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Engineering Longevity: A Multi-Scale Systems Framework Using Digital Twins and AI to Achieve Sustainable Public Health

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Abstract

(Background) The 20th-century reductionist medical paradigm is reaching its limits, facing unsustainable costs from aging populations and chronic multi-morbidity. This context necessitates a paradigm shift from reactively treating disease to proactively engineering healthspan, highlighting the purpose of this study: to establish the comprehensive rationale for adopting a systems engineering perspective to guide this transformation. (Methods) Through a structured literature review, this study synthesizes the theoretical foundations of Complex Adaptive Systems (CAS) and Systems Engineering as applied to healthcare. It surveys the emerging technological architecture, including high-level simulation toolkits like Digital Twins and AI, and the pervasive layer of personal health devices. The review further analyzes the practical implications of this shift across education, clinical practice, and policy. (Results) The synthesis reveals that Systems Engineering offers a robust methodology to manage the inherent complexity of health systems. This review identifies the possible technological architecture and confirms that a paradigm shift requires reforms across multiple areas of the healthcare ecosystem. (Conclusions) A systems engineering approach is a step forward, presenting a sustainable approach for the future of health systems: mandating the integration of new theoretical, technological, practical, and ethical frameworks to move beyond extending lifespan to truly engineering longevity

Keywords

Healthcare Sustainability; Systems Engineering; Complex Adaptive Systems; Digital Twin; Agent-Based Modeling; Artificial Intelligence; mHealth; Healthspan; Public Health Policy; Ethical AI; Medical Education; Sustainable Development Goals.

1. A New paradigm for 21st century healthcare

1.1.A Critique of the reductionist medical approach

In the evolution of medical care, the 20th century stands out as one of humanity's greatest achievements through incredible advancements. The historical success has been built on a reductionist approach that excelled at deconstructing complex health problems into manageable, linear components that can be analyzed and understood [1]. As described in Koch's postulates, the focus on a single cause-effect relationship yielded powerful protocols, pharmaceuticals, and surgical techniques that became the engine of modern medicine, proving remarkably effective against acute and infectious diseases [2].

However, this paradigm, once a source of unprecedented growth, is now revealing deep structural cracks under the weight of 21st-century challenges. The core assumptions of the reductionist approach—that a system can be well understood by analyzing its individual parts in isolation—are proving fundamentally inappropriate for the interconnected, multi-causal nature of contemporary health crises [3]. Critiques rooted in the philosophy of science argue that this model risks oversimplifying the subject to the point where it becomes separated from the complex, dynamic phenomenon it is intended to explain [4]. In medicine, this is evident in the development of highly targeted molecular agents that, despite sound theoretical grounds, often yield only modest benefits because they fail to address the intricate, non-linear interactions of the entire biological system from which a disease emerges [5].

In contrast, a holistic view postulates that health and disease must be comprehended through the constant interaction of their multiple components. A molecule, for instance, does not interact with a single enzyme in a vacuum; its effects ripple through a dense network of biochemical pathways, making the system's response emergent and unpredictable from the properties of any single part [6].

Today, the purely reactive, treatment-focused model is proving inefficient when confronted with the overwhelming complexity of aging populations and the prevalence of chronic multi-morbidity.

1.2.A Converging crises: Economic burden and demographic shifts

The financial unsustainability of the current paradigm is no longer a future projection but a harsh reality. The global economic burden of chronic diseases is astounding, with estimates projecting a cost of USD 47 trillion by 2030, a figure that presents a significant threat to global economic stability [7]. In the USA, the situation is particularly acute, with nearly 90% of the nation's USD 4.9 trillion in annual healthcare expenditures directed towards individuals with chronic and mental health conditions [8]. Costs associated with specific conditions are escalating; for instance, cardiovascular diseases are predicted to cost the U.S. economy almost USD 2 trillion by 2050, while cancer treatment could exceed USD 240 billion by 2030 [8,9]. Furthermore, the global cost of dementia alone was estimated at USD 1.3 trillion in 2019 and is on track to reach USD 2.8 trillion by 2030, placing immense pressure on health systems and caregivers [10].

