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Review Article

In-silico studies in Oral Medicine and Radiology

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ABSTRACT

The term in-silico originates from Latin, referring to the use of silicon, a p-block element prominent in computer chips. In the dynamic field of Oral Medicine and Radiology, in-silico studies have become crucial. This branch focuses on diagnosis, treatment planning, prognosis, and maxillofacial imaging. The adoption of model-driven approaches enhances the accuracy of treatment regimes, radiographic interpretations, and prognostic outcomes. The continued evolution of technology promises further integration of in-silico models with experimental and clinical data. This synergy is expected to enhance the precision and reliability of medical interventions, paving the way for more personalized and accurate healthcare solutions. The dynamic nature of in-silico studies will likely lead to ground breaking advancements in diagnostic and therapeutic strategies, revolutionizing patient care. As the field progresses, embracing in-silico methodologies will be vital for advancing medical science and improving patient outcomes. The fusion of computational power with clinical expertise offers a promising horizon for the health sciences, ensuring that the future of medicine is both innovative and transformative.

1. Introduction

In compliment with in vitro and in vivo experimentations; In- Silico is a term used in modern science for all those researches done through computers. In-silico is a Latin origin term IN SILICON pertaining to the presence of p block element silicon in computer chips. The idea germinates way back in 1987 by Christopher Langton who first hosted a conference on "Artificial Life" which highlights the importance of computer system mimicking the life. In 1991 the idea was first revolutionised by Danchin et al.,[1] by taking the data based on E. coli using data bank. Since then various milestones were achieved in this regard and in silico studies are now use in various realms of health sciences.

2. Precision Medicine

The five targeted goals i.e. proper patient, proper drug, proper time, proper dose, and proper route; in silico techniques come up as driving force for making this a realistic and promising avenue for precision therapies (Figure 1).[1]

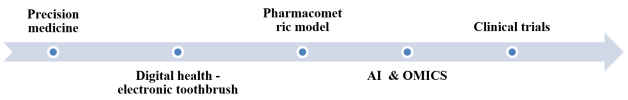

Figure 1: Workflow of precision medicine with AI in clinical trials

In silico studies had two categories i.e. comparative genomics and network based methods. While comparative genomics primarily used in infectious diseases, network-based methodology is for infectious and non-infectious

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diseases (Figure 2).

Figure 2: Categories of in- silico studies

Astra Zeneca's drug research and development programs found that program terminations in preclinical studies pertaining to safety issues were 82% in which target-related consoles 25%. Revolution of chemical informatics, bioinformatics and omics, in silico therapeutic target discovery methods had come to relief.[2]

Table 1: Software used in identification of potential therapeutic targets[2]

In Silico Tools	Summary	Usablility	Latest
Cytoscape	Network visualization and analysis.	Free	2020
Gephi	Network visualization and analysis	Free	2017
Network Analyst	Gene expression analysis	Free	2021
HIPPIE	Human protein–protein interaction networks	Free	2019
Pathway Linker	Physical and genetic interaction data with pathway information	Free	/
KOBAS	Gene/protein functional annotation and gene set enrichment	Free	2020
BioCyc	18,030 Pathway/Genome Databases (PGDBs)	Free	2021
Cfinder	Overlapping dense groups of nodes in networks	Free	2014
Pajek	Analysis and visualization of large network	Free	2021

3. Diagnosis

In silico studies uses computational models and simulations to deeply understand and identify the disease mechanism, better biomarkers identification and finally targeted therapeutic approach.

"The computer is incredibly fast, accurate, and stupid. Man is unbelievably slow, inaccurate and brilliant. The marriage of the two is a force beyond calculation." — Leo Cherne

Few in silico approaches that make the head turns are-

1. Oral cancer- in silico methods probe genetic and molecular data to unearth various biomarkers for precocious diagnosis and proper prognosis. For e.g. Intensity modulated dosage of X ray for particular SCC for specific anatomical location. E.g. miRWalk, GEPIA2 and TSVdb online tool used as database.
2. Premalignant Disorders- In silico techniques allow the identification of key biomarkers and pathways associated with them by analysing gene-protein interaction networks. These biomarkers could help in early diagnosis by predicting disease progression.[3]
3. Dental caries- computer driven models allow in silico cariogenic models to thoroughly visualise the different bacterial species involved in caries progression and biofilm production. In one the study by Head D et al.,[4] found out the significant contribution of in silico studies in plaque cariogenicity affected by total amount and frequency of sugar intake.
4. Pain management- In Silico studies are used to study the efficacy of mesenchymal stem cells interaction with immune cells and endogenous opioid system for better management of orofacial pains. Another approach is molecular docking for exploring the antinociceptive properties of various compounds. E.g. Efficacy of Geraniol a natural compound on pain relief by simulating its effect on pain receptors using molecular docking.[5]

