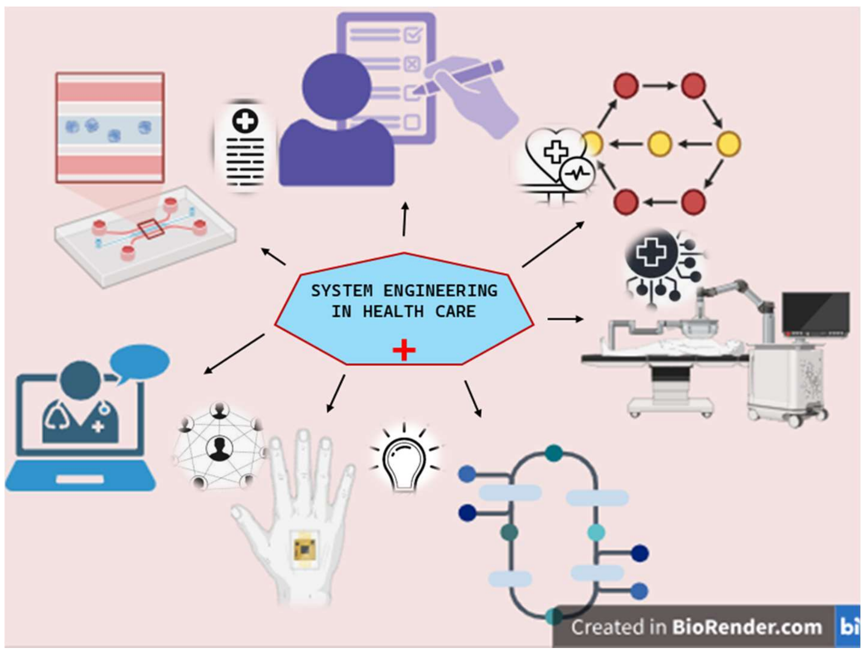
System Engineering in Healthcare: Integrative Strategies for Biofilm Control, Enhanced Wound Healing, and Cancer Management

Pritam Paul, Shivani Pralhad Amingad, Chetana Sanjai, Aakriti Lal, and Sushruta S Hakkimane*

Department of Biotechnology, Manipal Institute of Technology Bengaluru, Manipal academy of Higher education, Manipal India.

Graphical Abstract



Abstract:

The National Academy of Engineering and the Institute of Medicine recently advised using systems engineering methods to reform healthcare delivery. The systems engineering approach enhances healthcare quality by addressing its complexity and involving key stakeholders. It focuses on critical areas such as reducing harm, boosting productivity, improving patient experiences, and optimizing bed management. Additionally, it ensures smooth transitions of care between providers by identifying safety concerns early and engaging patients and stakeholders in the process. Strengthening healthcare systems relies on dedicated research and educational programs in health system engineering. In cancer research, systems engineering plays a vital role in enhancing healthcare by optimizing data to improve diagnostics, treatments, and prevention. Similarly, in bacterial detection, it integrates microbiology, engineering, automation, and computational modeling to enable rapid and accurate identification of bacteria. For wound healing, systems engineering employs advanced methods, such as engineered dressings, to accelerate recovery, reduce infections, and improve overall outcomes. Attracting professionals with expertise in systems engineering is essential to addressing healthcare challenges and driving innovative solution

Keywords: System engineering, Healthcare, Smart dressing, Biosensors, Biomarkers

Introduction

Healthcare, being a complex adaptive system (CAS), encounters many challenging issues that demand careful deliberation[1]. The National Academy of Engineering and the Institute of Medicine emphasized using systems engineering to enhance healthcare, highlighting the need for medical professionals and managers to understand its role in improving healthcare practices and environments[2]. This paper explores the applications of systems engineering in healthcare, including its role in cancer research, bacterial detection technologies, and smart dressing solutions for wound healing. It also examines computational and therapeutic optimization, healthcare delivery, pharmaceutical safety, healthcare system design, operations management, and patient safety through system-based approaches.

Applications of Systems Engineering in Healthcare

Systems engineering involves identifying the system, selecting performance measures, choosing the right modeling tools, analyzing the model's behavior, and making informed decisions for design and implementation. Medical product development teams often face challenges that slow progress, but many are turning to systems engineering to accelerate the process while ensuring products remain safe and effective. As design and process complexities in healthcare continue to rise, systems engineering helps developers manage these challenges, streamline workflows, and stay competitive in a rapidly evolving market. Additionally, models and simulations play a crucial role by predicting system changes, including both desired outcomes and potential issues, enabling better decision-making [3].

The Role of Systems Engineering in Cancer Research

A system engineer in cancer research plays an important role in improving healthcare and data to advance cancer diagnostics, treatment, and prevention. System Engineering is already being used by researchers, professionals, and educators to understand the quality of care delivery, transitions of care and coordination, usability, and implementation of health information technology, as well as managing a variety of healthcare activities, such as infection control, surgical readmissions, primary care workflows, and decision support[4]. A study demonstrated how they utilized the systems engineering approach, specifically the (System engineer for initiative for patient safety) SEIPS framework, to analyze cytology testing processes in cancer clinics, identifying error-prone areas and improving patient safety through visual process mapping and understanding work system components[5]. Systems engineering principles can optimize healthcare decision-making for complex cancers, such as HPV-positive oropharyngeal cancer, by evaluating patient preferences and treatment options[6]. Sanat and Ashish recently reviewed several papers from 2012 to 2022, related to automated approaches to lung cancer diagnosis. The paper survey showed that deep learning and machine learning-based models, which are subdomains of artificial intelligence-based models, provided an effective and efficient performance in diagnosing lung cancer with high accuracy in the minimum time frame[7]. Most malignancies lack approved screening methods, and those that do exist have a number of flaws that result in low patient compliance and unnecessary workups, which raises healthcare systems' expenses. Innovative, precise, and less invasive methods for early cancer detection are therefore desperately needed. Multi-cancer early detection (MCED) tests have become a promising screening tool in recent years. They use artificial intelligence and molecular analysis of tumor-related markers found in bodily fluids to simultaneously detect multiple cancers and further distinguish the underlying cancer type [8]. Another study used AI-intelligence for prostate cancer detection through dual channel tissue feature engineering using various FOS features where they analyzed textural dissimilarities in prostate tissue images[9].

