

The CZI foundation plans to train the new system using datasets from CZ Cell x Gene software, resources from the Chan Zuckerberg Biohub Network and [Chan Zuckerberg Institute](#) for Advanced Biological Imaging, and publicly available data. Upon completion, this computing system is expected to be one of the largest AI clusters dedicated to non-profit research.

Priscilla Chan highlighted the potential of AI models in understanding immune responses, rare diseases, and medication reactions, stating, "AI models could predict how an immune cell responds to an infection, what happens at the cellular level when a child is born with a rare disease, or even how a patient's body will respond to a new medication."

However, the scale of this endeavor raises questions about its feasibility with a \$3 billion (£2.3 billion) budget over the next decade, according to BBC reports.



NVIDIA's CEO Jensen Huang has introduced an Earth Climate Digital Twin, a platform designed to simulate and visualize weather and climate at an unprecedented scale. This new offering aims to accelerate efforts in combating the staggering \$140 billion in economic losses caused by extreme weather events driven by climate change.

Digital Humans: The Next Step in Human-AI Interaction

Digital humans represent a significant leap in human-AI interaction. These AI-driven entities can engage with users in a natural, empathetic manner, making them ideal for customer service roles and other interactive applications. NVIDIA's advancements in digital human technology aim to overcome the "uncanny valley" and create realistic, engaging virtual agents.

The potential applications of digital humans are vast, spanning healthcare, retail, education, and more. They can provide personalized support, enhance user experiences, and drive deeper engagement by simulating human-like interactions.

World Simulations: Earth 2 and Beyond

Huang also unveiled Earth 2, an ambitious project to create a digital twin of our planet. This simulation aims to predict climate change impacts, natural disasters, and other critical environmental factors, enabling better preparedness and adaptive strategies.

World simulations like Earth 2 utilize AI to generate synthetic data and improve predictive models, offering unprecedented insights into complex global phenomena. These simulations can aid in environmental conservation, urban planning, and disaster management, among other applications.

4. Government vision



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OSTI.GOV / Technical Report: *The First Virtual Human Global Summit: Prepublication Meeting Report*

