INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Paper

In Silico and Bioengineered Innovations in Wound Healing: Toward Personalized and Predictive Therapeutic Strategies

Prerana Kashyap[1], Pranabesh Sikdar*[2], Rajsekhar Das[3], Bipul Nath[4], Himanta Biswa Saikia[5], Anju Das[6], Subhashis Debnath[7]

[1,2,3,4,5,6] *Royal School of Pharmacy, The Assam Royal Global University, Guwahati, 781035*
[7] *Bharat Pharmaceutical Technology, Amtali, Agartala, 799130*

ARTICLE INFO

Published: 27 Nov 2025

Keywords:

Advanced wound healing, bioengineered skin grafts, chronic wounds, in silico modelling

DOI:

10.5281/zenodo.17736051

ABSTRACT

Severe and chronic wounds pose significant clinical, social, and economic challenges due to persistent inflammation, impaired tissue regeneration, and infection risks. Traditional wound management methods, such as dressings, debridement, and autografts, often fail to provide adequate healing for complex wounds. Advances in biomedical science have introduced innovative approaches including bioengineered skin substitutes, nanotherapeutics, stem cell therapy, and 3D bioprinting, which enhance tissue repair and reduce complications. Among these, bioengineered skin grafts offer major advantages by eliminating donor site morbidity, promoting angiogenesis, accelerating healing, and minimizing infection and scarring. Despite these innovations, wound healing remains influenced by several local and systemic factors such as hypoxia, diabetes, infection, poor nutrition, and aging. Recently, computational and mathematical models have emerged as valuable tools to simulate biological mechanisms, predict healing outcomes, and design personalized therapies. These in silico models integrate molecular, cellular, and tissue-level data to analyze healing dynamics, identify therapeutic targets, and optimize treatment strategies while reducing experimental burden. The integration of in silico and experimental data bridges the gap between laboratory research and clinical practice, paving the way for precision and predictive wound care. Although challenges such as biological complexity, limited data standardization, and clinical validation persist, continued advancements in artificial intelligence and computational modeling hold immense translational potential. Collectively, these approaches represent a paradigm shift in wound care—from empirical treatments to data-driven, personalized, and efficient healing strategies.

***Corresponding Author:** Pranabesh Sikdar

Address: *Royal School of Pharmacy, The Assam Royal Global University, Guwahati, 781035*

Email : pranawesh@rediffmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

INTRODUCTION

Severe and complicated wounds create a significant clinical, socio and economic challenges which provides an opportunity for advancements of wound healing ideas. Previously wound healing concepts like dressings autografts and debridement were never enough in serious wounds. Chronic wound includes persistent inflammation, impaired tissue regeneration and huge risk of infections. Chronic and complex wounds present a significant clinical and socioeconomic challenge, requiring the development of advanced wound healing strategies[1,2]. Traditional wound care methods includes dressings, debridement and autografts which are often not enough for chronic wounds, which are characterized by persistent inflammation, impaired tissue regeneration, and a high risk of infection. Wounds not only reduce patient's quality of life but also enforce a substantial financial burden on healthcare systems, with the global wound care market projected to grow from $12 billion in 2020 to nearly $19 billion by 2027 [3,4,].

Issues such as limited donor sites for grafts, risk of hypertrophic scarring, and repeated surgical interventions further complicate management. Recently innovative therapies such as nanotherapeutics, stem cell therapy, bioengineered skin substitutes, and 3D bioprinting are introduced which targets specific biological pathways, enhance tissue regeneration, and minimize complications[5]. Methods like advanced dressings and hydrogels are also designed to control inflammation, control exudate, and create optimal healing environments[6].

Inspite of these innovations, the management of chronic wounds remains challenging due to factors such as patient variability, comorbidities, and the need for personalized treatment plans. Due to which there is an increased need for continued research and the integration of advanced, cost-effective, and non-invasive therapies to improve wound healing outcomes and reduce the burden on patients and healthcare systems[7,8].