The systems engineering approach to anti-cancer drug development integrates various methodologies to optimize drug delivery and efficacy. This approach encompasses mathematical modeling, computer-aided drug design, and systems pharmacology, which collectively enhance the precision and effectiveness of cancer treatments. Automated control methods manage drug dosages, minimizing side effects and toxicity during chemotherapy[10]. A recent paper discussed smart drug delivery systems (SDDSs) that utilize a systems engineering approach to target tumor cells and immune cells, enhancing therapeutic efficacy by overcoming drug resistance and improving anti-cancer immunotherapy through various innovative strategies[11]. It has also played a crucial role in enhancing cancer detection through the integration of advanced technologies and methodologies. By employing machine learning, imaging techniques, and non-invasive devices, system engineering improves the accuracy and efficiency of cancer diagnosis, ultimately leading to better patient outcomes[12], [13], [14]. The integration of systems engineering principles in cancer treatment development faces several significant barriers that hinder effective implementation. These challenges stem from the complexity of cancer biology, technological limitations, and operational inefficiencies. The key barriers to the effective integration of systems engineering principles in cancer treatment development include financial, technological, operational, regulatory, and workforce challenges, which hinder the implementation of precision oncology at scale and disrupt unified clinical decision pathways essential for evidence-based care[15], [16]. The systems engineering approach in designing drug delivery systems. highlights the integration of the drug (warhead), targeting moiety (guidance system), and delivery vehicle (rocket) as crucial for effective therapy. It will help by ensuring the cohesive integration of various components involved in drug delivery, such as the drug, targeting mechanisms, and delivery vehicles. This holistic perspective allows for the optimization of each element to work synergistically, improving drug accumulation and penetration in tumors. Ultimately, it enhances the overall efficacy of cancer treatments while minimizing side effects[17].

System Engineering Approaches in Bacterial Detection Technologies

There is a need for highly specific, rapid, and sensitive identification and detection of a variety of harmful microorganisms to provide effective therapy for vulnerable populations. Application of Systems Engineering for bacterial detection is an interdisciplinary approach that integrates microbiology, engineering, automation, and computational modelling to detect specific bacteria in a highly rapid and sensitive manner. It involves designing and optimizing different technologies, tools, and workflows to accurately identify and quantify different bacteria in various settings[18].

Biosensors: These are cost-effective, instantaneous means of detecting disease-causing bacteria for quick diagnosis and treatment [18]. Biosensors can be categorized by the type of bioreceptor or the method of signal transduction. Affinity-based sensors are often preferred because they are more selective and specific [19].There are different types of biosensors, for example, Paper-based sensors: A key characteristic of paper-based sensors is their ability to transport liquid automatically through capillary action, eliminating the need for external pumps.[20] This type of sensor involves sampling, treatment, detection, and signal output. The detection can be direct or indirect.

Nanotechnology-based sensors can identify low levels of bacteria and can be made to be highly selective to a specific target. They can also offer real-time monitoring and remote data collection [21]. A branch of nanotechnology-based sensors includes Nanomechanical sensors, which is a subfamily of micro-electromechanical systems (MEMS) that can convert biological processes into measurable mechanical motion. They are fast, highly sensitive, and have a high throughput capability [22].

Smartphone apps: Smartphones, featuring user-friendly operating systems, internal storage, and high-resolution cameras, are becoming globally widespread and serve as ready-to-use platforms for developing instrument-free point-of-care (POC) systems[23]. Bacterial concentration can be detected using this smartphone platform.

Integrated catheter systems: To tackle Urinary tract infection, Integrated catheter system facilitates the reduction of biofilms through a bioelectric effect by applying a low-intensity electric field. This field enhances the vulnerability of biofilm bacteria to antimicrobials, which leads to a decrease in the necessary antibiotic dosage[24].

Digital imaging: A recent study talks about dipstick-format digital biosensor (digital dipstick) which detects bacteria directly from liquid samples using a simple process: dip, culture, and count, minimizing the number of steps required[25].

Laser scattering technology: The Rapid Bacterial Identification System (RBIS) operates on the principle that light scattering changes when a laser beam passes through bacterial cells. By analyzing these variations with a laser and using an algorithm to classify data, the system allows real-time identification of various pathogens, eliminating the need for biochemical processing[26].

Though there have been multiple studies conducted on the topic, some of the challenges of using systems engineering for bacterial detection include ensuring high sensitivity and specificity of pathogenic bacteria in complex sample matrices, minimizing false positives or negatives, and overcoming the limitations of existing detection methods. Additionally, there are difficulties in integrating different detection technologies into seamless, user-friendly platforms, achieving real-time results, and scaling systems for widespread use in diverse environments such as clinical or field settings. Ensuring cost-effectiveness and reducing detection time without compromising accuracy is also a significant challenge.

