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Insights into the in-silico research: Current scenario, advantages, limits, and future perspectives

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ABSTRACT

In silico refers to tests or simulations carried out on a computer or by theoretical analysis, as opposed to "in vivo" (in a real organism) or "in vitro" (in a laboratory). This sort of study has applications in many domains, including drug discovery and development, genetics, and bioinformatics. Many benefits of using in silico methods include the capacity to run tests more rapidly and at a lower cost, as well as test ideas that would be difficult or impossible to test in vivo or in vitro. However, it should be noted that the outcomes of in silico trials should be confirmed by experimental or observational investigations. In silico research is predicted to play an important role in many fields of study in the future, providing vital insights and allowing researchers to solve complex challenges and make educated decisions. This work provides an overview of in silico research, including the current scenario, advantages, several applications, limitations, and future perspectives.

1. Introduction

Bioinformatics is an interdisciplinary field of science that focuses on utilizing computer-based methods to understand and predict outcomes in laboratory experiments and clinical trials related to biomechanical and physicochemical systems. In silico research is employed to investigate various aspects of these systems, such as molecular interactions, protein folding, and genetic control. Through computer simulations, scientists can examine how a drug molecule interacts with a target protein or how a gene mutation affects protein function (Khan et al., 2022; Kumar et al., 2021; Yusuf et al., 2023a). Additionally, in silico research extends to exploring chemical processes and physical phenomena. For instance, computer simulations help represent material properties like strength, thermal conductivity, and electrical characteristics, enabling the development of novel materials with specific qualities. The advantages of in silico research are highlighted in **Figure 1**, emphasizing its ability to explore complex systems and phenomena, providing insights that traditional experimental approaches may struggle to achieve. Researchers have used computer techniques to select lead compounds from extensive chemical datasets obtained through high-throughput screening (HTS) (González-Medina et al., 2017; Naveja et al., 2019). Moreover, computational approaches have been instrumental in drug repurposing for epigenetic targets, and the DiaNat-DB molecular database (Madariaga-Mazón et al., 2021; Naveja et al., 2016) serves as a valuable resource for anti-diabetic plant chemicals. The concept of 'Constellation Plots' is proposed as a means to combine diverse molecular representations, enhancing the visualization and analysis of chemical space. This approach allows the identification of compound groupings known as "constellations" within chemical space, facilitating the discovery of informative Structure-Activity Relationships (StARs).

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Furthermore, in silico research serves as a tool for testing hypotheses and generating new theories. Computer simulations are employed to study the behavior of complex systems like climate or the economy, enabling the testing of assumptions regarding their functioning (Haensel et al., 2023; Yusuf & Khan, 2022). These simulations are also employed to generate new hypotheses, such as models explaining the operation of specific biological systems. Alberca et al. (2019) described a computational method for repurposing existing medicines into antimalarial agents. The researchers created and tested a set of ligand-based models capable of identifying falcipain-2 inhibitors. These models were used in a virtual screening (VS) campaign that utilized two distinct datasets (DrugBank and Sweetlead) (Novick et al., 2013). For example, a computational method was described for repurposing existing medications into antimalarial agents, where ligand-based models were developed and tested to identify falcipain-2 inhibitors. The models were employed in VS campaigns using two distinct datasets, resulting in the identification of four potential hits for further biological testing. Among these hits, odanacatib and methacycline were found to be falcipain-2 inhibitors, with methacycline demonstrating non-competitive inhibition. The effects of both medications on falcipain-2 hemoglobinase activity and P. falciparum proliferation were subsequently investigated (Alberca et al., 2019).

Sirous et al. (2019) created and tested an in silico approach for hit-to-lead optimization. The scientists, in particular, proposed a computational approach based on an in silico structure-based combinatorial library creation technique for micromolar HIV integrase (HIV IN) inhibitors. The methods described here are being used to combine the building of a combinatorial library and side-chain hopping with Quantum Polarized Ligand Docking (QPLD) and MD simulations (Caballero, 2021). This approach identified the most valuable scaffold decorations that are widely employed to assess the functional properties of particular synthesized drugs (Almehmadi et al., 2022) or phytoconstituents (Aijaz et al., 2022; Khanal et al., 2021; Kurya et al., 2022; Yusuf, 2022; Yusuf et al., 2022; Yusuf et al., 2023a; Yusuf et al., 2023b). In this work, in silico research is overviewed concerning the current scenario, advantages and several applications, limitations, and future perspectives.

2. Applications of in silico research

In silico-based approaches in research are expected to continue playing a significant role in many applied fields, including biology, chemistry, engineering, medicine, and other disciplines (Khan et al., 2022; Mocci et al., 2022; Sharma et al., 2021; Yusuf et al., 2023b). The advantages of in silico research are illustrated in **Figure 1**. It is being used to investigate complicated systems and events that are difficult or impossible to directly observe, as well as to test ideas and build new theories. It also enables cost-effective and time-efficient research, as well as insights that would be impossible to gain using standard experimental approaches. In silico research has a wide range of applications in different fields described herein.

Figure 1. Several advantages of in silico research

2.1. Chemistry and drug discovery

Computational chemistry relies on quantum chemistry computer programs to apply various quantum chemistry methods. These programs typically incorporate the Hartree-Fock (HF) method along with post-Hartree-Fock techniques (Table 1). Additionally, they may encompass Density Functional Theory (DFT) (Table 2), molecular mechanics, or semi-empirical quantum chemistry approaches. The available software comprises both open-source and commercial options. These programs tend to be extensive, often consisting of multiple distinct components, and have undergone extensive development spanning numerous years.