2. Overview of Wound Healing: Biological and Pathological Mechanisms

Bioengineered skin grafts accelerate healing more than traditional methods in several ways:

2.1. Elimination of Donor Site Morbidity: Classical autologous skin grafts require harvesting skin from another part of the patient's body, leading to additional wounds and potential complications at the donor site. In vitro produced bioengineered skin grafts do not require donor tissue which reduces patient morbidity[9].

2.2. Enhanced Tissue Regeneration and Integration: Bioengineered grafts are capable of being customized with growth factors, cytokines, and extracellular matrix (ECM) components such as collagen, fibronectin, and laminin those elements provide both structural support and biochemical cues which promote new blood vessel formation (angiogenesis), guide cell behavior and facilitate better integration with the host tissue[10].

2.3. Accelerated and Improved Healing: Numerous bioengineered skin substitutes are designed to mimic the structure and function of native skin which supports the growth of the patient's own skin cells. They promote rapid wound closure, reduce fluid loss, and create an optimal environment for re-epithelialization and tissue repair. For example, Apligraf and Biobrane have faster healing and reduced hospital stays in clinical studies[11,12].

2.4. Reduced Risk of Complications: Since bioengineered grafts are manufactured under controlled conditions and can be designed less immunogenic, they frequently result in fewer complications such as infection, graft rejection, and hypertrophic scarring compared to traditional grafts[13].

2.5. Improved Quality of Life: Bioengineered skin grafts diminishes symptoms, increase patient comfort, and improve overall quality of life for individuals with chronic wounds[14].

In conclusion, bioengineered skin grafts offers notable advantages over traditional methods by diminishing the need for donor sites, improving tissue regeneration, accelerating healing, reducing complications, and improving outcomes of patients.

3. Causes of Impaired Wound Healing and Clinical Challenges

3.1. Key Factors Responsible for Impaired Wound Healing

3.1.1. Local Factors

3.1.1.1. Oxygenation: Sufficient oxygen is crucial for both cellular metabolism and collagen production. Hypoxia, usually resulting from inadequate perfusion or venous insufficiency, delays wound healing by raising oxidative stress levels and promoting inflammation[15].

3.1.1.2. Infection: Bacterial contamination slows the healing process because the body focuses on combating infection instead of repairing tissue. Infected wounds exhibit greater inflammation, tissue damage, and an increased risk of becoming chronic[16].

3.1.1.3. Foreign Bodies and Repetitive Trauma: Foreign material or repeated trauma can sustain inflammation and interfere with the healing process[16].

3.1.1.4. Venous Insufficiency: Impaired venous return causes edema and limits nutrient supply, which further delays tissue repair[16].

3.1.2. Systemic Factors

3.1.2.1. Diabetes Mellitus: Diabetes is a leading cause of chronic wounds, particularly diabetic foot ulcers. Elevated blood glucose impairs immune cell activity, decreases angiogenesis, raises oxidative stress, and promotes the formation of advanced glycation end-products (AGEs), all of which hinder healing. Diabetic wounds also have elevated protease levels that break down new tissue and are affected by neuropathy, which lowers protective sensation and weakens the immune response[16,17].

3.1.2.2. Age: Healing in elderly individuals is delayed due to lower rates of cell growth, reduced new blood vessel formation, and other coexisting health conditions[18,19].

3.1.2.3. Chronic Illnesses: Conditions such as cardiovascular disease, obesity, and immune disorders reduce blood flow, hinder nutrient supply, and weaken immune responses, all of which contribute to slower healing[18,20].

3.1.2.4. Poor Nutrition: Deficiency of protein, vitamin C, zinc, and essential fatty acids hampers collagen formation and immune response, causing healing to be slower or inadequate[21,22].

3.1.2.5. Medications: Medications such as steroids, non-steroidal anti-inflammatory drugs, and chemotherapy agents suppress inflammation and cellular proliferation, which hinders tissue repair[23,24].

3.1.2.6. Smoking and Alcohol Use: Nicotine causes blood vessel constriction, which lowers oxygen transport, and alcohol impairs both immune response and nutrient absorption[25,26].

3.1.2.7. Stress and Hormonal Imbalances: Psychological stress and changes in sex hormones (like lowered estrogen) can adversely impact the healing process by increasing inflammation and decreasing cellular activity[27,28].