System Engineering Solutions for Smart Dressing in Wound Healing

Conventional or early wound care techniques include gauze and cotton, in this technique, we cannot see real-time monitoring, such as maintaining a moist environment, gas/vapour exchange, pH sensing, etc., influencing therapeutic outcomes towards excessive or overly cautious strategies [27], [28]. To overcome this problem, research has been done to develop smart dressing[29]. Smart dresses are designed not simply to promote wound healing but also to monitor the wound condition and to take preventive measures for the proper treatment of the wound, which will promote the wound healing process. Smart sensors like temperature sensing, moisture sensing and different biochemical markers sensing within the wound dressing will give healthcare professionals a deep insight and gather valuable information about the progression of the wound[30], [31]. In recent times, AI-integrated health wearables have been introduced to monitor real-time health conditions and suggest reasonable suggestions for patients[32]. AI can assist health professionals in predicting outcomes and managing wounds more effectively [33]. This type of technology can also used for novel domains like testing a novel medicine. By using this smart dressing, we can see in real-time all the biochemical activities and other factors that take place within the wound site or if the novel medicine is doing any unwanted activities in the wound site.

Potential Biomarkers for Monitoring Wound States:

Customarily, wounds are managed by applying bandages, which will minimise the risk of any pathogen or any microorganisms that lead to any kind of inflammation. The bandages are to be removed from time to time, which can interrupt the healing process. That’s why we need a dressing equipped with sensors that will monitor the real-time conditions of the wound. This will reduce the intensity of changing the dressing and also will reduce the risk of disrupting the newly formed tissues or the wound bed, which will overall reduce the time taken for the wound to heal, improve the patient’s comfort and also reduce the overall healthcare cost[34],[35].

Factors which are associated with the wound status pH, Temperature and Oxygen:

Monitoring pH is important for assessing wound condition, as it helps determine the wound's stage—whether it's in hemostasis, inflammation, proliferation, or maturation. Acute wounds typically have a pH of 4.0 to 6.0, while chronic wounds are more alkaline, with a pH around 10.0, which can encourage pathogen growth. Therefore, tracking pH is essential for evaluating the wound's healing stage and detecting potential infections [36] ,[37].

Temperature is a key biological indicator that affects enzymatic reactions in the body and helps detect wound infections. Normally, a wound's temperature matches the body temperature (31.1°C–36.5°C), but a rise of more than 2.2°C suggests an infection, often accompanied by swelling and redness. After treatment with antibiotics, the temperature typically decreases by 0.8–1.1°C. Thus, monitoring the wound's temperature is crucial for identifying infections and evaluating the effectiveness of treatment[38],[39],[40].

Oxygen is essential for wound healing, supporting collagen synthesis, bacterial defense, and cell growth. Inadequate oxygen can create a hypoxic environment at the wound site, hindering healing. Oxygen levels also influence the production of reactive oxygen species (ROS), which are important for tissue remodeling, immune defense, and cell signaling. However, excessive ROS can cause oxidative stress, damaging cells and delaying healing. Therefore, monitoring oxygen levels during the healing process is critical to ensure proper recovery[41],[42]. Temperature, pH and oxygen levels can be monitored through a microchip, which detects real-time changes and helps doctors provide appropriate care. AI can also offer patients a simple summary of the wound's condition and early signs of infection via wireless connection, advising them to visit a doctor if needed. This approach reduces doctor visits and healthcare costs[43].

Materials for smart wound healing dressing:

The use of smart wound healing dressing, including shape memory and reactive oxygen species responsive materials. Self-adjusting treatments have been included in the intricate wound-healing process using smart materials[44], [45]. A type of smart material known as shape memory polymers (SMPs) has the ability to retain its momentarily programmed shape and revert to its initial configuration in response to particular environmental inputs. Versatile SMP kinds that react to light, heat, pH, or moisture have been used to create wound monitoring dressings and intelligent controlled medication delivery. The most widely used SMPs for creating these intelligent wound dressings are polyurethane, polyester, poly-hydroxyproline, polysilamine, poly(N-isopropyl acrylamide) (PNIPAAm), and polythiophene hydrogels[46].

For wound healing applications, a copolymerised new zwitterionic shape memory polymer made of diol acrylate monomer (dihydroxypropyl methacrylate, or DHMA) and sulfobetaine methacrylate (SBMA)[47]. Boric acid was added to the polymeric complex in this research as a crosslinker. This hydrogel dressing's shape memory behaviour was produced via the electrostatic interactions of PSBMA chains with dynamically bound boron esters, which are activated by either absorbing moisture or temperature. The anti-electrolyte effect of salt content on the mechanical, shape memory, and self-healing capabilities of this hydrogel dressing was next investigated by incorporating sodium chloride into the produced zwitterionic polymer to investigate its shape memory properties. When salt was added to the hydrogel, the glass transition temperature dropped from 70 °C to room temperature[48]. As, PSBMA is hydrophobic, it can recover its shape by absorbing moisture from the wound. Thus, we can use SMP for a potential wound dressing[47], [48], [49].

Smart dressing for monitoring the skin wound status:

Chronic wounds which is hard to heal and very much susceptible to infections the current wound management of chronic wounds mostly acts as a coverage around the wound and poorly delivers the therapeutic agents to the wound, which makes it way longer to heal, and there is also a risk of infection[50]. We need a smart wound dressing that will monitor essential data of the wound's condition by sensing the stimulus around the wound environment[51]. Many types of wound dressing which is sensitive to the common bacterial illness indicators that are expressed, including pH, temperature, secreted enzymes and toxins, which will fit into hydrogel or electrospun nanofiber meshes. We can also incorporate these stimuli-responsive dressings with drug-delivery devices for efficient wound care and regulated drug release[52]. New methods for real-time wound condition monitoring without dressing replacement are made possible by the dressing's integration of sensors and actuator technology. Numerous wound parameters, including pH, temperature, moisture content, and oxygen concentration that were previously impossible to monitor with the previous dressing are now measurable because of the flexible microsensors integrated into the dressing[53], [54]. The smart bandages can be analysed both automatically or in a semi-automated style, which will affect the wound healing process[54].