Table 1. Hartree-Fock (HF) and Post-Hartree-Fock methods

Package	HF	MP2	CCSD
Gaussian	Yes	Yes	Yes
GAMESS	Yes	Yes	Yes
NWChem	Yes	Yes	Yes
Q-Chem	Yes	Yes	Yes
Psi4	Yes	Yes	Yes
ORCA	Yes	Yes	Yes

Table 2. Density Functional Theory (DFT)

Package	Local functionals	Hybrid functionals	Dispersion correction
Gaussian	Yes	Yes	Yes
NWChem	Yes	Yes	Yes
Q-Chem	Yes	Yes	Yes
ORCA	Yes	Yes	Yes
ADF	Yes	Yes	Yes

Table 3. Molecular mechanics and semi-empirical methods

Package	Molecular Mechanics	Semi-empirical methods
Gaussian	Yes	Yes
GAMESS	Yes	Yes
NWChem	Yes	Yes
MOPAC	Yes	Yes
ORCA	Yes	Yes
AMS	Yes	Yes

The Tables 1, 2 and 3 illustrates some of the main capabilities of notable quantum chemistry computer packages. These packages encompass a range of functionalities and have been developed and refined over many years to cater to diverse computational chemistry needs. Further, Table 4 indicates the software packages that offer a range of features and capabilities for quantum chemistry and solid-state physics simulations and calculations. In silico chemistry research refers to computer-based simulations and modeling investigations in chemistry. Among its applications are:

Prediction of effectiveness: In silico studies can be used to predict the effectiveness, toxicity, and pharmacokinetics of possible drug candidates, saving time and money throughout the drug development process, simply the absorption, distribution, metabolism, elimination, and toxicity (ADMET) and pharmacokinetics (Table 5). These ADMET properties and pharmacokinetic characteristics play a crucial role in understanding the behavior and effects of drugs or chemical compounds in the human body, ensuring their safety, efficacy, and proper utilization in various applications.

Materials chemistry: In silico studies are being used to research material characteristics and behavior at the molecular and nanoscale levels, leading to the discovery of novel materials and their potential uses.

Quantum chemistry: In silico techniques are being used to compute the electronic structure and thermochemistry of molecules, allowing molecular characteristics and reactions to be predicted.

Environmental chemistry: In silico research is being used to predict chemical behavior and destiny in the environment, as well as to assess the possible ecological and toxicological impacts of chemical contaminants.

Computer simulations may assist research reaction mechanisms and anticipate reaction rates and energies, allowing us to better understand and improve chemical processes.

Thus, in silico designing in research is a significant tool for studying and understanding chemical systems and processes, and it has the potential to dramatically improve the synthesis of novel chemicals and materials.

Table 4. Some software packages offer a range of features and capabilities for quantum chemistry and solid-state physics simulations and calculations

Software	Descriptions
Quantum chemistry software	
Gaussian	A widely used software package offering a range of methods and capabilities for quantum chemistry calculations.
NWChem	An open-source computational chemistry package with support for various quantum chemical and molecular dynamics simulations.
Q-Chem	A comprehensive software suite providing high-performance calculations for quantum chemistry, suitable for different molecular systems.
Psi4	An open-source quantum chemistry software emphasizing efficiency and accessibility, equipped with advanced methods and algorithms.
ORCA	A versatile quantum chemistry program with a wide range of methods, applicable to small and large systems.
GAMESS	A suite of computational chemistry software widely used for diverse quantum chemical calculations and simulations.
MOLPRO	A comprehensive quantum chemistry software package supporting various methods for molecules, clusters, and periodic systems.
TURBOMOLE	A powerful quantum chemistry package delivering accurate calculations for molecular systems and materials.
Solid-state physics software	
VASP	Vienna Ab initio Simulation Package for performing ab initio electronic structure calculations of solids, surfaces, and interfaces.
Quantum ESPRESSO	An integrated suite of open-source codes for electronic-structure calculations and materials modeling in solid-state physics.
CASTEP	A leading solid-state physics software package for simulating and predicting the properties of materials, including electronic structure and vibrations.
ABINIT	A popular software package for first-principles calculations of material properties, encompassing electronic structure, optical, and transport properties.
WIEN2k	A full-potential code for electronic structure calculations of solids, utilizing density functional theory and advanced methods.
SIESTA	A software package focused on electronic structure calculations of materials using density functional theory for nano-scale systems.
OpenMX	A software package for nano-scale materials simulations based on density functional theory, specialized in electronic structure calculations.
LAMMPS	Large-scale Atomic/Molecular Massively Parallel Simulator, widely used for molecular dynamics simulations in solid-state physics.

In silico research has been explored to identify potential drug targets and to predict the properties of new drugs concerning computational approaches. The process of identifying and developing novel medications using computational methods is referred to as in silico drug discovery. Its applications in drug discovery are:

a) In silico approaches are being used to swiftly screen huge numbers of chemical compounds for possible effectiveness against a targeted illness, assisting in the identification of lead compounds for future testing.

Table 5. Assessment of ADMET and pharmacokinetic parameters

Property	Descriptions
ADMET properties	
Absorption	
Bioavailability	The extent to which a drug or compound is absorbed into the systemic circulation.
Permeability	The ability of a compound to cross biological membranes.
Solubility	The ability of a compound to dissolve in a specific solvent or biological fluid.
Distribution	
Protein Binding	The degree to which a drug or compound binds to proteins in the blood, affecting its distribution.
Tissue Penetration	The ability of a drug or compound to penetrate and distribute in different tissues or organs.
Metabolism	
Metabolic Stability	The resistance of a drug or compound to enzymatic metabolism affects its duration of action.
Metabolites	The transformation of products of a drug or compound through enzymatic reactions in the body.
Excretion	
Renal Clearance	The elimination of a drug or compound through the kidneys.
Hepatic Clearance	The elimination of a drug or compound through the liver.
Half-Life	The time required for the concentration of a drug or compound in the body to decrease by half.
Toxicity	
ADME-Tox	The assessment of a drug or compound's potential toxicity based on its ADMET properties.
Drug-Drug Interactions	The potential interactions between multiple drugs, affect their pharmacokinetics and pharmacodynamics.
Pharmacokinetic parameters	
Clearance	The rate at which a drug is eliminated from the body.
AUC (Area Under the Curve)	The total exposure of a drug in the systemic circulation over time.
T_{max}	The time is taken to reach maximum concentration after administration.