3.2. Clinical Challenges

3.2.1. Chronic Wounds: Chronic wounds, including diabetic foot ulcers and pressure sores, are challenging to treat because of ongoing inflammation, infection, and inadequate blood supply. Such wounds are at high risk for complications like infection, tissue death, and possible amputation[1,2].

3.2.2. Patient Variability: Age, comorbidities, nutritional status, and lifestyle differences add complexity to treatment and demand tailored approaches[29,30].

3.2.3. Recurrent Infections: Chronic wounds with persistent or recurring infections may develop antibiotic resistance, which delays healing even more[31].

3.2.4. Resource-Intensive Care: Effective management typically demands multidisciplinary teams, specialized wound care products, and extended treatment periods, all of which raise healthcare costs and burden[32,33].

In summary, impaired wound healing arises from a mix of local and systemic factors — including hypoxia, infection, diabetes, poor nutrition, and chronic diseases — that interfere with normal repair and pose major clinical challenges in both acute and chronic care[3,33].

4. Progress and Applications of Computational and Mathematical Models for Wound Healing

Mathematical and computational models are now vital tools for exploring the complex biological mechanisms of wound healing, providing insights that are often hard to gain through experiments alone[34;35].

5. Advances in Mathematical Modeling of Wound Healing

5.1. EarlyModels: Initial models relied on basic reaction-diffusion equations to capture cell movement and growth at the wound area, providing a basis for simulating wound healing and fundamental tissue repair kinetics[36].

5.2. Multiscale and Hybrid Models: During the past decades, modeling has expanded to encompass different biological scales, from molecular pathways to tissue-level interactions. Hybrid multiscale models, for example, link discrete cell-based representations with continuum models of tissues and biochemical gradients, allowing researchers to study cellular processes in the context of the overall wound environment[37,38].

5.3. Mechanistic and Predictive Modeling: Modern modeling approaches include complex mechanisms like angiogenesis, extracellular matrix remodeling, and inflammation. For instance, today's mathematical models can simulate oxygen dynamics, growth factors (such as PDGF and VEGF), immune cell migration, and fibroblast functions, enabling predictions of wound closure in normal and diseased states like ischemia[39].

6. Applications and Impact

6.1. Insight into Biological Mechanisms:

The roles of cell migration, proliferation, angiogenesis, and inflammatory responses can be clarified with the help of mathematical models in wound healing. Through simulating these processes, Models can identify critical factors that influence healing outcomes and suggest potential therapeutic targets[40,41].

6.2. Prediction and Optimization:

The predictive capability of computational simulations to estimate wound closure rates and predict healing times helps clinicians to evaluate treatment strategies[42], designing personalized interventions and managing patient expectations.

6.3. Treatment Strategy Design:

Different models are used to test the efficacy of new therapies such as growth factor delivery, engineered scaffolds which further helps in optimizing various treatment parameters before clinical trials. Which can help simulate impaired healing, such as in diabetic or ischemic wounds, and suggest interventions to improve outcomes[43].

6.4.Reduction of Experimental Burden:

Generating theoretical predictions, mathematical models helps reduce the need of time consuming and costly animal or human experiments which also provide a framework for integrating clinical and experimental data[44] which helps in enhancing overall understanding of wound healing dynamics.

Mathematical and computational models are now integral for both basic research as well as development of new clinical strategies, providing predictive power and mechanistic insights[45] which has advanced from simple equations describing cell movement to more sophisticated multiscale framework that simulate the interplay of cellular, molecular, and tissue level processes in wound healing[43] .

7. Simulation of Impaired Healing Processes: Insights from In Silico Studies

Various insilico studies have become an invaluable tool for simulating impaired wound healing process which offers mechanistic insights and guides the development of various targeted therapies[46]. Computational models help in replicating biological complexities of chronic wounds offering researchers to investigate various causes of impaired healing and virtually test potential interventions[40].