Computational

Model transformations are an important process for system design, facilitating the refinement and evolution of behavior throughout its lifecycle[55]. The method is not particularly complex, as it begins with refinement in terms of modeling and design, followed by transforming the design tasks into computational tasks. The transformation process also involves generating a mathematical model that captures the underlying properties and relationships within the system, which can be analyzed and simulated[56]. Finally, the results of these transformations are fed back into the system model, providing continuous refinement and ensuring that the design remains aligned with the intended functionality and performance [57].Through this iterative process, model transformations help bridge the gap between abstract design concepts and practical implementation [58]. Few Free and Open Source Software (FOSS) are available which includes –OpenSCAD: Allows the scripted generation of CAD models. cadQuery: Uses Python to generate CAD models. PicoGK: An open-source framework for Computational Engineering.

Building on the foundational process of model transformations, it is important to recognize how they also support the integration of various design perspectives and technologies throughout the development lifecycle. As systems grow in complexity, they often involve multiple stakeholders with different goals, such as software engineers, system architects, and domain experts [59]. Model transformations facilitate communication across these disciplines by providing a common framework for translating between high-level specifications and low-level implementation details. This not only enhances collaboration but also reduces the potential for errors that can arise when translating between disparate models or systems[60].

Nowadays, The Cancer Genome Atlas (TCGA), TARGET, the cancer Cell Line Encyclopedia as well as experimental data resulting from methods such as mass spectroscopy and genomics provide detailed information on patients' genotypes and phenotypes[61].The comprehension of biological information flow, including how genotypes translate into functional phenotypes, is one of the primary problems in biology. Although conducting biological experiments has been challenging, resulting in a lack of data, advances in experimental high-throughput measurements have made biology a data-rich field, necessitating the use of analytical tools to make biological data easier to analyze and interpret[62].

Therapeutic Optimization, Health care delivery and pharmaceutical safety

Therapeutic optimization in radiation therapy helps target cancerous regions with precise doses while minimizing damage to surrounding healthy tissue using advanced computerized beam modulation. Systems engineering has great potential to improve healthcare delivery, but its acceptance faces significant challenges. We are optimistic about healthcare engineering's future, but its success depends on more organizations recognizing its value and driving necessary changes[63],[64],[65],[66]. Address practical issues in applying a systems engineering approach and identify tools to implement its key elements[67].

Engineering techniques are used in developing medical devices and healthcare processes, while system safety focuses on identifying and controlling hazards through modeling and analysis. This approach demonstrates how to apply new safety engineering modeling and analysis to healthcare systems, using pharmaceutical safety as an example, with potential for other complex healthcare systems[68]. The goal is to apply methods and tools from fields outside traditional medical and biological disciplines to improve healthcare delivery processes. Key fields in health systems engineering include industrial engineering, systems engineering, human factors, operations research, biostatistics, informatics, social sciences, organizational psychology, health services research, and epidemiology. Healthcare informatics focuses on providing software tools and an information system to enhance healthcare delivery[69].

System approaches in Healthcare, System healthcare design, healthcare operations management and Patient safety

Use of system approach in healthcare will likely grow, but more work is needed to show its effectiveness, particularly in measuring its impact on patient and service outcomes. It offers capabilities like automation, security, transparency, and fault tolerance, improving applications such as healthcare by replacing traditional systems with a more advanced, distributed approach[70], [71].

Systems engineering plays a vital role in improving healthcare by making it more efficient, adaptable, and patient-focused through structured development. It focuses on coordinating departments, staff, and technology to streamline processes like patient admissions, diagnostics, and treatment planning, while integrating diagnostic tools and monitoring systems to drive medical innovations. Technologies such as digital health tools, virtual reality, and mobile apps can enhance coordination, but further research is needed to advance patient care and communication. Accurate data management systems ensure the safe and efficient transfer of confidential healthcare data, while user-friendly technologies enable quick data transfer, ensuring high-quality patient care that meets the needs of both patients and organizations[72], [73].

Healthcare operations management focuses on coordinating processes to deliver services efficiently, such as managing costs while ensuring quality care. Recent research highlights six key areas: service quality, operations strategy, information technology, service scheduling, service performance, and other factors. Future research should explore these themes further to improve healthcare operations[74].

Healthcare quality and safety are essential for delivering effective and safe care to patients, with patient safety being the foundation of high-quality healthcare. The main approach to improving healthcare quality and safety has significantly influenced how policy, research, and practice aim to enhance the organization and delivery of patient care[75].

Conclusion:

By offering an organized, multidisciplinary method of resolving difficult problems, systems engineering is transforming healthcare and medicine. It makes it possible to optimize procedures, manage resources, and make decisions in therapeutic settings by combining cutting-edge technologies, data analytics, and human-centered design. Through computer modeling and precise delivery systems, it speeds up innovation in medication research while improving accuracy and efficiency in diagnostics. Though there has been a lot done, more focus should be given to misguided diagnoses or patient-specific diagnoses and make a better model to compare reports. As the discipline develops, its all-encompassing approaches will keep pushing for breakthroughs in early disease detection, personalized medicine, and creative treatments, ultimately influencing the direction of healthcare. Improving healthcare systems requires focused research, education in health systems engineering, and attracting experts to tackle challenges. Collaboration and technology are key to improving healthcare efficiency and access

Acknowledgement: The image was partly created using free images from Biorender.com

References:

[1] R. Kopach-Konrad *et al.*, "Applying Systems Engineering Principles in Improving Health Care Delivery," *J Gen Intern Med*, vol. 22, no. S3, pp. 431–437, Dec. 2007, doi: 10.1007/s11606-007-0292-3.