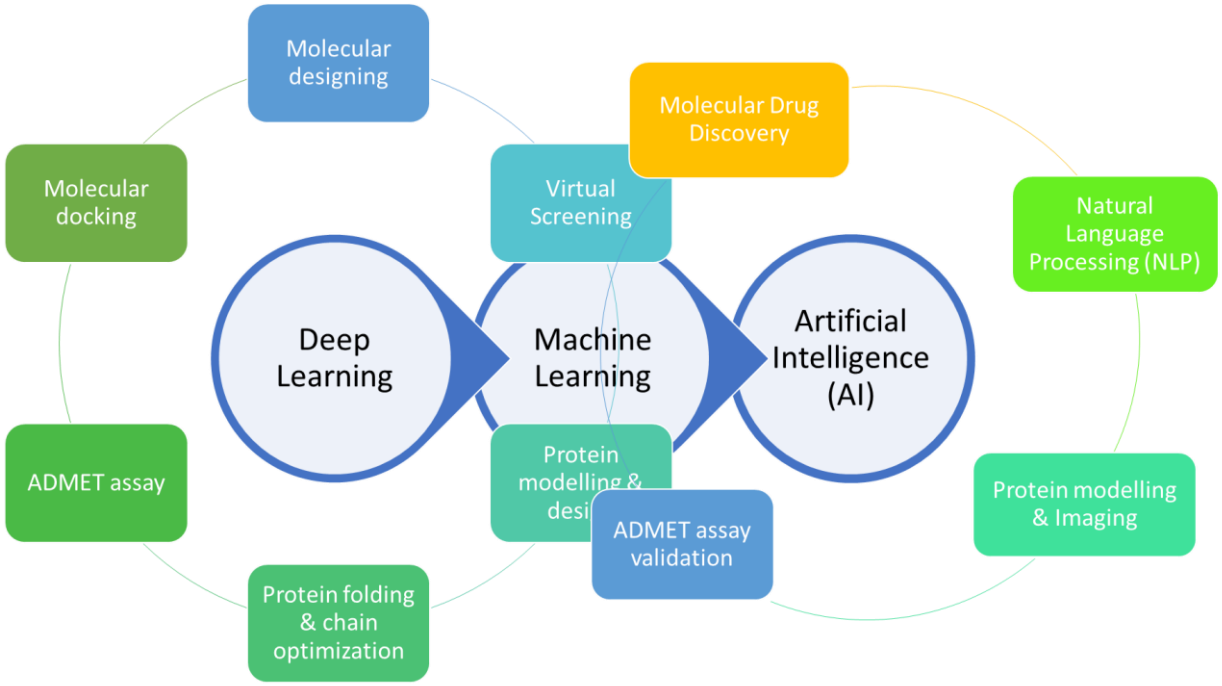

Figure 2. Various scientific disciplines leveraging artificial intelligence (AI)

b) In silico approaches are used to optimize the attributes of lead compounds such as potency, pharmacokinetics, and toxicity, hence increasing the chance of success in preclinical and clinical studies.

c) In silico approaches are being used to analyze the interactions between possible drug candidates and their target proteins, offering insights into how drugs bind to their targets and how they might be optimized to strengthen the binding affinity.

d) ADMET prediction: Computer simulations are being used to forecast possible drug candidates' absorption, distribution, metabolism, elimination, and toxicity (ADMET) qualities, minimizing the requirement for animal research and assisting in the identification of molecules with enhanced pharmacokinetics.

e) Drug-drug interactions: In silico approaches are being used to forecast the possibility of drug-drug interactions, assisting in the identification of possible adverse effects and improving the safety of new medications to represent drug activity in the body and interactions with diverse biomechanical and physicochemical systems, offering a forwarded-level knowledge of drug action.

The advancement of big data and artificial intelligence (AI) has revolutionized the strategies employed to expedite the drug development process. The utilization of AI has enabled the creation of drug candidates more systematically and cost-effectively, significantly reducing the time required. By harnessing computational resources and algorithms, the drug discovery process leverages existing data to enhance analytics and assessment. This

process encompasses the identification of potential drug candidates and the implementation of manufacturing procedures within the pharmaceutical industry (Dash et al., 2019; Kalyane et al., 2020). As a result, AI-driven analysis plays a significant role in quickly and effectively discovering and screening prospective drug candidates for the targeted illness before the synthesis and experimental assessment of a therapeutic molecule. This method makes the best possible use of the data that is already available to optimize the selection procedure and raise the overall success rate of drug development.

The drug discovery process encompasses several stages, from target identification to clinical trials. The recent breakthrough in AI technology has significantly benefited each phase of this process and the pharmaceutical industry as a whole. AI provides innovative solutions across multiple aspects of drug discovery, including target identification, lead compound screening from vast data libraries, drug repurposing, compound toxicity prediction, compound bioactivity prediction, de novo drug design, and automation of compound synthesis (Dash et al., 2019; Kalyane et al., 2020; Mak & Pichika, 2019).

The effective execution of AI relies on computer resources, which have undergone significant advancements. These include the emergence of high-performance computing clusters, improvements in graphics processing unit (GPU) power, the availability of cloud-based sources, and the accumulation of vast amounts of chemical informatics data. These developments have greatly influenced the evolution of AI technology (Grelck et al., 2019). Consequently, the application of AI has revolutionized the work culture in the pharmaceutical industry, particularly in the challenging field of drug discovery. Unlike the traditional trial and error approach, AI leverages predictive hypotheses derived from large datasets (Dash et al., 2019).