This escalating financial strain is inextricably linked to a global demographic shift. The successes of 20th-century medicine have contributed to an extended human lifespan, leading to a worldwide aging population. In 2021, 18% of the population in OECD countries was aged 65 or over, a demographic that places a disproportionately high demand on healthcare services [11]. In 2022, OECD nations spent an average of 9.2% of their GDP on healthcare, a proportion that is becoming difficult to sustain [12]. The World Bank confirms this trend, noting that population aging is a primary driver of the surge in non-communicable diseases (NCDs), which now account for 70% of all deaths worldwide [13]. This creates a perilous economic feedback loop: a shrinking working-age population is tasked with supporting a growing elderly population with an ever-increasing healthcare burden, a dynamic negatively correlated with long-term economic growth [14]. Concurrently, the rise of multi-morbidity—the co-occurrence of two or more chronic conditions in an individual—magnifies this challenge. Multi-morbidity is now the norm in aging populations, and its impact on healthcare costs is exponential rather than additive [15]. Patients with multiple conditions utilize a wide array of services, leading to higher rates of physician visits, medication use, and hospitalizations [16]. This complexity fundamentally challenges the prevailing single-disease model of care, which struggles to manage patients with interconnected health issues, often leading to fragmented care, polypharmacy, and poor health outcomes [17].

The convergence of these economic and demographic crises creates an imperative for a new approach that can manage this complexity, ensuring the long-term viability of our health systems.

1.3. Redefining sustainability in healthcare

To address these converging crises, a new guiding principle must be sustainability. In the healthcare context, sustainability is not merely environmentalism but a multi-dimensional imperative that integrates socio-economic and environmental viability [18,19]. A truly sustainable health system is one that can consistently deliver high-quality, equitable, and efficient care over time without depleting the financial, human, or social resources necessary for its continued function [20,21].

This holistic definition aligns with the United Nations Sustainable Development Goals (SDGs). While directly linked to SDG 3 ("Good Health and Well-being"), a sustainable healthcare approach must also satisfy other global objectives, such as SDG 1 ("No Poverty"), SDG 10 ("Reduced Inequalities"), and SDG 9 ("Industry, Innovation and Infrastructure") [22].

Another key characteristic is resilience: the ability of a health system to prepare for, manage, and learn from shocks and stressors [23]. The COVID-19 pandemic served as a global "stress test," exposing the fragility of health systems optimized for stable, predictable conditions [24], (Table 1).

Table 1. A Tale of Two Paradigms: Contrasting Reductionist Medicine with a Systems Engineering Approach to Health. This table summarizes the fundamental differences between the traditional, 20th-century approach to medicine and the proposed 21st-century systems-oriented paradigm across key dimensions, from primary goals to the role of technology

Dimension	20th-Century Reductionist Paradigm	21st-Century Systems Engineering Paradigm
Overview	The body as a machine; disease as a broken part.	The health system as a Complex Adaptive System (CAS). [3]
Primary Goal	Increase Lifespan (life expectancy).	Engineer Healthspan (quality of life) and sustainable wellbeing.
Key Methodology	Linear, single-cause-single-effect analysis; Randomized Controlled Trials (RCTs).	Holistic, multi-scale analysis; Systems Engineering principles; In silico simulation. [26]
Locus of Intervention	The individual patient; the specific disease or pathology.	The entire system; interactions, feedback loops, and policies. [27]
Approach to Problems	Deconstruct and isolate variables.	Synthesize and understand and focus on interrelationships. [27]
Measure of Success	Mortality rates; disease-specific biomarkers.	National Wellbeing Score; Healthspan Gap; System Resilience; Equity.
Role of Technology	Diagnostic and treatment tools (e.g., imaging, drugs).	Policy sandboxes; Discovery agents (e.g., Digital Twins, AI).
Overview	The body as a machine; disease as a broken part.	The health system as a Complex Adaptive System (CAS). [3]

The pandemic highlighted weaknesses in governance, resource allocation, and the ability to maintain essential services during a crisis, underscoring the urgent need for frameworks and tools to build resilient health systems [24,25].

The paradigm that created longer lives is now putting the very system at risk. The linear, reductionist model was exceptionally effective at combating acute diseases, leading to a dramatic increase in human lifespan. However, this success, combined with other socioeconomic factors, has given rise to an aging global population susceptible to chronic, multi-morbid conditions. The management of this growing burden is the primary driver of the unsustainable growth in healthcare costs that now threatens national economies. The linear success in extending lifespan has created a non-linear, complex crisis of sustainability. The paradigm is a victim of its own success, creating a new reality for which it is fundamentally unprepared. This is not a single-point failure but a systemic evolution that demands an equally profound transformation.

1.4. The systems engineering proposition

The current healthcare paradigm is facing a system unsuitability problem. This paper makes a stand with a new proposition: the transition from reactively treating diseases to proactively engineering health span can only be achieved by adoption of a Systems Engineering mindset and strategy, enabled by new key computational tools. The proposal stands on three foundational pillars that form the logical backbone of this paper.