The First Virtual Human Global Summit: Prepublication Meeting Report

TECHNICAL REPORT

03 October 2023

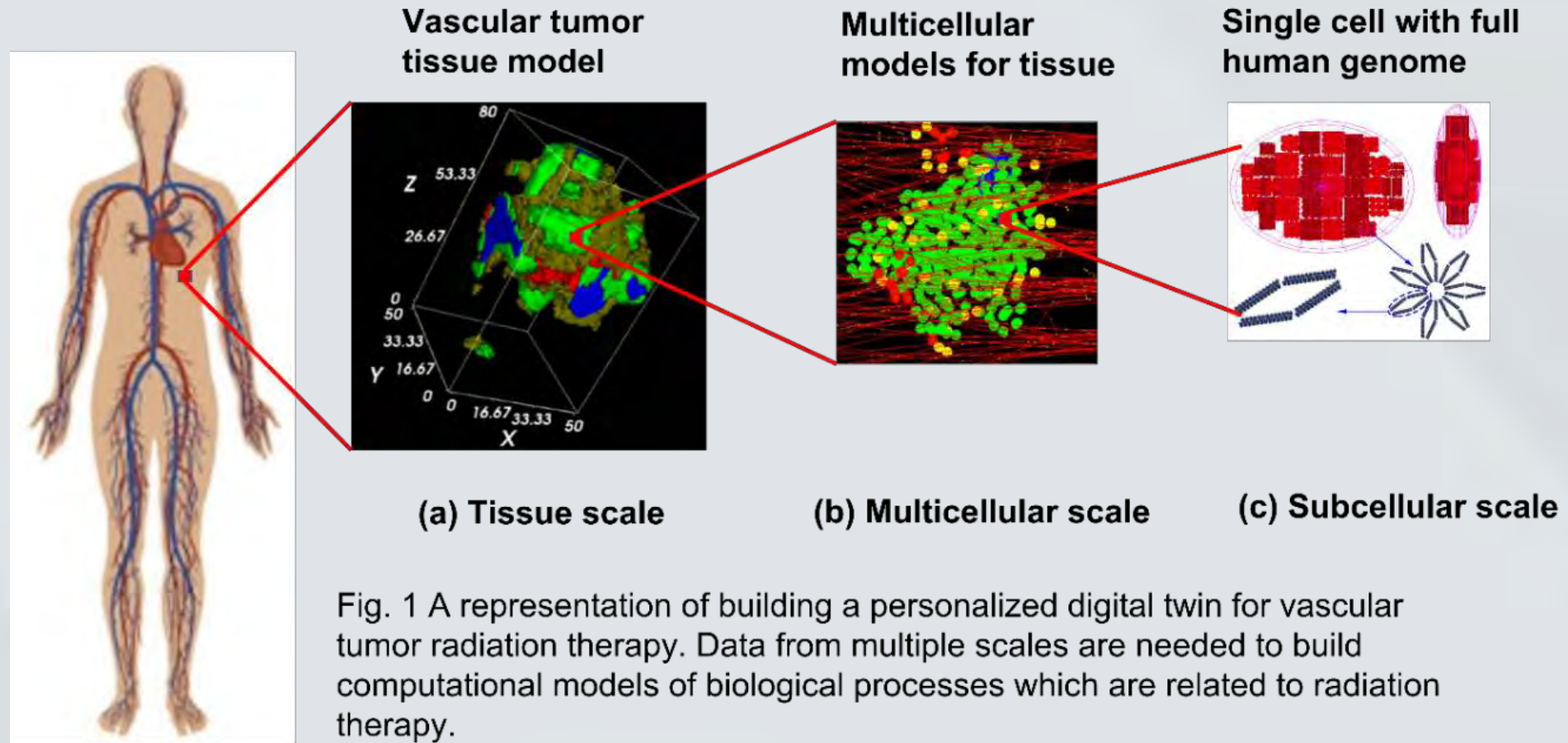
OSTI ID: 2428904

Lin, Meifeng; Stahlberg, Eric 

This is the prepublication report for the Xirst Virtual Human Global Summit held in October 2023. Organized collaboratively by Frederick National Laboratory for Cancer Research, Brookhaven National Laboratory, University College London, and Eviden, the 2023 Virtual Human Global Summit convened global thought leaders to bring together multiple perspectives across domains and organizations. The intent of the Summit was to foster collaboration among key...