[2] *Building a Better Delivery System*. Washington, D.C.: National Academies Press, 2005. doi: 10.17226/11378.

[3] R. Kopach-Konrad *et al.*, "Applying systems engineering principles in improving health care delivery," *J Gen Intern Med*, vol. 22, no. SUPPL. 3, pp. 431–437, Dec. 2007, doi: 10.1007/S11606-007-0292-3/FIGURES/3.

[4] A. J. Tevaarwerk, J. R. Klemp, G. J. van Londen, B. W. Hesse, and M. E. Sesto, "Moving beyond static survivorship care plans: A systems engineering approach to population health management for cancer survivors," *Cancer*, vol. 124, no. 22, pp. 4292–4300, Nov. 2018, doi: 10.1002/cncr.31546.

[5] K. Dowers and K. A. Jurewicz, "Using a Systems Engineering Approach to Study Processing Errors in Cytology Testing at a Cancer Clinic," *Proceedings of the Human Factors and Ergonomics Society Annual Meeting*, vol. 67, no. 1, pp. 2501–2507, Sep. 2023, doi: 10.1177/21695067231192194.

[6] R. T. Aarhus and E. Huang, "A Proposed Application of Systems Engineering Principles to Healthcare Decision-Making: Evaluating Patient Decision Regret in the Treatment of Oropharyngeal Cancer," in *Systems Engineering in Context*, Cham: Springer International Publishing, 2019, pp. 205–215. doi: 10.1007/978-3-030-00114-8_17.

[7] S. K. Pandey and A. K. Bhandari, "A Systematic Review of Modern Approaches in Healthcare Systems for Lung Cancer Detection and Classification," *Archives of Computational Methods in Engineering*, vol. 30, no. 7, pp. 4359–4378, Sep. 2023, doi: 10.1007/s11831-023-09940-x.

[8] T. Brito-Rocha, V. Constâncio, R. Henrique, and C. Jerónimo, "Shifting the Cancer Screening Paradigm: The Rising Potential of Blood-Based Multi-Cancer Early Detection Tests," *Cells*, vol. 12, no. 6, p. 935, Mar. 2023, doi: 10.3390/cells12060935.

[9] C.-H. Kim *et al.*, "Artificial Intelligence Techniques for Prostate Cancer Detection through Dual-Channel Tissue Feature Engineering," *Cancers (Basel)*, vol. 13, no. 7, p. 1524, Mar. 2021, doi: 10.3390/cancers13071524.

[10] S. Mohan and T. Jarin, "State-of-the-Art Techniques For Design Of Anti-Cancer Drug Delivery System Based On Optimal Control Methods: A Review," in *2023 International Conference on Control, Communication and Computing (ICCC)*, IEEE, May 2023, pp. 1–6. doi: 10.1109/ICCC57789.2023.10164826.

[11] W. Yi, D. Yan, D. Wang, and Y. Li, "Smart drug delivery systems to overcome drug resistance in cancer immunotherapy," *Cancer Biol Med*, vol. 20, no. 4, pp. 248–267, May 2023, doi: 10.20892/j.issn.2095-3941.2023.0009.

[12] Prof. R. Waghmare, Ronak Jagade, Swayam Chopda, and Varad Salgar, "Breast Cancer Detection System," *International Journal of Advanced Research in Science, Communication and Technology*, pp. 376–378, Mar. 2024, doi: 10.48175/IJARSCT-15964.

[13] U. K. Das, J. Sikder, U. Salma, and A. M. S. Anwar, "Intelligent Cancer Detection System," in *2021 International Conference on Intelligent Technologies (CONIT)*, IEEE, Jun. 2021, pp. 1–6. doi: 10.1109/CONIT51480.2021.9498410.

[14] A. Sunder, N. Kumar, S. B Rao, S. P, and M. V. John, "BREAST CANCER DETECTION SYSTEM," *International Journal of Innovative Research in Advanced Engineering*, vol. 9, no. 8, pp. 233–235, Aug. 2022, doi: 10.26562/ijirae.2022.v0908.16.

[15] S. R. MacEwan and A. Chilkoti, "From Composition to Cure: A Systems Engineering Approach to Anticancer Drug Carriers," *Angewandte Chemie International Edition*, vol. 56, no. 24, pp. 6712–6733, Jun. 2017, doi: 10.1002/anie.201610819.

[16] N. Lajmi *et al.*, "Challenges and solutions to system-wide use of precision oncology as the standard of care paradigm," *Cambridge Prisms: Precision Medicine*, vol. 2, p. e4, Mar. 2024, doi: 10.1017/pcm.2024.1.

[17] M. R. Dreher and A. Chilkoti, "Toward a Systems Engineering Approach to Cancer Drug Delivery," *JNCI Journal of the National Cancer Institute*, vol. 99, no. 13, pp. 983–985, Jul. 2007, doi: 10.1093/jnci/djm042.

[18] S. E. A. P. F. T. Mohammed Zourob, "Principles of Bacterial Detection: Biosensors, Recognition Receptors and ... - Google Books." Accessed: Nov. 18, 2024. [Online]. Available: https://books.google.co.in/books?hl=en&lr=&id=b3vgZkxROWYC&oi=fnd&pg=PA3&dq=system+engineering+for+bacterial+detection&ots=6y8Y8RFhok&sig=C4AQWLG9CyDgkKlTEbnMuPEwmsE#v=onepage&q=system%20engineering%20for%20bacterial%20detection&f=false

[19] M. A. Arugula and A. Simonian, "Novel trends in affinity biosensors: current challenges and perspectives," *Meas Sci Technol*, vol. 25, no. 3, p. 032001, Feb. 2014, doi: 10.1088/0957-0233/25/3/032001.