7.1. Key Insights from In Silico Studies

7.1.1. Modeling Pathogenic Mechanisms

In silico models have been employed to simulate the molecular and cellular disruptions observed in impaired healing, such as those in diabetic wounds. For example, pathogenic markers (e.g., nuclear localization of β-catenin and upregulation of c-myc) which are related with prolonged wound healing. These models also helps in tracking the dysregulation of various essential pathways, such as Wnt/β-catenin and TGF-β signaling, which are crucial for repair of tissue and regeneration[47,48].

7.1.2. Simulation of Chronic Inflammation

Chronic wounds can be depicted by continuous inflammation, excessive production of pro-inflammatory cytokines like IL-1β, TNF-α and increased protease activity, which leads to extracellular matrix degradation[49]. In silico simulations can model these processes, revealing how prolonged inflammatory responses and ECM destruction disrupt normal healing and contribute to chronic wound pathology[50].

7.1.3. Target Identification and Drug Screening

Computational approaches like molecular docking and dynamics simulations enables the identification of various compounds which might modulate impaired pathways. For example: In silico screening has been used to detect natural compounds that inhibit GSK3-β, thereby restoring the balance in the Wnt/β-catenin pathway and promoting tissue repair[51].

7.1.4. Therapeutic Scenario Testing

Advanced mathematical models helps in predicting impact of growth factor delivery, anti-inflammatory agents or novel biomaterials in impaired healing, which helps in optimizing treatment for chronic wounds[52]. It also allows researchers to represent various therapeutic interventions in silico before shifting to clinical trials.

7.1.5. Patient Specificity and Variability

Nowadays in silico models are capable of incorporating patient-specific data like genetic, metabolic, and physiological differences, to simulate responses of healing[53].Therefore helps to understand why some patients experience impaired healing and also helps in designing personalized therapies.

8. Clinical and Research Applications

8.1. Reduction of Experimental Burden

In silico models helps in simulating impaired healing and testing interventions virtually thereby reducing the ned for broad animal or human experiments which accelerates the discovery of successful treatments[54].

8.2. Mechanistic Understanding

These replication provide a platform for dissecting the interplay between inflammation, cell proliferation, ECM remodeling, and angiogenesis under impaired conditions, which offers a thorough understanding of chronic wound pathophysiology[55].

9. Identification of Therapeutic Targets Using Computational Approaches.

Computational approaches have revolutionized the identification of therapeutic targets, and have accelerated the drug discovery process. These methods make use of high-throughput biological data, molecular modeling, and advanced algorithms and helps in predicting and validating drug-target interactions smoothly and with high precision[56].

9.1. Structure-based computational methods

Molecular docking and virtual screening helps researchers to figure out the protein targets of bioactive compounds by modeling their interactions at the atomic level. For example, the IVS (In silico Validation System) approach can validate observed drug effects as well as side effects, ultimately helps to uncover new therapeutic strategies and repurpose existing drugs[57,58].

9.2. Network-based and omics-driven approaches

It uses data from genomics, proteomics, and transcriptomics to map out molecular interactions within cells. This model can identify potential drug targets and elucidate mechanisms of action for new and existing compounds by assessing protein-protein interaction and integrating pharmacological data[59]. For example, drugs with similar gene expression signatures or side effect profiles may share common targets, which can be predicted using supervised learning and network analysis[60].

9.3. Machine learning and high-performance computing

These technologies are capable to discovery novel targets that may not be apparent through traditional experimental methods, supporting the development of precision medicine and personalized therapies[56].

In summary, computational approaches—ranging from structure-based modeling to network analysis and machine learning have become indispensable for identifying therapeutic targets, offering a fast and cost-effective alternative to traditional laboratory screening[61].

9.4. Integration of Experimental and In Silico Models: Bridging the Gap

Experimental and in silico models is revolutionizing wound healing research by narrowing the gap between laboratory findings and computational predictions. This synergy leverages the strengths of both approaches and provides a more comprehensive understanding of wound healing dynamics as well as accelerates the development of effective therapies[62].

Experimental models like in vitro, ex vivo, and in vivo provides essential biological data and validation for computational models, while in silico models offers the ability of simulating complex scenarios, predict outcomes, and identify mechanisms that may be difficult to test via experiments[62].