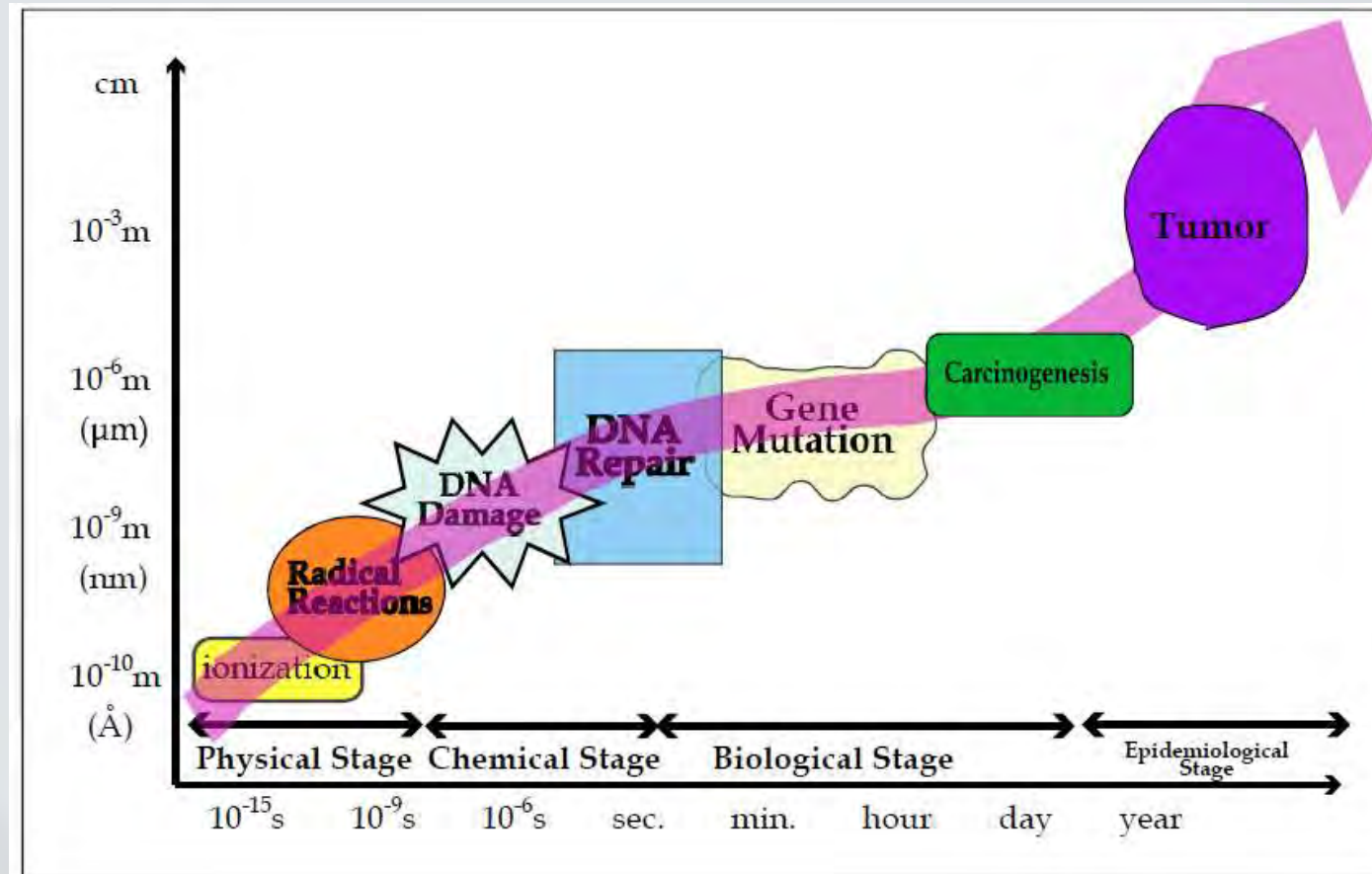
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5. Towards building a digital twin for radiation therapy



Challenges and philosophy

- Simulating radiation-induced biological effects deals with huge multiscale problems in spatial and temporal domain

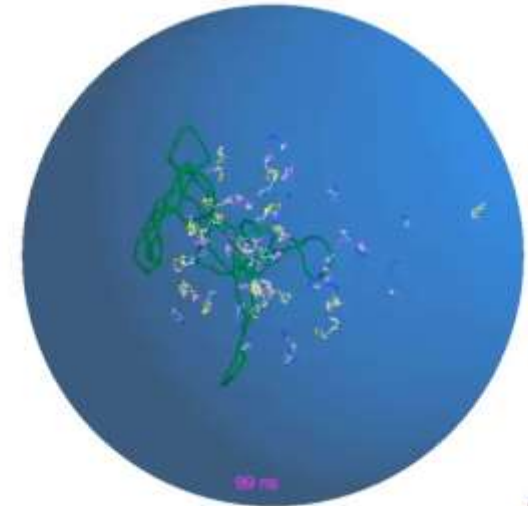


- A robust digital twin modeling framework should incorporate models at subcellular, multicellular, and tissue scales to study and predict patient response.
- This multiscale approach ensures a detailed and accurate representation of the biological processes involved.
- One crucial component of a digital twin framework is a mathematical model that simulates radiation-induced cellular effects at the cellular scale