Firstly, we argue that the healthcare crisis of the 21st century stems from a fundamental mismatch between the problems leading to it and the current methods used to manage it. The public health space and the national economies models are not linear mechanisms, but deeply interconnected Complex Adaptive Systems (CAS). The exhibited behaviour emerges from a multitude of local interactions, is governed by feedback loops and is inherently nonlinear and adaptive. The failure of the 20th century reductionist paradigm is therefore not a failure of the individual tools and algorithms, but one that spawns from its core assumption that a complex system can be understood by analysing its parts in isolation.

Secondly, we envision that the Systems Engineering methodology offers necessary tools to manage the complexity of the healthcare systems in dependency of the economical ones. On one hand, CAS theory showcases why health systems behave unpredictably, while Systems Engineering provides a structured and holistic framework for how to design and manage them effectively throughout their lifecycle. The principles that govern it are a direct and logical response to the challenges posed by a CAS: the non-linearity of the system is managed through Risk Management and Sensitivity Analysis, its adaptive nature through Iterative Development, and its emergent properties through continuous Requirements Analysis and Verification.

We also assess that this methodological shift is now finally practically possible and achievable for the first time due to the convergence of new technological advancements and new architectures. We conceptualise this a synergetic “trinity of simulation” formed by:

1. **Digital Twins** at the population level that serve as virtual "policy sandboxes" for safe, in silico experimentation;
2. **Agent Based Modeling (ABM)** as an adaptive engine that can capture the emergent, bottom-up dynamics of a CAS;
3. **Artificial Intelligence (AI)** acting as a discovery agent that can navigate the vast policy landscape to spot novel, high impact strategies.

Taken together, those three pillars provide the means to apply the rigorous principles of Systems Engineering to the immense scale and complexity of public health, a task that has been considered unsolvable.

2. Theoretical Foundations: CAS and Systems engineering

Attempting to solve the sustainability crisis in healthcare requires a fundamental shift in our theoretical understanding of the system itself. The linear, mechanistic assumptions of the past must be replaced with a framework that embraces the inherent complexity, dynamism, and unpredictability of public health. This section introduces two complementary disciplines: Complex Adaptive Systems (CAS) theory, which offers a descriptive framework for understanding health systems, and Systems Engineering, which provides a prescriptive methodology for their design and management.

2.1. Redefining sustainability in healthcare

Public health and the national economy are not simple, predictable mechanisms but are deeply interconnected Complex Adaptive Systems (CAS) [3]. A CAS is a dynamic network of autonomous agents—patients, clinicians, hospitals, policymakers—who interact with each other and their environment according to a set of rules [28]. The collective behavior of the system is not centrally controlled but emerges from these local interactions, often in non-linear and unpredictable ways [3,29]

This theoretical framework is crucial for understanding why well-intentioned, linear interventions frequently fail or produce unforeseen detrimental results in healthcare. Health systems exhibit all the key properties of a CAS, and a failure to recognize these properties leads to policies mismatched with the system's reality. A detailed understanding of these properties, as described in Table 2, is a prerequisite for effective and sustainable reform.

2.2. Systems Engineering: A Methodology for Managing Complexity

While CAS theory provides the descriptive language, Systems Engineering offers the practical methodology to manage this complexity. Originating in aerospace and defense, it provides a structured, holistic framework for designing and managing complex systems throughout their lifecycle [26].

Table 2. Key Properties of Complex Adaptive Systems in a Public Health Context. This table defines the core properties of Complex Adaptive Systems (CAS) and provides concrete public health examples for each, illustrating why healthcare is best understood through a complexity lens

CAS Property	Definition	Public Health Example
Emergence	Macro-level patterns arise from micro-level interactions that are not predictable from the sum of the parts. [28]	The sudden, unexpected outbreak of an infectious disease in a community, driven by countless individual interactions. [30]
Feedback Loops	The outputs of a system's actions are routed back as inputs, influencing the subsequent behaviour (which in turn can be reinforcing or balancing). [31]	The "Virtuous Cycle of Development": investment in public health improves workforce productivity, which boosts the economy, providing more resources for future health investment (a reinforcing loop).
Non-linearity	The relationship between cause and effect is disproportional; small inputs can lead to massive, system-wide changes. [32]	A small, targeted investment in a childhood vaccination program yielding massive societal returns by preventing widespread disease and long-term disability.
Adaptation	Agents within the system learn and modify their behaviour based on experience and their changing environment. [3]	Patients changing their adherence to a medication based on side effects; the public altering social distancing based on perceived risk.
Path Dependence	The history of the system matters; small, early events can have lasting consequences that lock in future trajectories. [33]	The historical layout of a hospital or the initial decision to fund disease-specific research silos can constrain options for integrated care decades later.