[20] F. Mazur, A. D. Tjandra, Y. Zhou, Y. Gao, and R. Chandrawati, "Paper-based sensors for bacteria detection," *Nature Reviews Bioengineering 2023 1:3*, vol. 1, no. 3, pp. 180–192, Feb. 2023, doi: 10.1038/s44222-023-00024-w.

[21] S. Prajapati, B. Padhan, B. Amulyasai, and A. Sarkar, "Nanotechnology-based sensors," *Biopolymer-Based Formulations: Biomedical and Food Applications*, pp. 237–262, Jan. 2020, doi: 10.1016/B978-0-12-816897-4.00011-4.

[22] F. Pujol-Vila, R. Villa, and M. Alvarez, "Nanomechanical sensors as a tool for bacteria detection and antibiotic susceptibility testing," *Front Mech Eng*, vol. 6, p. 544080, Jul. 2020, doi: 10.3389/FMECH.2020.00044/BIBTEX.

[23] J. Wen, Y. Zhu, J. Liu, and D. He, "Smartphone-based surface plasmon resonance sensing platform for rapid detection of bacteria," *RSC Adv*, vol. 12, no. 21, pp. 13045–13051, Apr. 2022, doi: 10.1039/D2RA01788A.

[24] R. C. Huiszoon, J. Han, S. Chu, J. M. Stine, L. A. Beardslee, and R. Ghodssi, "Integrated System for Bacterial Detection and Biofilm Treatment on Indwelling Urinary Catheters," *IEEE Trans Biomed Eng*, vol. 68, no. 11, pp. 3241–3249, Nov. 2021, doi: 10.1109/TBME.2021.3066995.

[25] E. Iseri, M. Biggel, H. Goossens, P. Moons, and W. Van Der Wijngaart, "Digital dipstick: miniaturized bacteria detection and digital quantification for the point-of-care," *Lab Chip*, vol. 20, no. 23, pp. 4349–4356, Nov. 2020, doi: 10.1039/D0LC00793E.

[26] M. Hussain *et al.*, "Design of Rapid Bacterial Identification System Based on Scattering of Laser Light and Classification of Binned Plots," *J Nanosci Nanotechnol*, vol. 20, no. 7, pp. 4047–4056, Jan. 2020, doi: 10.1166/JNN.2020.17491.

[27] N. Bhardwaj, D. Chouhan, and B. B. Mandal, "Tissue Engineered Skin and Wound Healing: Current Strategies and Future Directions," *Curr Pharm Des*, vol. 23, no. 24, pp. 3455–3482, May 2017, doi: 10.2174/1381612823666170526094606.

[28] D. Prakashan, P. R. Ramya, and S. Gandhi, "A Systematic Review on the Advanced Techniques of Wearable Point-of-Care Devices and Their Futuristic Applications," *Diagnostics 2023, Vol. 13, Page 916*, vol. 13, no. 5, p. 916, Feb. 2023, doi: 10.3390/DIAGNOSTICS13050916.

[29] D. Chouhan, N. Dey, N. Bhardwaj, and B. B. Mandal, "Emerging and innovative approaches for wound healing and skin regeneration: Current status and advances," *Biomaterials*, vol. 216, p. 119267, Sep. 2019, doi: 10.1016/J.BIOMATERIALS.2019.119267.

[30] M. Falcone *et al.*, "Challenges in the management of chronic wound infections," *J Glob Antimicrob Resist*, vol. 26, pp. 140–147, Sep. 2021, doi: 10.1016/J.JGAR.2021.05.010.

[31] R. Dong and B. Guo, "Smart wound dressings for wound healing," *Nano Today*, vol. 41, p. 101290, Dec. 2021, doi: 10.1016/J.NANTOD.2021.101290.

[32] P. Manickam *et al.*, "Artificial Intelligence (AI) and Internet of Medical Things (IoMT) Assisted Biomedical Systems for Intelligent Healthcare," *Biosensors 2022, Vol. 12, Page 562*, vol. 12, no. 8, p. 562, Jul. 2022, doi: 10.3390/BIOS12080562.

[33] M. Dabas, D. Schwartz, D. Beeckman, and A. Gefen, "Application of Artificial Intelligence Methodologies to Chronic Wound Care and Management: A Scoping Review," *https://home.liebertpub.com/wound*, vol. 12, no. 4, pp. 205–240, Jan. 2023, doi: 10.1089/WOUND.2021.0144.

[34] F. A. R. Mota, S. A. P. Pereira, A. R. T. S. Araújo, M. L. C. Passos, and M. L. M. F. S. Saraiva, "Biomarkers in the diagnosis of wounds infection: An analytical perspective," *TrAC Trends in Analytical Chemistry*, vol. 143, p. 116405, Oct. 2021, doi: 10.1016/J.TRAC.2021.116405.

[35] M. S. Brown, B. Ashley, and A. Koh, "Wearable technology for chronic wound monitoring: Current dressings, advancements, and future prospects," *Front Bioeng Biotechnol*, vol. 6, no. APR, p. 350710, Apr. 2018, doi: 10.3389/FBIOE.2018.00047/BIBTEX.

[36] E. M. Jones, C. A. Cochrane, and S. L. Percival, "The Effect of pH on the Extracellular Matrix and Biofilms," *https://home.liebertpub.com/wound*, vol. 4, no. 7, pp. 431–439, Jun. 2015, doi: 10.1089/WOUND.2014.0538.

[37] L. A. Schneider, A. Korber, S. Grabbe, and J. Dissemond, "Influence of pH on wound-healing: A new perspective for wound-therapy?," *Arch Dermatol Res*, vol. 298, no. 9, pp. 413–420, Feb. 2007, doi: 10.1007/S00403-006-0713-X/FIGURES/2.