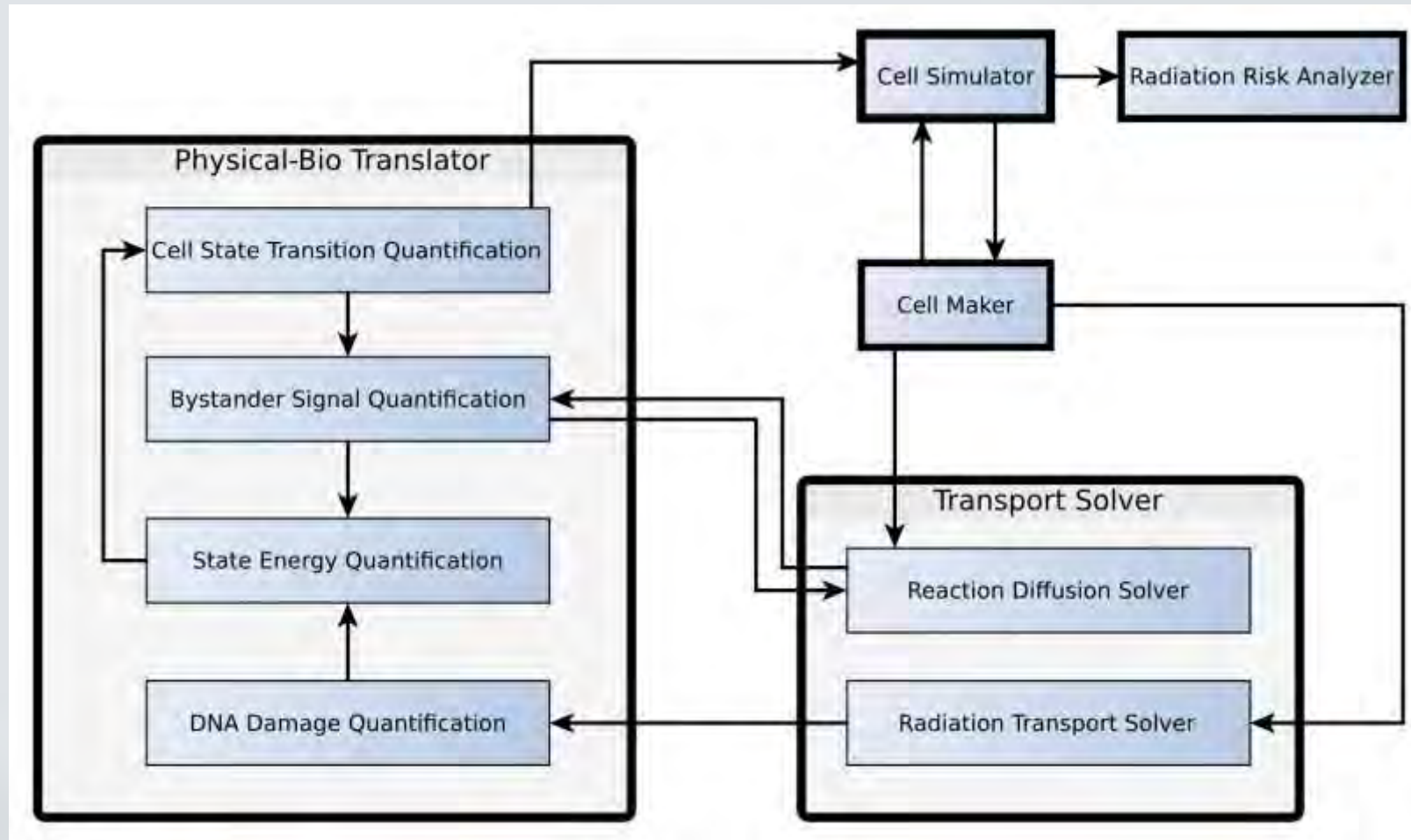
Near Track-End Primary Ion Hit



Complex
Strand Breaks
& Base Losses



A modularized approach for building the digital twin framework



Balance the biological complexity and simulation capability

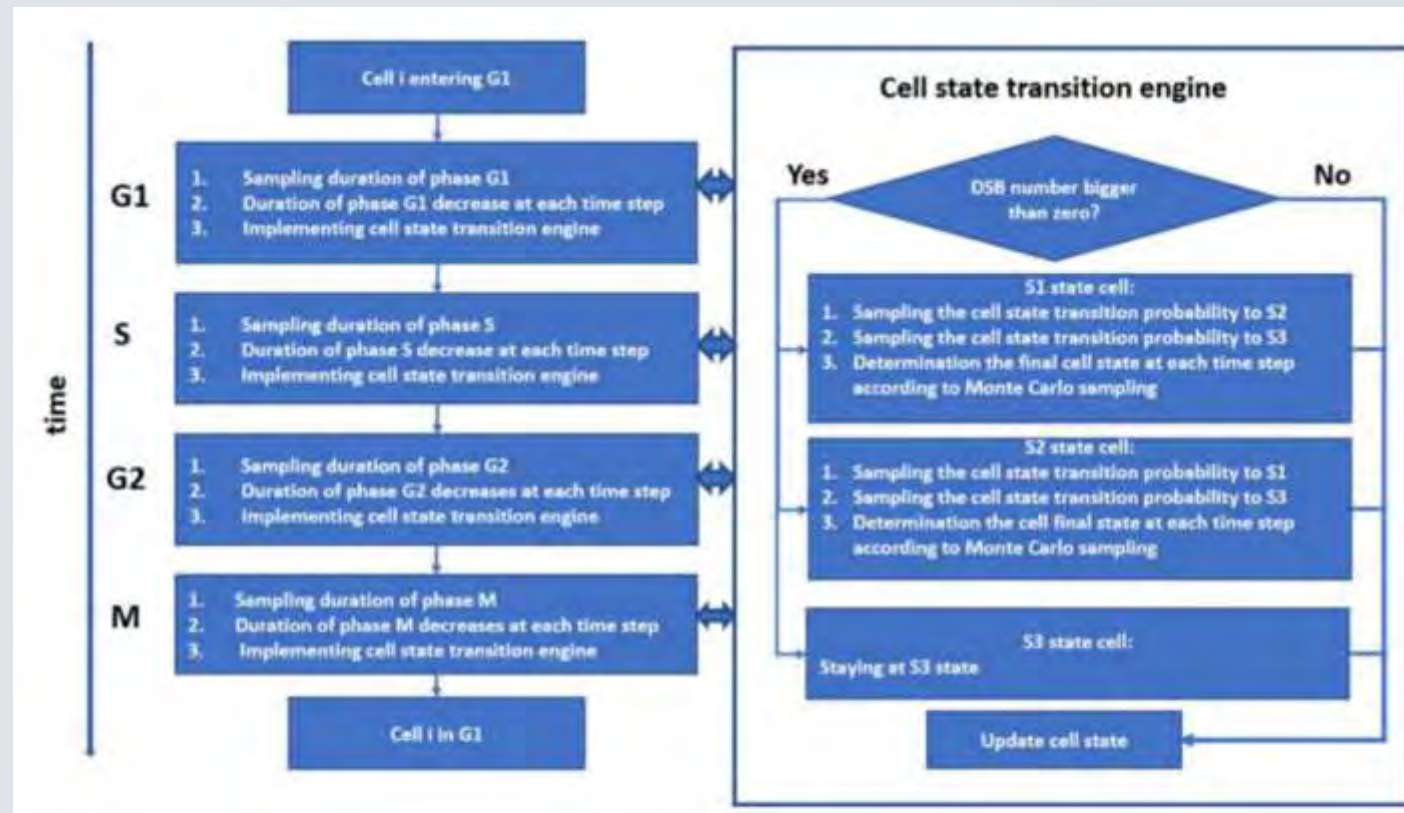


Fig 2. Process of updating cell state in one time-step. During simulation, the state of all the cells will be updated in each time step which could be defined in the simulation. Cell phase transition is modeled by comparing the sampled cell phase duration and time of cell staying in the cell phase. If the time of cell staying is larger than the sampled cell phase duration, then cell phase transition will occur. If mitosis occurs, then two new cells will be added to the cell system. Cell state transition in each cell phase are also modeled through the defined cell state transition rules. In each time step, the cell phase and cell state transition are updated.