It is a disciplined approach that moves from identifying stakeholder needs to defining requirements, and from conceptual design through to operation and sustainment [27].

Applications of Systems Engineering in healthcare have already demonstrated significant improvements in patient safety and operational efficiency, from redesigning hospital workflows to large-scale care integration initiatives [34]. Its success stems from its ability to identify and address true systemic constraints rather than optimizing isolated components. The synergy between CAS theory and Systems Engineering is foundational. CAS explains the *why*—the inherent non-linearity and emergent behavior of health systems. Systems Engineering provides the *how*—the applied processes and tools to work *with* this complexity.

Table 3 illustrates this direct correspondence, showcasing how specific engineering methodologies are created to address the challenges that may arise in the public health sector.

3. The digital toolkit for engineering longevity

Advanced computational tools are enabling the practical application of the systems engineering paradigm in public health. These technologies represent a new class of instruments capable of modeling, simulating, and navigating the complexity of health systems.

This section details the specific digital tools that form the core of this new approach.

3.1. Population-level digital twins as policy sandboxes

The "Digital Twin" concept is a key enabling technology for this paradigm shift. A Digital Twin is a virtual, dynamic representation of a real-world system that is continuously updated with data from its physical counterpart, allowing it to mirror the state, behavior, and evolution of the physical entity over time [35]. While initial healthcare applications focused on high-fidelity models of individual organs or hospital wards, the true challenge is scaling this concept to create comprehensive, population-level Digital Twins for public health [36,37]. This focus on high-fidelity, specialised models continues to grow in different domains, like ophthalmology [85].

These population-level Digital Twins can function as virtual "policy sandboxes"—akin to flight simulators for governance [38]. This approach provides a safe, cost-effective, and ethical environment for policymakers to test the potential impacts of complex interventions *in silico* before committing vast resources to real-world deployment. In this virtual environment, users can model the effects of a new prevention campaign, assess the system's resilience to future pandemics, or visualize how a policy might affect different demographic cohorts, thereby understanding the long-term, non-linear consequences of their decisions. This aligns with broader efforts to create digital twins for more sustainable and resilient infrastructure [39]. The implementation of these systems requires robust architectural frameworks and significant computational power, and major initiatives like the European Virtual Human Twins Initiative are already working to establish the necessary platforms and standards.

Table 3. Key Properties of Complex Adaptive Systems in a Public Health Context. This table defines the core properties of Complex Adaptive Systems (CAS) and provides concrete public health examples for each, illustrating why healthcare is best understood through a complexity lens

CAS Concept (The Challenge)	Systems Engineering Principle (The Solution)	Application in Public Health
Emergence (Unpredictable outcomes)	Requirements Analysis & Verification	Defining clear public health goals (e.g., reduce hospital readmissions by 15%) and continuously verifying that interventions are meeting them, allowing for course correction.
Feedback Loops (Interconnectedness)	System Architecture & Interface Management	Mapping the entire patient journey from primary care to hospital to home, identifying key handoffs (interfaces) and designing protocols to ensure smooth information flow.
Adaptation (Changing agent behavior)	Iterative Development & Prototyping	Launching a pilot mHealth app for diabetes management, gathering user feedback, and iteratively refining its features based on real-world patient and clinician behavior.
Non-linearity (Disproportional effects)	Risk Management & Sensitivity Analysis	Using simulation models to identify which small interventions (e.g., a targeted nutritional program) could have the largest positive impact on population health, while also identifying potential negative tipping points.
Path Dependence (Historical constraints)	Lifecycle Planning & Sustainment	Designing a new digital health record system not just for current needs, but with a modular architecture that allows for future technologies and care models to be integrated without a complete overhaul.

3.2. Agent-Based Modeling (ABM) as the Engine of Complexity

Agent-Based Modeling (ABM) is the engine that powers these dynamic, population-level Digital Twins. ABM is a bottom-up computational methodology that simulates the actions and interactions of numerous autonomous, heterogeneous agents (e.g., individuals, households, pathogens) within a defined environment [40]. The power of ABM lies in its ability to generate emergent, macro-level phenomena from simple rules governing micro-level interactions. This makes it exceptionally well-suited for capturing the key properties of CAS that are often missed by

traditional aggregate models, such as non-linear dynamics and social contagion effects [41].