Model Development and Validation:

Computational models are often built using data such as cell migration rates, cytokine levels, and tissue responses. These models can then be refined and validated by comparing their predictions with new experimental results, creating a feedback loop which improves both model accuracy and experimental design[63].

Mechanistic Understanding:

Comprehensive approaches allows researchers to dissect the roles of specific cell types, signaling pathways and molecular events in wound healing. For example, agent-based models have been used to simulate immune cell dynamics in burn wounds, incorporating experimental data from animal models to validate the predicted inflammatory response and cell transitions[64].

Therapeutic Strategy Design:

By combining experimental and in silico data, researchers can test the impacts of new drugs, biomaterials, interventions virtually before moving to animal or human trials. This approach enables the simulation of impaired healing scenarios, optimize treatment parameters, and identify potential therapeutic targets[65].

Personalization and Prediction:

Integrated models can incorporate patient-specific experimental data, like genetic or metabolic profiles, to replicate individualized healing responses and forecast clinical outcomes, facilitating personalized wound care[66].

10.Challenges and Future Directions

10.1. Data Availability and Standardization:

The precision of combined models depends on the quality and completeness of experimental data. Limitations in longitudinal and spatial data acquisition may restrict model validation and predictive power.

10.2. Continuous Model Improvement:

As new experimental data emerges, computational models can be updated and refined, creating a dynamic, learning system that evolves with advancements in both experimental as well as computational methods[67].

11.Limitations and Future Directions in In Silico Wound Healing Research

11.1. Limitations

11.1.1. Biological Complexity and Model Simplification: In silico models requires simplifications to make computations manageable. Previously mathematical and computational models of wound healing focused on a limited number of variables which were not fully capable to grasp biological complexity of real wounds like cellular heterogeneity, dynamic tissue remodeling, and multifactorial influences[68].

11.1.2. Data Availability and Calibration: Accurate representation depends on high-quality, quantitative biological data for model calibration and validation. However, many critical parameters—such as concentrations of cytokines, growth factors, or local tissue properties are difficult to measure noninvasively and vary significantly between individuals and wound types. Which might limit predictive accuracy and generalizability of current models[69,70].

11.1.3. Patient-Specific Variability: Agent-based models (ABMs) and combined strategies can be standardized for individual patients, varied wound etiology, patient underlying illness, and healing trajectories causes a challenge for developing universally applicable models. Personalized predictions require widespread patient-specific data, which may not always be present[71].

11.1.4. Computational and Technical Challenges: Computational demands raises as models become more detailed and tissue-realistic. High-resolution agent-based require significant processing power and specialized software, that could constrain accessibility and flexibility for routine clinical use[55].

11.1.5. Integration with Clinical Practice: Connecting the gap between simulated results and clinical decision-making is still emerging. Need for standardized protocols to integrate model predictions with clinical imaging, wound assessment, and treatment planning increases[72].

12. Future Directions

12.1. Increasing Biological Realism: Future models aims to incorporate cellular stress generation, vascular growth, and immune responses, to better mimic the wound healing environment. Advancements of imaging and molecular profiling will support the integration of more comprehensive datasets[54].

12.2. Personalized and Predictive Modeling: Development of models which can be calibrated to individual patients, using clinical imaging, blood flow measurements, and genetic or metabolic data, is a key goal. This enables personalized risk prediction, diagnostics, and therapy optimization[73].

12.3. Integration with Artificial Intelligence (AI): AI as well as machine learning helps in improving wound assessment, systemize image analysis, and improve the predictive power of computational models. However, these approaches require large, diverse datasets for training and validation, and careful management of data bias and quality[74].

12.4. Translational and Clinical Applications: Next parameter is the seamless integration of in silico models with clinical workflows, enabling simulation-guided treatment planning, real-time decision support, and also allowing continuous model refinement based on new experimental data and patient outcomes[72].

12.5. Bridging Experimental and Computational Approaches: Current attempts focus on connecting simulation outputs with clinical images and experimental data, using machine learning and image analysis to extract features that correlate with healing outcomes[75] which helps identify new therapeutic targets and diagnostic indicators.