Cross platform integration enables powerful simulation



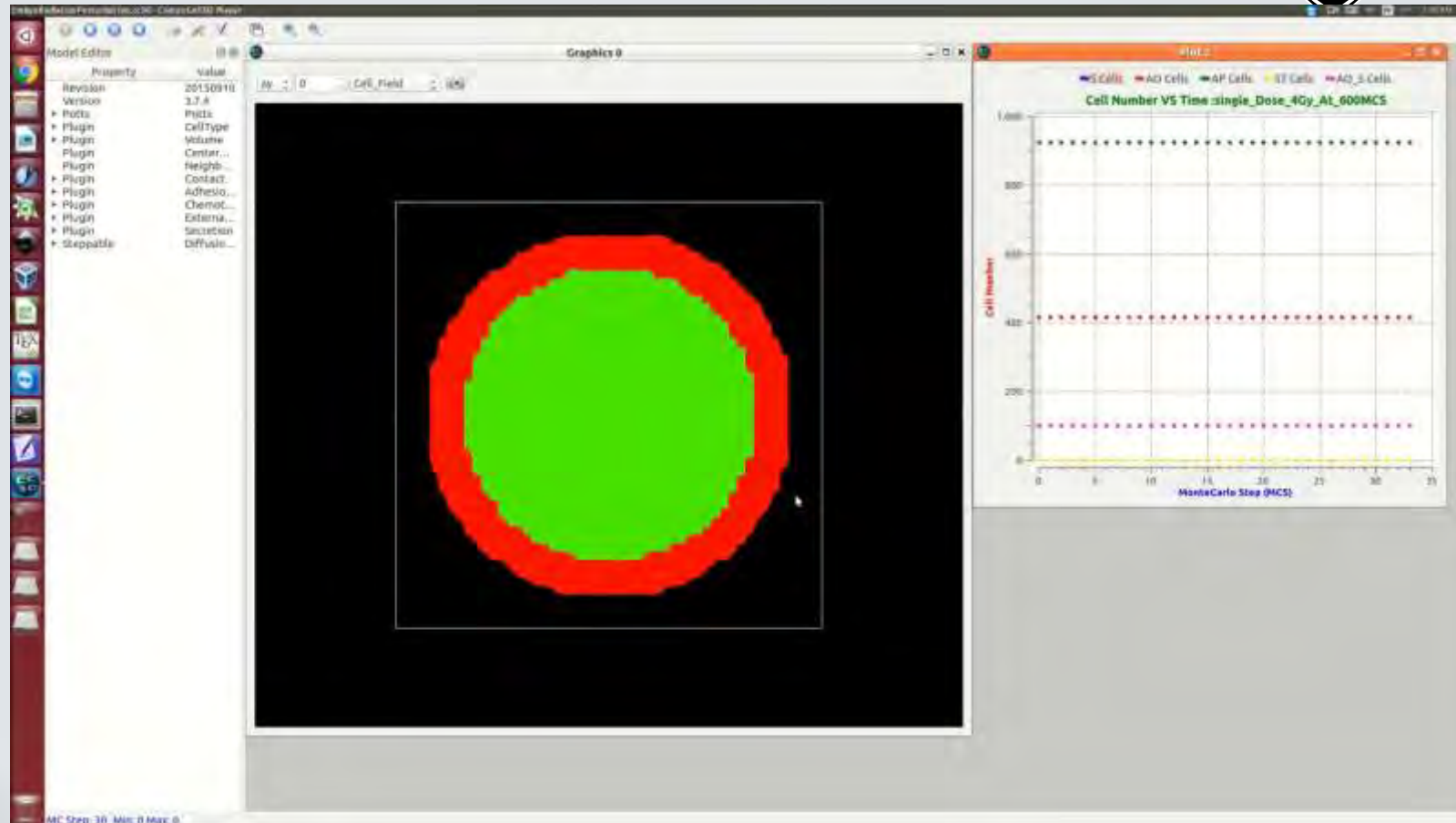
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```
CC3D Project
CC3D Simulation
Main Python Script
VascularTumor.py
NM, Script
VascularTumor.xml
Python
VascularTumorStepable...
ScalarField