Leading pharmaceutical companies such as Pfizer, GlaxoSmithKline, Novartis, Merck, Sanofi, Genentech, and Takeda have embraced machine learning and AI to effectively manage massive volumes of generated data and deliver cost-effective solutions. It is projected that the AI-based drug discovery market will reach $1.43 billion in 2024, with an annual growth rate of ~41 % (Tripathi et al., 2021). This growth can be attributed to the increasing number of cross-industry collaborations and partnerships aimed at controlling the rising costs associated with drug discovery and development (Ramesh et al., 2004). Figure 2 illustrates the diverse areas where AI has made significant contributions to the various stages of drug design.

So, in silico approach for novel drug discovery is a powerful tool for expediting and optimizing the drug development process, allowing for more efficient and effective identification and optimization of novel medications.

2.2. Biology

In silico research can be used to study a wide range of biomechanical and physicochemical systems, including molecular interactions, protein folding, genetic regulation, and drug discovery. The application of computational tools and computer simulations in the study of biology is referred to as 'in silico' biology'. Its applications in biology are given below:

a) Genomics and proteomics: Large-scale genomic and proteomic data, such as gene and protein sequences, expression patterns, and interactions, are being analyzed and elucidated using in silico techniques.

b) Computer simulations are being used to estimate the effectiveness, toxicity, and pharmacokinetics of possible drug candidates, lowering the time and expenses associated with the drug discovery process.

c) In silico approaches are being used to model and study biomechanical and physicochemical systems at various levels of complexity, from molecular to cellular to organismal, assisting in the understanding of biological processes and interactions.

d) Evolutionary biology: Computer simulations are being used to explore species evolution, including genetic change patterns and processes, as well as the development of complex features.

e) Structures of proteins and nucleic acids: In silico investigations are being used to anticipate and evaluate protein and nucleic acid structures, assisting in the understanding of the molecular basis of biological activity.

f) Toxicology prediction: In silico approaches are being used to forecast the toxicity of chemical compounds, decreasing the requirement for animal testing and enhancing chemical product safety evaluation.

There are several software tools commonly used in biology for in silico research and computational modeling. Some examples can be found in Table 6.

Table 6. Some software tools commonly used in biology for in silico research and computational modeling

Application	Software/Tools
Molecular Dynamics Simulation	GROMACS, NAMD, Amber, CHARMM
Protein Structure Prediction	SWISS-MODEL, Phyre2, I-TASSER, Rosetta
Sequence Analysis and Alignment	BLAST, Clustal Omega, MUSCLE, MAFFT
Genomics and Transcriptomics	Genome Browser (UCSC, Ensembl), Trinity, Cufflinks, DESeq2
Molecular Docking and Virtual Screening	AutoDock, Vina, DOCK, GOLD
Systems Biology and Network Analysis	Cytoscape, Ingenuity Pathway Analysis (IPA), GeneMANIA, STRING
Quantitative Structure-Activity Relationship (QSAR)	ChemDraw, Open Babel, RDKit, KNIME
Pharmacokinetics and Drug Design	Schrödinger Suite (Maestro, Glide), Discovery Studio, MOE (Molecular Operating Environment), ADMEWORKS Predictor

Moreover, in silico approaches in biology are a helpful tool for studying and comprehending complicated biomechanical and physicochemical systems and processes, and it has the potential to significantly improve the discovery of novel medications, treatments, and technologies in the area of biology.

2.3. Materials science

In silico research can be used to study the properties of materials and design new materials with specific properties. Material science in silico research uses computational tools and computer

simulations to create, optimize, and comprehend materials and their characteristics, such as:

a) Nanomaterials: Nanoscale materials and their attributes, such as size, shape, and composition, are being designed and optimized using in silico approaches.

Table 7. Some commonly used software/tools for computational research in material science

Application	Software/Tools
Molecular Dynamics Simulation	LAMMPS, GROMACS, NAMD, Materials Studio
Density Functional Theory (DFT) Calculations	VASP, Quantum ESPRESSO, CASTEP, GPAW
Monte Carlo Simulations	GIBBS, DL_POLY, LAMMPS
Molecular Mechanics Simulations	Materials Studio, CHARMM, AMBER, GROMACS
Finite Element Analysis (FEA)	COMSOL, Abaqus, ANSYS
Electronic Structure Calculations	Quantum ESPRESSO, VASP, SIESTA, NWChem
Atomistic Modeling and Visualization	VESTA, Avogadro, OVITO, VMD
Crystal Structure Prediction	Materials Studio, USPEX, XtalOpt
Phase Diagram Calculations	Thermo-Calc, CALPHAD, FactSage, Pandat
Electronic and Optical Properties	Quantum ESPRESSO, VASP, Exciting, WIEN2k
Kinetic Monte Carlo Simulations	KMC-Lattice, DAKOTA, OpenKMC, SLIK

Table 8. Some software/tools used for modeling and analysis of Climate-interaction research

Application	Software/Tools
General Climate Modeling	Community Earth System Model (CESM), GFDL CM3, HadGEM
Regional Climate Modeling	Weather Research and Forecasting (WRF), RegCM, MM5
Ocean Modeling	Regional Ocean Modeling System (ROMS), MOM, NEMO
Atmospheric Chemistry and Aerosol Modeling	Community Multiscale Air Quality (CMAQ), GEOS-Chem
Land Surface Modeling	Community Land Model (CLM), Noah, JULES
Ice Sheet and Glacier Modeling	Community Ice Sheet Model (CISM), PISM, Elmer/Ice
Earth System Data Analysis	Climate Data Operators (CDO), NCO, Xarray
Paleoclimate Modeling	LOVECLIM, PISM, CLIMBER
Climate Model Evaluation and Visualization	Climate Explorer, Ferret, NCL, Panoply
Climate Data Assimilation	Data Assimilation Research Testbed (DART), WRFDA
Climate Impact Assessment	Integrated Assessment Modeling (IAM) frameworks