"We are now embarking on exploring the potential for personalized medicine of mechanistic computational modeling. Specially, the agent-based approach could permit delineation among subjects who have different wound-healing trajectories. Soon we may use the output of mechanistic simulations as a guide to understand a given patient's wound-healing path and, ideally, treat that patient based on model forecast."

In conclusion, challenges are faced during in silico wound healing research related to biological complexity, data availability, and clinical integration, continuous advances in modeling, data acquisition, and AI are prepared to create these tools increasingly valuable for personalized, predictive, and translational wound care[76].

13. Translational Potential: From Computational Models to Clinical Practice

Translational potential of computational models in wound healing lies in their capacity to bring together the gap between research and real-world patient care. These models are able to synthesize complex biological, clinical, and imaging data to generate actionable insights for diagnosis, prognosis, and treatment planning.

13.1.Key Aspects of Translational Potential[77,78]

13.1.Clinical Decision Support: Computational models, like those powered by machine learning and deep learning, are progressively used as clinical-decision support systems which can analyze large, heterogeneous datasets to identify patterns, predict outcomes, and assist clinicians in making more informed choice about diagnosis and therapy. For example, machine learning models have been successfully implemented in radiology, pathology, and intensive care to predict patient risk, automate image analysis, as well as guide treatment adjustments.

13.2. Personalized: Integrating patient-specific data like genomics, metabolomics, and imaging—computational models permits the development of personalized risk scores and tailored treatment plans. For example: Polygenic risk scores derived from genome-wide association studies.

13.3. Simulation of Clinical Scenarios: Computational models are able to reproduce various clinical scenarios, including virtual clinical trials and hypothesis testing before actual implementation in patients. Which reduces the need for extensive animal or human studies and accelerates the translation of new therapies.

13.4. Model Validation and Uncertainty Quantification: Clinical translation to be successful, it is essential that computational models provide transparent predictions, disclose their confidence levels, and openly discuss underlying assumptions and uncertainties that builds trust amongst clinicians and ensures that models are used responsibly, avoiding misapplication[79].

13.5. Challenges and Safeguards: Clinical adoption of computational models faces challenges like data quality, model explainability, and potential biases. Validation against community standards, and continuous monitoring are important to assure models remain accurate and equitable across diverse patient populations.[80]

DISCUSSION

In silico studies have appeared as a revolutionary tool in the field of wound healing, particularly in understanding the complex disruptions which lead to chronic wounds. These models mimic complex biological processes like inflammation, angiogenesis, reepithelialization, and extracellular matrix remodeling, providing insights into how these processes deviate in pathological states. Combining omics data, patient-specific variables, and clinical observations, computational platforms facilitates high-throughput screening of potential therapeutic targets and simulate the effects of various interventions in silico before progressing to costly and time-consuming experimental trials which not only accelerates the drug development process but also enhances the precision of clinical decision-making the symbiotic relationship between integration of experimental data along with computational modelling creates a feedback loop where in vivo and invitro findings inform model refinement and vice versa. This relationship boosts our understanding of wound biology. Furthermore, in silico models support the development of personalized treatment strategies by incorporating individual patient parameters, such as age, comorbidities, and genetic background, thereby advancing the field toward precision medicine. However, despite the vast potential, the clinical adoption of computational models hinges on several critical factors like availability of high-quality, standardized dataset robustness and transparency of the model and their seamless integration into clinical workflows.

CONCLUSION

In conclusion, in silico modeling act as a connecting link between theoretical prediction and clinical practice, offering a ethical, cost effective and scalable approach for improving wound treatment. By integrating data-driven insights with experimental validation, these models can foster innovation in therapeutic strategies, and ultimately reduce time for treatment, and improve patient output in the management of reduced wound healing.

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HOW TO CITE: Prerana Kashyap, Pranabesh Sikdar, Rajsekhar Das, Bipul Nath, Himanta Biswa Saikia, Anju Das, Subhashis Debnath, In Silico and Bioengineered Innovations in Wound Healing: Toward Personalized and Predictive Therapeutic Strategies, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 11, 4459-4473. https://doi.org/10.5281/zenodo.17736051