64 #
65 # 12 mcs == 100000
66 # 14 mcs == 140000
67 # 17 mcs == 140000
68 # 12 mcs == 10000 or mcs == 20000 or mcs == 30000 or mcs == 40000 or mcs == 50000 or mcs == 60000 or mcs == 70000 or mcs == 80000 or mcs == 90000
69 # 17 mcs == 12000 or mcs == 13000 or mcs == 14000 or mcs == 15000 or mcs == 16000;
70 DCF = 10
71
72 dx = self.dim.x*DCF/float(1000) # distance cell to cell
73 dy = self.dim.y*DCF/float(1000)
74 dz = self.dim.z*DCF/float(1000)
75
76 #
77 # radSource = RTM.RadiationSource('testInputSource')
78 # radSource.PlaneSource_MRT(0,0,dZ/2.0,dX/2.0,dY/20.0,'e-',1000,1000)
79 # radSource.PlaneSource_MRT(0,dZ/2.0,dX/2.0,dY/20.0,'e-',1000,1000)
80 #
81 # radTransport = RTM.RadiationTransport(self.dim,self.celllist,DCF) # importing disease and cell geometry from
82 # ccd3transport - but "self" radSource, self.celllist // I think geometry and radiation source
83 #
84
85 radSource = RTM.RadiationSource('testInputSource')
86 radSource.PlaneSource_MRT(0,0,dZ/2.0,dX/2.0,dY/20.0,'e-',1000,1000)
87 radSource.PlaneSource_MRT(0,dZ/2.0,dX/2.0,dY/20.0,'e-',1000,1000)
88 radTransport = RTM.RadiationTransport(self.dim,self.celllist,DCF) # importing disease and cell geometry from
89 runMode = 'cat' + self.simulationID
90 print 'the runMode is: ', runMode
91 #
92 # radTransport.Run("self", radSource.GetSourceID()) # check geometry and radiation source
93 # radTransport.Run("self", radSource.GetSourceID(), self.dim, self.dim, self.dim, self.dim, self.dim)
94 radTransport.Run(runMode, radSource.GetSourceID()) # check geometry and radiation source
95 simResult = RTM.CellSimulationResult(self.simulationID)
96 simResult.ReadTransportTally(self.pDose)
97
98 for cell in self.cellList:
99
100 alpha = 0.25 # alpha value for quantifying alternative energy
101 beta = 0.03 # beta value for quantifying alternative energy
102 E1 = 0 # mean state energy of G1 state
103 E2 = 48.47 # mean state energy of G2 state
104 sigma = 6.35 # sigma of state energy distribution
105
```

Simulation vascular tumor response after irradiation



Simulation the egg gastrulation process with irradiation



6. What AI can help us here?

- At body scale: AI aids identifying suitable patients, make diagnosis, treatment planning, etc.,
- Tissue scale: tissue response relates to solving complex partial differential equations (PDEs), i.e., chemical' reaction and diffusion within tissue, AI can aid solving PDEs, such as the using deep learning solving PDEs,
- Multicellular scale: validating the multicellular simulation models relates to comparing the simulation results and experimental data from cellular irradiation, microbeam irradiation etc., AI can aid us conducting results analysis, data validation,
- Subcellular scale: AI aid predicting DNA damages, radiation induced DNA damage simulation relates vast data analysis, such as clustering analysis, AI is good at feature extraction and can be used to do DNA damage analysis.



7. Conclusions

- Undoubtedly, the development of these digital twins will better promote the advancement of radiation therapy, as digital twins can help us understand, observe, and even predict patient's response, which can enable patient-specific treatment,
- Building the framework for digital twin is a complex process, it relates many fields, and it needs cross platform integration,
- Artificial intelligence can provide tremendous benefits for building the digital twin framework, which can make the whole process more efficient and powerful.