[38] V. Dini, P. Salvo, A. Janowska, F. Di Francesco, A. Barbini, and M. Romanelli, "Correlation Between Wound Temperature Obtained With an Infrared Camera and Clinical Wound Bed Score in Venous Leg Ulcers.," *Wounds*, vol. 27, no. 10, pp. 274–278, Oct. 2015, Accessed: Nov. 17, 2024. [Online]. Available: https://europepmc.org/article/med/26479211

[39] A. M. Wijlens, S. Holloway, S. A. Bus, and J. J. van Netten, "An explorative study on the validity of various definitions of a 2·2°C temperature threshold as warning signal for impending diabetic foot ulceration," *Int Wound J*, vol. 14, no. 6, pp. 1346–1351, Dec. 2017, doi: 10.1111/IWJ.12811.

[40] A. Chanmugam *et al.*, "Relative Temperature Maximum in Wound Infection and Inflammation as Compared with a Control Subject Using Long-Wave Infrared Thermography," *Adv Skin*

Wound Care, vol. 30, no. 9, pp. 406–414, Sep. 2017, doi: 10.1097/01.ASW.0000522161.13573.62.

[41] D. M. Castilla, Z.-J. Liu, and O. C. Velazquez, "Oxygen: Implications for Wound Healing," *Adv Wound Care (New Rochelle)*, vol. 1, no. 6, pp. 225–230, Dec. 2012, doi: 10.1089/WOUND.2011.0319/ASSET/IMAGES/LARGE/FIGURE2.JPEG.

[42] C. Dunnill *et al.*, "Reactive oxygen species (ROS) and wound healing: the functional role of ROS and emerging ROS-modulating technologies for augmentation of the healing process," *Int Wound J*, vol. 14, no. 1, pp. 89–96, Feb. 2017, doi: 10.1111/IWJ.12557.

[43] G. Xu *et al.*, "Battery-Free and Wireless Smart Wound Dressing for Wound Infection Monitoring and Electrically Controlled On-Demand Drug Delivery," *Adv Funct Mater*, vol. 31, no. 26, p. 2100852, Jun. 2021, doi: 10.1002/ADFM.202100852.

[44] F. Piraino and Š. Selimović, "A Current View of Functional Biomaterials for Wound Care, Molecular and Cellular Therapies," *Biomed Res Int*, vol. 2015, no. 1, p. 403801, Jan. 2015, doi: 10.1155/2015/403801.

[45] B. A. Badeau and C. A. Deforest, "Programming Stimuli-Responsive Behavior into Biomaterials," *Annu Rev Biomed Eng*, vol. 21, no. Volume 21, 2019, pp. 241–265, Jun. 2019, doi: 10.1146/ANNUREV-BIOENG-060418-052324/CITE/REFWORKS.

[46] A. Lendlein, M. Behl, B. Hiebl, and C. Wischke, "Shape-memory polymers as a technology platform for biomedical applications," *Expert Rev Med Devices*, vol. 7, no. 3, pp. 357–379, May 2010, doi: 10.1586/ERD.10.8.

[47] G. Li, Y. Wang, S. Wang, Z. Liu, Z. Liu, and J. Jiang, "A Thermo- and Moisture-Responsive Zwitterionic Shape Memory Polymer for Novel Self-Healable Wound Dressing Applications," *Macromol Mater Eng*, vol. 304, no. 3, p. 1800603, Mar. 2019, doi: 10.1002/MAME.201800603.

[48] L. K. Jang, G. K. Fletcher, M. B. B. Monroe, and D. J. Maitland, "Biodegradable shape memory polymer foams with appropriate thermal properties for hemostatic applications," *J Biomed Mater Res A*, vol. 108, no. 6, pp. 1281–1294, Jun. 2020, doi: 10.1002/JBM.A.36901.

[49] T. L. Landsman *et al.*, "A shape memory foam composite with enhanced fluid uptake and bactericidal properties as a hemostatic agent," *Acta Biomater*, vol. 47, pp. 91–99, Jan. 2017, doi: 10.1016/J.ACTBIO.2016.10.008.

[50] R. G. Frykberg and J. Banks, "Challenges in the Treatment of Chronic Wounds," *Adv Wound Care (New Rochelle)*, vol. 4, no. 9, pp. 560–582, Sep. 2015, doi: 10.1089/WOUND.2015.0635/ASSET/IMAGES/LARGE/FIGURE4.JPEG.

[51] M. Bates, "The Future of Wound Care," *IEEE Pulse*, vol. 11, no. 4, pp. 22–25, Jul. 2020, doi: 10.1109/MPULS.2020.3008460.

[52] H. B. Schultz, R. B. Vasani, A. M. Holmes, M. S. Roberts, and N. H. Voelcker, "Stimulus-Responsive Antibiotic Releasing Systems for the Treatment of Wound Infections," *ACS Appl Bio Mater*, vol. 2, no. 2, pp. 704–716, Feb. 2019, doi: 10.1021/ACSABM.8B00577/ASSET/IMAGES/LARGE/MT-2018-00577V_0007.JPEG.

[53] S. O'Callaghan, P. Galvin, C. O'Mahony, Z. Moore, and R. Derwin, "'Smart' wound dressings for advanced wound care: a review," *J Wound Care*, vol. 29, no. 7, pp. 394–406, Jul. 2020, doi: 10.12968/jowc.2020.29.7.394.

[54] A. M. Ribeiro and T. H. S. Flores-Sahagun, "Application of stimulus-sensitive polymers in wound healing formulation," *International Journal of Polymeric Materials and Polymeric Biomaterials*, vol. 69, no. 15, pp. 979–989, Oct. 2020, doi: 10.1080/00914037.2019.1655744.