In a public health context, ABM is an indispensable tool for realistically simulating complex scenarios. It can model the spread of infectious diseases through social networks, the adoption of health behaviors like vaccination, and the impact of health misinformation on public trust [42]. Frameworks can be created to link the health states of individual agents to emergent macroeconomic outcomes like GDP, a crucial step in testing policies aimed at fostering a virtuous cycle where investments in population health drive sustainable economic prosperity.

3.3. AI as a discovery agent

The vast number of variables and potential policy combinations within a high-fidelity, population-level ABM creates a policy landscape too complex for exhaustive human analysis. Here, Artificial Intelligence (AI) becomes transformative, evolving from a predictive tool into an agent for discovery and optimization. Techniques like Reinforcement Learning (RL) can be employed to create AI agents that act as high-level policymakers, navigating the complex policy space to identify novel, high-impact intervention strategies.

In an RL framework, an AI agent learns by repeatedly interacting with the simulation environment (the Digital Twin) and receiving rewards or penalties based on its performance against predefined goals, such as maximizing a "National Wellbeing Score" [43]. Over millions of simulated years, the RL agent can uncover complex, non-linear relationships between policy inputs and emergent outcomes, discovering non-intuitive strategies that significantly outperform traditional, human-designed interventions (figure 1).

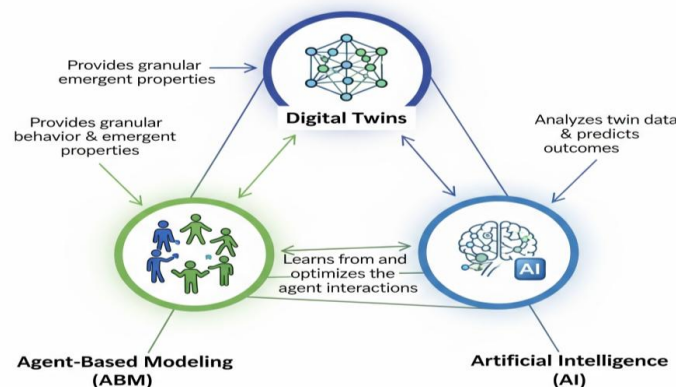


Figure 1. The Synergistic Relationship Between Core Technologies. This diagram illustrates the symbiotic relationship between Digital Twins, Agent-Based Modeling (ABM), and Artificial Intelligence (AI). The Digital Twin provides the data-rich environment, the ABM simulates complex behaviors, and AI optimizes and discovers policies within that simulation, creating an integrated system for public health analysis.

Furthermore, the advent of Large Language Models (LLMs) offers a revolutionary capability to enhance the realism of the agents within the ABM. Instead of following simple, predefined rules, LLMs can be used to create "generative agents" with rich backstories, nuanced beliefs, and human-like communication patterns [44]. This allows for the simulation of difficult-to-quantify social factors such as cultural beliefs, health literacy, and the viral spread of misinformation, adding a new layer of social fidelity to public health models [45]. This allows for the creations of more socially intelligent agents, with recent research demonstrating that LLM-based agents, termed *Homo silicus*, can successfully replicate many human behaviours in different experiments [89].

These three technologies—Digital Twins, ABM, and AI—form a single, integrated system. The Digital Twin provides the context and data link to reality, the ABM provides the dynamic engine of complexity, and AI provides the intelligence for discovery and optimization. Their integration is the core technological innovation that enables the paradigm shift to a systems-oriented public health.

4. The enabling technology layer: Real-world data

High-level computational tools like Digital Twins and AI do not operate in a vacuum. Their power is contingent upon a continuous stream of high-velocity, high-accuracy, real-world data that reflects the dynamic health status of the population. This data is increasingly generated by a growing ecosystem of personal and home-based health technologies.

4.1. Wearable Devices and Personal Monitoring

The proliferation of consumer wearable devices—smartwatches, fitness trackers, smart rings—represents a revolution in health data collection [46]. These devices passively and continuously capture a wide range of physiological and behavioral data points, such as heart rate, sleep patterns, and physical activity levels, outside of the traditional clinical setting [47].

This creates a longitudinal, high-frequency dataset that provides a far more nuanced picture of an individual's health status, moving beyond the sporadic snapshots of episodic clinic visits [48].

This data is a cornerstone of a personalized, preventative approach to health, a key tenet of a sustainable system [49].

4.2. Wearable devices and personal monitoring

In parallel with consumer wearables, clinically validated, medical-grade devices for home use are becoming more common.