4. Maxillofacial Imaging

"In Silico Imaging" refers to a computer-simulated imaging system that encompasses the source, object, detection, and image interpretation elements utilized for research, development, optimization, technology revaluation, and regulatory assessment of new technologies, serving as a complement to traditional bench testing methods. In Silico studies can simulate various imaging modalities like CT, CBCT and MRI etc.

"Computers are the eyes that see beyond surfaces." - Anonymous.

1. Adaptive radiotherapy: In silico studies have been used to evaluate the feasibility and benefits of CBCT-guided adaptive radiotherapy. For instance, the Ethos^{TM} system by varian medical systems uses AI and machine learning to perform adaptive radiotherapy, which can improve the accuracy and efficiency of treatments by adjusting plans based on daily anatomical changes.
2. Dosimetric studies: These studies often involve simulating different radiation doses and their effects on tissues. For example, an in silico study assessed the benefits of adaptive radiation therapy for head and neck squamous cell carcinoma, showing potential

improvements in treatment precision and reduced toxicity.

3. Image quality improvement: New algorithms, such as iterative CBCT (iCBCT), have been developed to enhance the quality of CBCT images. These improvements are crucial for better diagnosis and treatment planning.
4. Organ-at-risk (OAR) Constraints: In silico trials can help optimize treatment plans to minimize radiation exposure to healthy tissues. For example, a study on CT-guided stereotactic adaptive radiation therapy (CT-STAR) demonstrated how adaptive plans could reduce violations of OAR constraints compared to non-adaptive plans.[6]

These studies are instrumental in advancing the field of radiology by providing a safer, more efficient, and cost-effective way to test and implement new technologies.

5. Therapeutics

Choosing the right candidate targets can significantly enhance the success rate and portfolio value of drug discovery projects, while also cutting down on time and costs. Historically, target discovery has depended on wet lab experiments, which are often time-consuming, costly, and not very accurate.[2]

Antimicrobial targeted therapy & resistance – Global outbreak of multi-drug resistant (MDR) microbial strains has caused havoc due to antibiotic resistance. Addressing this issue requires a thorough understanding of antimicrobial resistance (AMR) genes and their mechanisms. In this context, in silico studies can be incredibly effective in providing valuable insights and solutions.

"Medicine is not only a science; it is also an art. It does not consist of compounding pills and plasters; it deals with the very processes of life, which must be understood before they may be guided." — Paracelsus

For e.g. Naha et al.,[1] Using in silico studies listed efflux pumps genes, beta lactams, glycopeptide resistance and high direct interactions genes for potent antimicrobial target in E. faecalis (Figure 3).

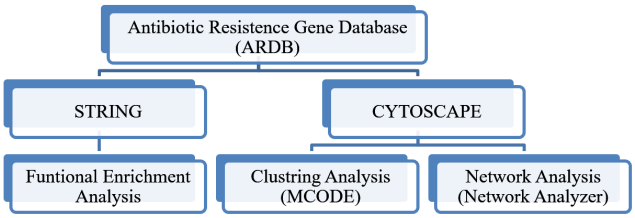

Figure 3: AIin antibiotic resistance of *E. faecalis*

5.1. OSCC

In recent decades, with the increasing bioinformatics tools, microarray database and high throughput sequencing data have emerged as important resources to associate altered gene expression in the disease. E.g. Yadav et al.,[7] in their in silico based study found out nine DEGs including APP, EHMT1 etc. as hub genes. All nine hub genes in OSCC are dose-dependently inhibited by Fisetin. These hub genes act as diagnostic biomarkers and drug targets.