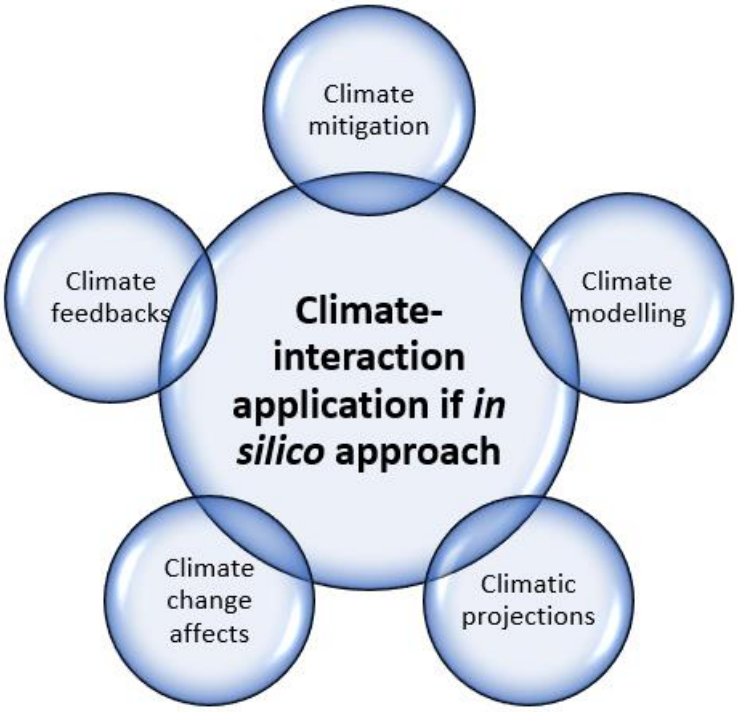

Figure 3. In silico applications: Climate-interaction research

b) In silico research is being used to create and improve novel materials with specified attributes such as high strength, high conductivity, or high thermal stability.

c) Computer simulations are being used to investigate the physical, chemical, and mechanical characteristics of materials, such as thermal conductivity, elastic modulus, and yield strength.

d) Computer simulations are being used to investigate the electrical and optical characteristics of materials, such as electronic band structures, and optical absorption spectra.

e) In silico research is being used to find novel materials and forecast their properties, assisting in the identification of new materials for diverse purposes such as energy, electronics, and biomedical engineering.

f) Computer simulations are being used to optimize and understand material production, including the development of crystal structures, phase transitions, and solid-state processes.

In material science research, various software tools are used for in silico studies and modeling. Below can be found some commonly used software tools for in silico research in material science (Table 7).

In light of modern research, in silico research in material science is a significant tool for studying and understanding material characteristics and behavior, and it may considerably improve the discovery, design, and optimization of novel materials for a variety of applications.

2.4. Climate-interaction research

In silico climate-interaction research use computer simulations and models to investigate the interactions between the Earth's climate and diverse physical, chemical, biomechanical, and physicochemical systems. Its applications are given below (Figure 3):

a) In silico research is being used to assess the efficacy of various climate mitigation measures such as carbon capture and storage, renewable energy, and land-use planning.

b) In silico research is used to create and enhance climate models that replicate the Earth's climate system, such as atmospheric and oceanic circulation, heat and moisture transfer, and greenhouse gas emissions.

c) Climate models are being used to forecast future climate changes and their consequences, which can assist influence climate adaptation and mitigation policies.

d) In silico research is being used to analyze climate change implications on many systems such as agriculture, water resources, biodiversity, and human health.

e) Computer simulations are being used to investigate the connections between the Earth's climate system and numerous feedback processes including the carbon cycle and ocean-atmosphere interactions.

In climate-interaction research, several software tools are used for modeling and analysis indicated in Table 8.

Therefore, climate-interaction in silico research is a powerful tool for understanding the intricate interactions between the Earth's climate and many physical, chemical, biomechanical, and physicochemical systems, and it may assist guide policy decisions on climate change.

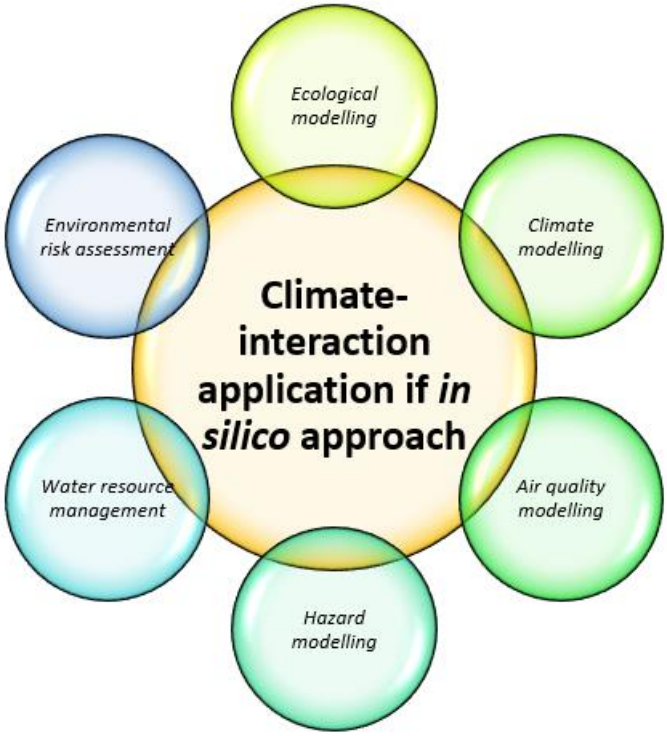

Figure 4. In silico applications: Environmental science research

2.5. Environmental science research

Environment-based in silico research uses computational methodologies and computer simulations to analyze and comprehend environmental systems and processes. These applications include (Figure 4):

a) Ecological modeling: Computer simulations are being used to investigate ecosystems, including the interactions between species and their environments, as well as to forecast the effects of environmental change on biodiversity.

b) Climate modeling: In silico methods are being used to analyze the Earth's climate, including historical, present, and future climate scenarios, assisting in the understanding of the causes and consequences of climate change.

c) Air quality modeling: Computer simulations are being used to investigate and forecast air quality, including the distribution and

consequences of air pollutants, as well as to aid in the development of air quality control plans.

d) Hazard modeling: In silico approaches are being used to probe and forecast natural hazards such as earthquakes, hurricanes, and volcanic eruptions, assisting in understanding their sources and repercussions and improving disaster planning and response.

e) Water resource management: In silico studies are being used to analyze and manage water resources, such as water flow and quality prediction, as well as the optimization of water supply and distribution.

f) Environmental risk assessment: Computer simulations can assist to enhance environmental protection and management by assessing the environmental hazards associated with diverse human activities such as chemical usage, energy generation, and land use.