This trend, known as Remote Patient Monitoring (RPM), is critical for managing the growing burden of chronic diseases [50].

Devices like continuous glucose monitors (CGMs) for diabetes and smart blood pressure cuffs for hypertension are enabling a shift from hospital-centric to home-based care, which can reduce costs and improve patient quality of life [51]. This trend is supported by extensive evidence, with 2024 systematic reviews confirming that Remote Patient Monitoring can significantly improve clinical outcomes for a range of chronic diseases and conditions (e.g. hypertension, diabetes etc.). The

reviews also showcase that RPM can increase patient engagement and adherence to treatment plans, which are critical for long-term healthspan improvements [88]. RPM allows health systems to monitor high-risk patients more effectively, intervene earlier to prevent acute events, and empower patients to take a more active role in managing their conditions [52].

4.3. Mobile health (mhealth) for engagement

The ubiquity of the smartphone has made it a powerful platform for both data collection and health intervention delivery. Mobile health (mHealth) applications serve a multitude of functions, from collecting patient-reported outcomes (PROs) and tracking medication adherence to gathering data on symptoms and quality of life [53].

Beyond data collection, mHealth apps are a scalable and cost-effective channel for delivering personalized health coaching, educational content, and behavioral change interventions [54].

This creates a crucial feedback loop: the population-level Digital Twin can identify a high-risk group, targeted mHealth interventions can be deployed to that group, and the results can be continuously monitored and fed back into the system to refine the approach [55].

5. Case Studies in Systems Thinking

To ground these concepts in reality, this section presents three brief case studies illustrating the application of a systems perspective to real-world public health challenges.

5.1. Case study: A National Cancer Screening Program as a CAS

A national breast cancer screening program is a classic example of a CAS.

The "agents" include patients, primary care physicians, radiologists, and policymakers. Their interactions are governed by rules (screening guidelines) but also influenced by individual beliefs, access to care, and communication. *Emergence* is seen in population-level screening rates, which arise from countless individual decisions, not a central command.

Feedback loops occur when a high rate of false positives (output) leads to public anxiety and reduced participation (input), prompting policymakers to adjust guidelines. An intervention that focuses only on one component—like buying more mammography machines—without considering the adaptive behaviors of patients and physicians is likely to underperform (Table 4).

A systems approach would model these interactions to design a more resilient and effective program [77].

Table 4. Case Study 1. Breast cancer screening as a complex adaptive system

Dimension	Application in Public Health
Goal	Improve early detection while reducing over-diagnosis and unnecessary biopsies.
System Elements	Mammography infrastructure, radiologists, population risk stratification, national screening guidelines.
Intervention Tested in Sandbox	Use of explainable AI to standardize BI-RADS classification and reduce inter-observer variability.
Outcome / Trade-offs	Higher consistency in reporting, reduced false positives, but requires large annotated datasets and workflow integration.

5.2. Case Study: The COVID-19 vaccination rollout as an adaptive system

The global COVID-19 vaccination rollout was a real-time exercise in managing a complex adaptive system.

The system had to *adapt* constantly to changing vaccine supply, emerging virus variants, and evolving scientific evidence.

Public trust and vaccine uptake were subject to powerful *feedback loops*, influenced by health communication and the spread of misinformation through social networks. Policies had to be adjusted dynamically, from changing eligibility criteria to deploying mobile vaccination units to reach underserved communities.

The success of the rollout depended less on a rigid, top-down plan and more on the system's ability to learn and adapt in response to real-time data and changing agent (public) behavior [78].

5.3. Case Study: A Digital Twin for Chronic Disease Management

Consider the management of Type 2 diabetes at a population level. A Digital Twin could integrate data from multiple sources: electronic health records, wearable glucose monitors (RPM), and pharmacy records. An ABM within the twin would simulate patient "agents," each with unique characteristics (age, diet, adherence to medication). The system could then test different interventions *in silico*. For example, it could compare the projected long-term impact of a broad public health campaign promoting exercise versus a targeted mHealth intervention for high-risk individuals. The AI layer could identify that for a specific demographic, a small investment in community-based dietary coaching yields a disproportionately large reduction in long-term complications (*non-linearity*), providing an evidence base for a highly efficient and sustainable policy [79].

6. Thinking Redefining Success: From Lifespan to Healthspan

Just the deployment of the new technologies is not the end goal. Its ultimate purpose is to enable a fundamental shift in our societal goals for health and wellbeing. This requires moving beyond the narrow metrics of the 20th century and embracing more holistic, ambitious and sustainable northstar metrics to measure success.