5.2. OSMF

Pre-malignant disorder affecting oral mucosa. The major challenge in early stage of drug cycle is predicting the toxic effects of molecules especially in this PMDs. Enhancement of development of drug success rate depends on understanding of ADME phenomenon, thus reducing cost of drug. Rai. A et al.,[8] uses in silico study and their docking results suggest that ligands—Curcumin and its derivatives have good binding affinity and high docking scores for both TGF-b type I & II receptors involved in OSMF. Using ChEMBL database ligand library comprising of FDA approved drug was made. Molecular docking done using GOLD suite 5.2.2. The docked complexes having large binding affinities and below average energy were simulated using MDweb server.

5.3. Oral lichen planus (OLP)

It is a chronic T cell-mediated muco-cutaneous disease. Heart shock protein and the pro-inflammatory mediator TNFα have been involved in its etiopathogenesis. In the study by Ramakrishnan P et al.,[9] for treating OLP at HSP70 and TNFα were evaluated for action of 27 drugs by ligand library by molecular docking using Maestro Schrodinger version 10.1. X-ray crystallographic structures[10] were retrieved from Protein Data Bank (PDB). The ligands (27 drugs) structure was obtained from PubChem in.sdf format. Using Ligprep, pre-processing of the ligands was done.

6. Forensics

In silico studies for forensics involve the use of advanced computational models and imaging techniques to perform non-invasive post-mortem examinations.

"Digital evidence is the silent witness that never lies, never forgets, and never leaves the crime scene."

1. Imaging techniques: Virtopsy employs imaging methods such as computed tomography (CT) and magnetic resonance imaging (MRI) to create detailed 3D reconstructions of the body. These images can be analysed using in silico models to identify injuries, diseases, and other forensic details.
2. 3D surface scanning: This technique captures the external surface of the body in high detail, which can

Table 2: Summarizing the software tools for in silico studies in oral disease therapies [11]

Computer Tool	Inference	Usage
Auto Dock	Predict small molecule binding to receptors	Drug-receptor interaction
Schrödinger Suite	Comprehensive suite for molecular modelling, drug design, and computational chemistry	Virtual screening, molecular dynamics simulations
BIOVIA Discovery Studio	Tools for protein modelling, molecular docking, and simulation	Targeted therapy studies
MOE (Molecular Operating Environment)	Platform for computational chemistry, molecular modelling, and bioinformatics	Structure-based drug design, protein-ligand docking
GROMACS	Molecular dynamics simulation software	Studying physical movements of atoms and molecules
PyMOL	Molecular visualization tool	Preparing and analysing molecular structures

be integrated with internal imaging data to provide a comprehensive view of the body.

3. Data integration and analysis: Advanced software tools are used to integrate and analyse data from various imaging modalities. This includes tools for image processing, 3D reconstruction, and virtual dissection.
4. Simulation and visualization: In silico models can simulate different forensic scenarios, helping forensic experts to visualize and interpret complex findings. These simulations can be used for educational purposes, expert witness reports, and tele-medical consultations.

7. Limitations [1,2,6,8]

1. Theoretical nature of the methodology.
2. To close the equations various simplifying assumptions required.
3. Planktonic parameters in vitro experiments
4. Rather than individual cells aggregate of cells as the structural units to reduce the computational load.
5. Data is not physiologically plausible.
6. To treat information that is not directly related to the sequence itself (e.g. keywords, features, comments).
7. Sequences cannot be entered error free or inaccuracies, e.g. sometimes authors omit predictions.

Table 3: Notable software tools used in virtopsy [12]

Software Tool	Description	Applications
Amira	3D visualization and analysis software	3D reconstruction, image analysis
Mimics	Medical image processing software	3D modelling, virtual dissection
OsiriX	DICOM viewer	Image processing, 3D visualization
3D Slicer	Open-source software for medical image computing	Image segmentation, 3D reconstruction
Virtobot	Robotic system for automated virtopsy	3D surface scanning, post-mortem imaging

8. Once gene has been thus studied, not much more is done to it using computers.
9. Giant information present in the sequence is not exploited.
10. Approximations of the physical world not feasible.
11. Identification of gene is computational and the gene signature may not cater to the wide heterogeneity of tumour samples.
12. Limited acceptance for in silico models for regulatory approach that may hinder the work in drug development or other fields that needs regulatory approach.