In environmental science research, a variety of software tools are used for data analysis, modeling, and simulation. Some commonly used software tools in environmental science research are depicted in Table 9.

Table 9. Some commonly used software tools in environmental science research

Application	Software/Tools
Geographic Information System (GIS)	ArcGIS, QGIS, GRASS GIS, ENVI, SAGA GIS
Remote Sensing	ERDAS Imagine, ENVI, Google Earth Engine, SNAP
Environmental Data Analysis	R, MATLAB, Python (with libraries such as pandas, NumPy, and matplotlib)
Air Quality Modeling	AERMOD, CALPUFF, WRF-Chem, CMAQ, ADMS
Water Quality Modeling	EPA SWMM, CE-QUAL-W2, WASP, HEC-RAS, Delft3D
Ecological Modeling	STELLA, Ecopath with Ecosim, RAMAS Ecological Modeling, Vensim
Environmental Impact Assessment	AIMSUN, SimaPro, OpenLCA, Impact Assessment Tools
Climate Data Analysis	Climate Data Operators (CDO), NCL, R, Python
Soil and Water Management	SWAT, HEC-HMS, DSSAT, WEAP, MODFLOW
Environmental Risk Assessment	@RISK, Crystal Ball, Risk Assessment Tools
Environmental Monitoring and Sampling	LabCollector, EQuIS, Open Data Kit (ODK)

In silico research in environmental science is a vital tool for understanding and forecasting environmental systems and processes, and it may significantly improve the creation of environmental protection and management methods.

2.6. Pure and applied engineering

In silico research can be used to optimize the performance of existing products and design new products. In pure and practical engineering, in silico research include the use of computational tools and computer simulations to develop, optimize, and comprehend engineering systems and processes. The applications of in silico research in pure and applied engineering are given below:

a) Product design and optimization: In silico approaches are being used to optimize the design of engineering goods, including product performance prediction and manufacturing process optimization.

b) Computer simulations and optimization: Computer simulations are being used to analyze fluid flow, including the prediction of fluid flow patterns, heat transfer, and mixing, assisting in the optimization of the fluid system and process design.

c) Process simulation: Computer simulations are being used to investigate and optimize industrial processes, including process performance prediction and parameter optimization.

d) Structural analysis: In silico methods are being used to investigate the behavior of structures, including stress, strain, and deflection prediction, assisting in the optimization of mechanical systems and structures.

e) Thermodynamics: Computer simulations are being used to analyze thermodynamic systems, including temperature, pressure, and energy transfer prediction, assisting in the optimization of the energy system and process design.

f) Control systems: In silico approaches are being used to research and optimize control systems, including system behavior prediction and control algorithm creation.

As a result, in silico research in pure and applied engineering is a vital tool for improving the design and performance of engineering systems and processes, and it may significantly improve the development of creative and efficient engineering solutions.

2.7. Tissue engineering

In silico research in tissue engineering uses computational methodologies and computer simulations to design and optimize the engineering of biological tissues and organs, described further as:

a) Tissue design: In silico approaches are being used to design and optimize tissue architectures, including tissue mechanical property prediction and tissue composition and organization optimization.

b) Tissue mechanics: In silico approaches are being used to examine the mechanical characteristics of tissues, such as the prediction of tissue response to mechanical stress, strain, and deformation, assisting in the optimization of implantable devices and artificial organs.

c) Drug screening: In silico methods are being used to screen and assess medications for their effects on tissues and organs, including drug effectiveness, toxicity, and pharmacokinetics prediction.

d) Optimization of tissue structure: Computer simulations are being used to examine the interactions between cells and tissues, including the prediction of cell activity, migration, and differentiation, which can aid in the optimization of tissue structure development.

e) Tissue imaging: Computer simulations are being used to observe and understand tissue structures and functions, including tissue morphology prediction and data analysis.

f) Tissue engineering approaches: Computer simulations are being used to analyze and optimize tissue engineering techniques, such as tissue development, remodeling, and repair prediction, as well as scaffold design and material characteristics optimization.

As a result, in silico tissue engineering research is a vital tool for understanding and enhancing the engineering of biological tissues and organs, and it can significantly improve the development of innovative solutions for regenerative medicine and tissue repair.

2.8. Finance and economics

In silico research can be used to study the behavior of financial markets and predict future market trends. In silico research in finance and economics entails analyzing financial and economic systems and processes using computational methodologies and computer simulations, described below:

a) Financial modeling: In silico methods are being used to model and evaluate financial systems, including stock price prediction, interest rate prediction, and currency exchange rate prediction.

b) Portfolio optimization: Computer simulations are being used to optimize investment portfolios, including portfolio performance prediction and asset allocation optimization.

c) Risk management: In silico methods are being used to analyze and manage financial risk, including financial stress prediction and risk mitigation strategy evaluation.

d) Market microstructure: Computer simulations are being used to research market microstructure, such as order flow analysis, trading methods, and market efficiency.

e) Monetary policy: In silico methods are being used to examine monetary policy, including interest rate, inflation, and economic growth forecasting.

f) Behavioral economics: Computer simulations are being used to investigate economic agents' behavior, such as consumer behavior, decision-making, and market results.