6.1. The New Northstar: Engineering Healthspan

In the last century, the primary goal and measure of success for medicine and public healthcare was related to the increase of lifespan: the total number of years and individual lives. At a societal level, average numbers have been computed to track how lifespan is increased for a nation. While the increase of this metric (by dropping the infant death rate and increasing the capabilities of treatment for the chronically ill) has been one of the best achievements of the last century, it also contributed to the current sustainability crisis, as additional years of life don't mean a good quality of life. Usually, many individuals spend their last part of life chronically ill, with a low satisfaction for their life and feeling like a burden for their family.

The goal for a sustainable 21st century health system must shift to engineer longevity or healthspan: the period of life spent in good health, free from the functional limitations of chronic diseases and disability.

The northstar objective is not merely to live long, but to live well.

This shift needs a corresponding evolution in our measurement frameworks as well. Trending towards a longer healthspan requires a suite of metrics that go beyond simple mortality rates.

The updated proposed metrics include established public health measures such as:

- Health-Adjusted Life Expectancy (HALE): which is a good counter metric for DALY;

- Quality-Adjusted Life Years (QALYs): which measure the number of years a person can expect to live in good health.

Furthermore, new combined metrics are needed to be designed in order to track a population's health status across the entire life course, including the "Healthspan Gap" (a disparity metric that calculates the delta in healthy years between the most and least privileged demographic groups) which serves as a direct measure of health equity.

6.2. Beyond GDP: A "National Wellbeing Score"

Considering that our health metrics need to evolve, the same applies for the ones tracking the success of our society. For many decades, Gross Domestic Product (GDP) has been the primary metric, and many times, the only indicator of a nation's prosperity and progress. Currently there is a growing global consensus that GDP alone is an incomplete and often misleading metric, as it fails to account for critical dimensions of societal progress, like population health, social equity, and environmental sustainability [56,57]. A nation can have a rising GDP while its population's health deteriorates, its environment degrades, and its social fabric frays.

The systems engineering framework proposed in this work requires a more holistic optimization target that reflects this broader understanding of societal value.

A new metric that is the composite score between economic prosperity (measured by GDP) with public health outcomes (measured by HALE), while simultaneously penalizing the societal burden of disease (measured by DALYs) could have a higher impact, namely, "National Wellbeing Score". By optimizing for this multi-dimensional score, the AI-driven policy discovery process is guided towards strategies that create a virtuous cycle of development, where health and economic prosperity are mutually reinforcing. This approach aligns with a broader global movement towards "Beyond GDP" indicators that seek to provide a more accurate and sustainable measure of societal well-being [57].

6.3. Aligning with UN Sustainable Development Goals (SDGs)

Applying a system-oriented approach to public health, having a dual focus on engineering healthspan and maximizing a holistic national wellbeing score is linked to the United Nations' 2030 Agenda for Sustainable Development. The current goals are highly linked to the SDG 3 (Good Health and Well-being) but also with multiple other goals [58].

The connections are multiplicative:

- SDG 8 (Decent Work and Economic Growth): Improving population health, the framework directly enhances workforce productivity and creates the conditions for long-term economic growth;

- SDG 10 (Reduced Inequalities): By explicitly measuring and seeking to reduce the "Healthspan Gap," the framework targets the root causes of health disparities, directly supporting to minimize them;

- SDG 9 (Industry, Innovation and Infrastructure) and SDG 11 (Sustainable Cities and Communities): On the other hand, the development of resilient and data driven health systems that use advanced technologies represent a form of critical infrastructure development.

Analyzing healthspan not just as a health metric, but as an engine for indicating national sustainability reveals its *true* importance. In general, a population cohort that has a high equitable healthspan is considered healthier and more functional for a larger portion of their life.

This approach can generate a positive impact on the economy, productivity and innovation scores of that population, driving societal resilience and creating economic sustainability. Concurrently, many of the public health initiatives required to improve healthspan (e.g. promoting active transportation, ensuring access to nutritious food, and reducing air pollution) are amplifying exponentially the sustainability goal. Also, the "Healthspan Gap" between different socioeconomic groups represents a quantifiable measure of social inequity. Policies that successfully close this gap are, by their nature, the ones that advance social sustainability. By elevating healthspan into a primary policy objective for a nation means that investments are placed in multiple areas touching economic vitality, environmental health, and social cohesion. This positions health not as a cost that needs to be managed and reduced, but as a critical asset to be cultivated for a holistic and sustainable national prosperity.