8. Discussion

Pertaining to the dynamic branch Oral Medicine and Radiology which focuses on diagnosis, treatment planning, prognosis and maxillofacial imaging uses model-driven approach for burnishing the accuracy of treatment regimes, radiographic interpretation and prognostic outcomes.1 With the growing complexity of oral and maxillofacial disorders it's a need of hour to shift from culture plates to chip decreasing the cumbersome data handling and relieving the calculations and result. In-silico methodologies, while innovative, face several challenges: they are largely theoretical, requiring numerous simplifying assumptions to close equations, and often use in vitro planktonic parameters which may not be physiologically plausible. Furthermore, approximations of the physical world are not always feasible, and gene identification through computational methods may not cater to the heterogeneity of tumour samples. Regulatory acceptance of in-silico models remains limited, posing a barrier to advancements in drug development and other fields requiring stringent regulatory approaches. [12,13]

9. Conclusion

In silico studies hold significant promise for advancing the fields of oral medicine and radiology. These computational approaches enable researchers to model complex biological processes, predict disease progression, and evaluate potential treatments with greater efficiency and cost-effectiveness. Despite their limitations, such as the need for high-quality data and computational power, in silico studies complement traditional experimental methods and provide valuable insights that can accelerate scientific discovery and clinical application. As technology continues to evolve, the integration of in silico models with experimental and clinical data will likely enhance their accuracy and reliability, paving the way for more personalized and precise medical interventions.

"It always seems impossible until it's done." – Nelson Mandela

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None.

11. Conflict of Interest

None.

References

1. Danchin A, Médigue C, Gascuel O, Soldano H, Hénaut A. From data banks to data bases. *Res Microbiol*. 1991;142(7-8):913–6.
2. Naha A, Miryala SK, Debroy R, Ramaiah S, Anbarasu A. Elucidating the multi-drug resistance mechanism of Enterococcus faecalis V583: A gene interaction network analysis. *Gene*. 2020;748:144704.
3. Zhang X, Wu F, Yang N, Zhan X, Liao J, Mai S, et al. In silico Methods for Identification of Potential Therapeutic Targets. *Interdiscip Sci*. 2022;14(2):285–310.
4. Ukey S, Ramteke A, Choudhury C, Purohit P, Vishnoi JR, Chugh A, et al. In-silico, interactomic based screening and identification of differentially expressed miRNAs in oral submucous fibrosis and oral squamous cell carcinoma. *Human Gene*. 2022;33:201041.
5. Head D, Devine DA, Marsh PD. In silico modelling to differentiate the contribution of sugar frequency versus total amount in driving biofilm dysbiosis in dental caries. *Sci Rep*. 2017;7(1):17413.
6. Costa T, Barros MS, Braga RM, Viana JO, Sousa FB, Scotti L, et al. Orofacial antinociceptive activity and anchorage molecular mechanism in silico of geraniol. *Braz Oral Res*. 2020;34:e094.
7. Badano A. In silico imaging clinical trials: cheaper, faster, better, safer, and more scalable. *Trials*. 2021;22(1):64.
8. Yadav M, Pradhan D, Singh RP. Integrated analysis and identification of nine-gene signature associated to oral squamous cell carcinoma pathogenesis. *3 Biotech*. 2021;11(5):215.
9. Rai A, Qazi S, Raza K. In Silico Analysis and Comparative Molecular Docking Study of FDA Approved Drugs with Transforming Growth Factor Beta Receptors in Oral Submucous Fibrosis. *Indian J Otolaryngol Head Neck Surg*. 2022;74(Suppl 2):2111–21.
10. Saddala MS, Huang H. Identification of novel inhibitors for TNFα, TNFR1 and TNFα-TNFR1 complex using pharmacophore-based approaches. *J Transl Med*. 20192;17(1):215.
11. Ramakrishnan P, Kumar TP, Saraswathy GR, Sujatha S. In silico evaluation of drugs used in treatment of oral lichen planus. *J Oral Pathol Med*. 2020;49(9):926–32.
12. Zayed SO, Abd-Rabou RY, Abdelhameed GM, Abdelhamid Y, Khairy K, Abulnoor BA, et al. The innovation of AI-based software in oral diseases: clinical-histopathological correlation diagnostic accuracy primary study. *BMC Oral Health*. 2024;24(1):598.
13. Thali MJ, Yen K, Schweitzer W, Vock P, Boesch C, Ozdoba C, et al. Virtopsy, a new imaging horizon in forensic pathology: virtual autopsy by postmortem multislice computed tomography (MSCT) and magnetic resonance imaging (MRI)–a feasibility study. *J Forensic Sci*. 2003;48(2):386–403.

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