Nonetheless, in silico research in finance and economics is a vital instrument for understanding and forecasting financial and economic systems and processes, and it may significantly improve the creation of financial stability and economic growth plans.

Thus, in silico research has broad applications in many different fields, and its potential is still being explored as technology and computational power continues to evolve.

3. Limitations of in silico research

There are various limits to in silico research, which refers to a study done using computer simulations and mathematical models. Some of the major restrictions (Lugli et al., 2019) **(Figure 5)** are as follows:

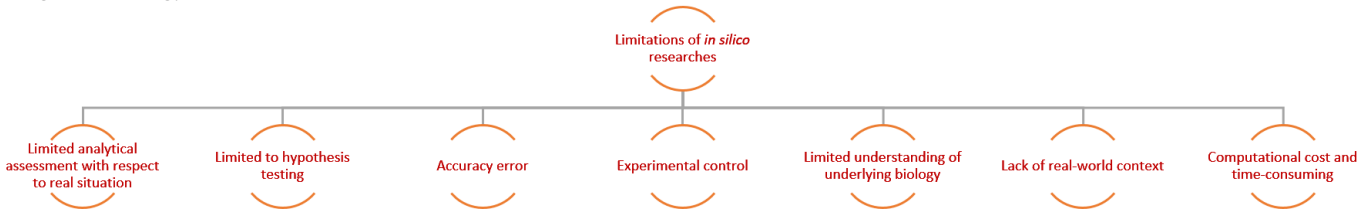

Figure 5. Limitations of in silico research

a) Limited analytical assessment concerning real situation: In silico research is limited by the analytical assessment concerning the real situation used for the model, and may not be generalizable to a larger population.

b) Limited to hypothesis testing: In silico research is typically used for hypothesis testing and prediction, rather than for discovering new knowledge or understanding the underlying mechanisms of biomechanical and physicochemical systems.

c) Accuracy error: Computer models may not perfectly replicate the complexity and variability of biomechanical and physicochemical systems, leading to inaccurate or incomplete results.

d) Experimental control: In silico research can be difficult to validate and replicate, as it lacks the experimental controls that are possible in vitro or in vivo research.

e) Limited understanding of underlying biology: In silico research relies on our current understanding of biomechanical and physicochemical systems, which are incomplete or inaccurate.

f) Lack of real-world context: Computer simulations do not account for the complexity and dynamic nature of the real-world context, where the system operates.

g) Computational cost and time-consuming: In silico research can be computationally expensive and time-consuming, particularly for large or complex systems.

4. Significance and future directions

In general, in silico research is poised to become an increasingly crucial tool for academics shortly, offering a cost-effective and powerful means of gaining new insights into complex biological and engineering systems and processes. In silico research is expected to grow in importance soon owing to various variables, like:

a) Big data analysis: Researchers will be able to apply in silico approaches to obtain new insights into biomechanical and physicochemical systems and processes when vast volumes of data, such as genomic, proteomic, and metabolomic data, become available.

b) Computer advancements: Computer advancements, such as the development of more powerful computers and cloud-based computing platforms, will allow researchers to execute increasingly complicated simulations and analyses.

c) Collaborative easiness: Collaboration between researchers in the life sciences, engineering, and computer science will drive the development of novel in silico methodologies and applications,

allowing researchers to tackle complicated issues that might otherwise be intractable.

d) Savings on time and money: In silico research may save time and money on animal testing, reagents, and laboratory equipment while still giving useful knowledge on biological and engineering systems.

e) Predictive power: In silico approaches are being used to forecast real-world phenomena, such as the behavior of biological and engineering systems, assisting researchers in optimizing processes, improving results, and making better-informed decisions.