[55] "Modeling Reactive Systems with Statecharts | Guide books." Accessed: Nov. 18, 2024. [Online]. Available: https://dl.acm.org/doi/10.5555/552084

[56] J. Bézivin, "Model driven engineerings: An emerging technical space," *Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics)*, vol. 4143 LNCS, pp. 36–64, 2006, doi: 10.1007/11877028_2.

[57] K. Czarnecki and S. Helsen, "Feature-based survey of model transformation approaches," *IBM Systems Journal*, vol. 45, no. 3, pp. 621–645, 2006, doi: 10.1147/SJ.453.0621.

[58] S. Kent, "Model Driven Engineering," *Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics)*, vol. 2335, pp. 286–298, 2002, doi: 10.1007/3-540-47884-1_16.

[59] B. Das, R. Patgiri, S. Bandyopadhyay, V. E. Balas, and S. Roy, Eds., "Modeling, Simulation and Optimization," vol. 373, 2024, doi: 10.1007/978-981-99-6866-4.

[60] A. Rodrigues Da Silva, "Model-driven engineering: A survey supported by the unified conceptual model," *Comput Lang Syst Struct*, vol. 43, pp. 139–155, Oct. 2015, doi: 10.1016/J.CL.2015.06.001.

[61] M. M. Papathanasiou, M. Onel, I. Nascu, and E. N. Pistikopoulos, "Computational tools in the assistance of personalized healthcare," *Computer Aided Chemical Engineering*, vol. 42, pp. 139–206, Jan. 2018, doi: 10.1016/B978-0-444-63964-6.00006-4.

[62] S. S. Fong, "Computational approaches to metabolic engineering utilizing systems biology and synthetic biology," *Comput Struct Biotechnol J*, vol. 11, no. 18, pp. 28–34, Aug. 2014, doi: 10.1016/j.csbj.2014.08.005.

[63] F. Preciado-Walters, M. P. Langer, R. L. Rardin, and V. Thai, "Column generation for IMRT cancer therapy optimization with implementable segments," *Ann Oper Res*, vol. 148, no. 1, pp. 65–79, Nov. 2006, doi: 10.1007/s10479-006-0080-1.

[64] F. Preciado-Walters, R. Rardin, M. Langer, and V. Thai, "A coupled column generation, mixed integer approach to optimal planning of intensity modulated radiation therapy for cancer," *Math Program*, vol. 101, no. 2, Nov. 2004, doi: 10.1007/s10107-004-0527-6.

[65] D. M. Shepard, M. C. Ferris, G. H. Olivera, and T. R. Mackie, "Optimizing the Delivery of Radiation Therapy to Cancer Patients," *SIAM Review*, vol. 41, no. 4, pp. 721–744, Jan. 1999, doi: 10.1137/S0036144598342032.

[66] R. Kopach-Konrad *et al.*, "Applying Systems Engineering Principles in Improving Health Care Delivery," *J Gen Intern Med*, vol. 22, no. S3, pp. 431–437, Dec. 2007, doi: 10.1007/s11606-007-0292-3.

[67] G. M. Samaras and R. L. Horst, "A systems engineering perspective on the human-centered design of health information systems," *J Biomed Inform*, vol. 38, no. 1, pp. 61–74, Feb. 2005, doi: 10.1016/j.jbi.2004.11.013.

[68] N. Leveson *et al.*, "Applying System Engineering to Pharmaceutical Safety," *J Healthc Eng*, vol. 3, no. 3, pp. 391–414, Jan. 2012, doi: 10.1260/2040-2295.3.3.391.

[69] J. W. Fowler, J. C. Benneyan, P. Carayon, B. T. Denton, P. Keskinocak, and G. C. Runger, "An introduction to a new journal for Healthcare Systems Engineering," *IIE Trans Healthc Syst Eng*, vol. 1, no. 1, pp. 1–5, Mar. 2011, doi: 10.1080/19488301003645051.

[70] A. Komashie, S. Hinrichs-Krapels, and P. J. Clarkson, "SYSTEMS APPROACHES TO HEALTHCARE SYSTEMS DESIGN AND CARE DELIVERY: AN OVERVIEW OF THE LITERATURE," *Proceedings of the Design Society*, vol. 1, pp. 2941–2950, Aug. 2021, doi: 10.1017/pds.2021.555.

[71] A. Kumar, R. Krishnamurthi, A. Nayyar, K. Sharma, V. Grover, and E. Hossain, "A Novel Smart Healthcare Design, Simulation, and Implementation Using Healthcare 4.0 Processes," *IEEE Access*, vol. 8, pp. 118433–118471, 2020, doi: 10.1109/ACCESS.2020.3004790.

[72] E. Falconer, D. Kho, and J. P. Docherty, "Use of technology for care coordination initiatives for patients with mental health issues: a systematic literature review," *Neuropsychiatr Dis Treat*, vol. Volume 14, pp. 2337–2349, Sep. 2018, doi: 10.2147/NDT.S172810.

[73] K. Adane, M. Gizachew, and S. Kendie, "<p>The role of medical data in efficient patient care delivery: a review</p>," *Risk Manag Healthc Policy*, vol. Volume 12, pp. 67–73, Apr. 2019, doi: 10.2147/RMHP.S179259.

[74] R. K. Jha, B. S. Sahay, and P. Charan, "Healthcare operations management: a structured literature review," *DECISION*, vol. 43, no. 3, pp. 259–279, Sep. 2016, doi: 10.1007/s40622-016-0132-6.

[75] J. Waring, D. Allen, J. Braithwaite, and J. Sandall, "Healthcare quality and safety: a review of policy, practice and research," *Sociol Health Illn*, vol. 38, no. 2, pp. 198–215, Feb. 2016, doi: 10.1111/1467-9566.12391.