Table 10. AI-enabled computational tools for drug designing

No	Tools	Url	Associated algorithm	Reference
1	AlphaFold	https://deepmind.com/blog/alphafold	Predicts tertiary structure of a protein using deep neural network (DNN)	(Senior et al., 2020)
2	Atomwise	https://www.atomwise.com/	AI platform for virtual screening and drug discovery, predicting the binding affinity of small molecules	(Singh et al., 2006)
3	AutoDock	https://autodock.scripps.edu/	Software for molecular docking, predicting binding affinity and modes of small molecules to target proteins	(Wang & Zhang, 2017)
4	Chemputer	https://zenodo.org/record/1481731	Give detailed recipe for compound synthesis	(Steiner et al., 2019)
5	Conv_qsar_fast	https://github.com/connorcoley/conv_qsar_fast	Predict molecular properties based CNN method	(Coley et al., 2017)
6	Chemical variational autoencoder (CVAE)	https://github.com/aspuru-guzik-group/chemical_vae	Automated chemical design using VAE	(Gómez-Bombarelli et al., 2018)
7	DeepChem	https://github.com/deepchem/deepchem	An open-source Python library uses a deep learning algorithm for compound identification	(Zhu, 2020)
8	DeepSynergy	www.bioinf.jku.at/software/DeepSynergy https://github.com/KristinaPreuer/DeepSynergy	A deep learning-based model for predicting the synergism of anticancer drugs	(Preuer et al., 2018)
9	DeepTox	www.bioinf.jku.at/research/DeepTox	Predict the toxicity of chemical compounds using a deep learning algorithm	(Mayr et al., 2016)
10	DeepNeuralNetQSAR	https://github.com/Merck/DeepNeuralNetQSAR	Predict molecular activity using multilevel deep neural network (DNN)	(Ghasemi et al., 2018)
11	DeltaVina	https://github.com/chengwang88/deltavina	Predict small molecule binding affinity with drug with a combination of random forest (RF) and AutoDock scoring function	(Wang & Zhang, 2017)
12	Exscientia	https://www.exscientia.ai/	AI-driven drug discovery platform combining machine learning models with high-throughput screening	(Burki, 2020)
13	Hit Dexter	http://hitdexter2.zbh.uni-hamburg.de	Predict frequent hitter by using machine learning (ML) algorithm	(Stork et al., 2019)
14	IBM Watson for Drug Discovery	https://www.ibm.com/common/ssi/ShowDoc.wss?docURL=/common/ssi/rep_sm/9/897/ENUS5737-B19/index.html	AI-powered platform analyzing scientific literature and data to identify drug targets and predict activities	(Martin et al., 2018)
15	InnerOuterRNN	https://github.com/Chemoinformatics/InnerOuterRNN	Predicts the physical, chemical, and biological properties using inner- and outer recursive neural networks	(Urban et al., 2018)
16	JunctionTree VAE	https://github.com/wengong-jin/icml18-jtnn	De novo molecule design using junction tree variational autoencoder (VAE)	(Tripathi et al., 2021)
17	Neural graph fingerprint	https://github.com/HIPS/neural-fngerprint	Predict the property of novel compounds using CNN	(Tripathi et al., 2021)
18	NNScore	http://www.nbcr.net/software/nnscore	Predict the affinity of protein-ligand interaction using the neural network-based scoring function	(Durrant & McCammon, 2011)
19	ORGANIC	https://github.com/aspuru-guzik-group/ORGANIC	De novo design of organic molecule and polymer using ML algorithm	(Sanchez-Lengeling et al., 2017)
20	OpenEye Scientific Software	https://www.eyesopen.com/	Suite of AI-enabled tools for molecular docking, virtual screening, and molecular dynamics simulations	(Siafaka et al., 2023)
21	Open Drug Discovery Toolkit (ODDT's)	https://github.com/oddt/oddt	Chemoinformatics pipeline using random forest score (RF)-Score and NNScore	(Wójcikowski et al., 2015)
22	PotentialNet	https://pubs.acs.org/doi/full/10.1021/acscentsci.8b00507	Predict binding affinity using graph convolutional neural network (CNN)	(Feinberg et al., 2018)
23	PPB2	https://ppb2.gdb.tools/	Predict the target of the query molecule using the nearest neighbor and machine learning algorithm	(Awale & Reymond, 2018)
24	QML	https://www.qmlcode.org/	Python toolkit for quantum machine learning	(Cho, 2020)
25	REINVENT	https://github.com/MarcusOlivecrona/REINVENT	De novo design of molecule using RNN (recurrent neural network) and RL (reinforcement learning)	(Blaschke et al., 2020)
26	Schrödinger Suite	https://www.schrodinger.com/suites/Schro%CC%88dinger	Comprehensive software package for molecular modeling, drug design, virtual screening, and simulations	(Chandel et al., 2022)

Future directions of in silico research could include:

a) Developing new methods for hypothesis generation: In silico research has traditionally been used for hypothesis testing, but new methods could be developed to allow for hypothesis generation as well.

b) Developing experimental controls for in silico research: Developing experimental controls for in silico research could make it easier to validate and replicate results, increasing confidence in the findings.

c) Increasing the accuracy of computer models: Advances in computational power and machine learning techniques could allow for more accurate and detailed simulations of biomechanical and physicochemical systems.

d) Incorporating new data and knowledge: Integrating new data and knowledge from experimental research into computer models could improve our understanding of biomechanical and physicochemical systems and help identify new research directions.

e) Improving the generalizability of results: Developing ways to increase the sample size of in silico research could make the results more generalizable to a larger population.

f) Optimizing the computation cost and reduction of time: Developing more efficient algorithms and using distributed computing could reduce the computational cost and time needed for in silico research.

g) Combining in silico research with experimental research: Combining in silico techniques with experimental research could provide a more comprehensive understanding of biomechanical and physicochemical systems.

h) Developing new ways to simulate real-world context: Improving the way to simulate the real-world context where the system operates, could lead to more realistic predictions.

The advancement of computer resources, including high-performance computing clusters, powerful GPUs, cloud-based sources, and vast amounts of chemical informatics data, has significantly impacted the application of AI technology. This has revolutionized the pharmaceutical industry, particularly in drug discovery. AI enables predictive hypotheses derived from large datasets, replacing the traditional trial and error approach. Table 10 illustrates AI-enabled computational tools for drug designing. Major pharmaceutical companies such as Pfizer, GlaxoSmithKline, Novartis, Merck, Sanofi, Genentech, and Takeda have embraced machine learning and AI to manage extensive data and provide cost-effective solutions.

However, in silico research has the potential to be a powerful tool for understanding biomechanical and physicochemical systems, but it is important to consider its limitations and work to overcome them. By continuing to develop and improve computer models, integrating new data and knowledge, and combining in silico research with experimental research, we can move closer to understanding the complexity of biomechanical and physicochemical organizations.

4. Conclusions

Nowadays, in silico research is a valuable tool for understanding biomechanical and physicochemical systems, but it has its limitations. Advances in computer power and machine learning approaches, as well as the creation of experimental controls and novel hypothesis-generating methods, may assist to overcome some of these constraints. Furthermore, merging in silico research with an experimental approach and integrating fresh data and expertise can give a more thorough understanding of biomechanical and physicochemical systems. Based on individual genetic and proteomic data, in silico technologies will be utilized to generate more personalized medical treatments, including the prediction of patient-specific medication reactions. Predictive toxicology will employ in silico approaches to anticipate the toxicity of chemicals and medications, decreasing the need for animal testing and enhancing consumer product safety. In the energy and environmental research field, in silico approaches will be utilized to examine energy systems, including energy consumption forecasts, renewable energy sources, and the environmental effect of energy use. In silico approaches will be merged with AI and machine learning techniques, allowing researchers to perform increasingly complicated and sophisticated simulations and analyses. In silico research is a developing discipline that will play an increasingly essential role in understanding and predicting the behavior of complex systems in the future. Overall, it is critical to recognize the limits of in silico models and utilize them in conjunction with actual research to gain a better understanding of biomechanical and physicochemical systems.

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Supplementary File

None.

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