7. Implications and Recommendations

Embedding systems engineering science and moving towards this paradigm is not just a high level strategic or technological adjustment. This change drives a fundamental shift in culture and operational transformation across the entire healthcare ecosystem. The shift mandates new skills, new organizational structures and hierarchies, new ways of thinking for the stakeholder.

This section explores the practical changes needed for a paradigm shift for key domains and representatives.

7.1. Governance and Policy: From Reaction to Anticipation

The paradigm shift has profound implications for governance and policymaking as well, where the traditional policy cycle can be described as linear and reactive: a problem is identified, a solution is designed and implemented, and its effects are evaluated years later. This approach is ill-suited for governing complex adaptive systems, where interventions can have unforeseen consequences and the environment is constantly changing [27].

The systems engineering approach creates the context for a more adaptive, iterative and anticipatory model of governance. In this new workflow, the "policy sandboxes" created by population-level Digital Twins allow policymakers to move from a model where decisions are made and then implemented to a model where simulations are first run and then decisions are implemented [38].

This way policies can be tested, refined, and compared in a virtual environment, allowing for the identification of potential negative impacts and unintended consequences before they occur in the real world.

In this new model, the role of the policymaker changes from a central planner to a system designer, who guides and adapts the system's evolution based on real-time data and simulated foresight [73]. This approach, coupled with the ethical frameworks discussed in the following section, allows for a more dynamical and responsible form of governance that is better equipped to navigate the complexities of 21st-century public health.

A commonly proposed safeguard is the "Human-in-the-Loop" (HITL) model. However, this is often insufficient, as cognitive biases can lead supervisors to become overly reliant on AI, paradoxically decreasing accountability [76]. A more robust approach is needed.

We propose an "Ethical Sandbox" model for proactive, pre-deployment validation. This concept is inspired by the successful use of regulatory sandboxes in other fields, such as the UK Financial Conduct Authority's (FCA) sandbox for fintech or Singapore's AI Governance Sandbox, which allow for innovation in a controlled environment [80,81]. In public health, this would involve creating automated, adversarial "ethics committee" frameworks that rigorously stress-test proposed AI-driven policies. These frameworks would use simulations to test policies against diverse synthetic populations to identify potential negative outcomes—especially for vulnerable groups—before they are ever deployed [82]. The recent push for a European Health Data Space (EHDS) provides a potential large-scale infrastructure where such sandboxes could be implemented, allowing for secure, ethical testing of AI models on anonymized, pan-European health data [83].

This process would generate a transparent, data-driven ethical report to help policymakers make informed, value-aligned decisions. The oversight of such a system must be a multi-stakeholder effort, including ethicists, clinicians, and community representatives, to ensure its embedded values are legitimate and accountable. Even more, recent studies of early healthcare AI sandboxes emphasise the critical need for multi-stakeholder collaboration to define robust metrics for fairness and efficiency before deployment [86]. Figure 2 contrasts this anticipatory model with traditional reactive governance.

7.2. Recommendations for Action

To translate this framework into practice, we offer targeted recommendations for key stakeholder groups:

For Researchers:

-Develop Integrated Simulation Tools: Focus on creating open-source simulation platforms that integrate CAS, ABM, and Digital Twin functionalities for modeling chronic diseases and health system resilience;

-Advance Explainable AI (XAI): Prioritize research into XAI methods that can make the recommendations of complex AI models transparent and trustworthy for clinicians and policymakers, bridging the gap between black-box algorithms and real-world decision-making [84];

-Conduct Pragmatic Trials: Design and execute implementation studies that evaluate systems-level interventions in real-world settings to build an evidence base for what works at scale.

For Policymakers:

-Establish National Policy Sandboxes: Create regulatory sandboxes to test AI-driven public health programs under strict oversight, fostering innovation while safeguarding public trust and safety;

-Incentivize Value over Volume: Reform healthcare payment models to reward outcomes that improve healthspan and reduce the "Healthspan Gap," rather than simply reimbursing for the volume of services delivered;

-Invest in Data Infrastructure: Champion the development of secure, interoperable health data infrastructure, aligned with principles like the EHDS, to serve as the foundation for a 21st-century learning health system. This includes fostering collaborative platforms that will integrate e-Health services at the community level, creating the necessary digital fabric for a truly connected and intelligent health ecosystem [87].

For Practitioners and Health System Leaders:

-Adopt Systems Thinking in Management: Train clinical and administrative leaders in systems engineering principles to redesign care pathways and optimize patient flow across the entire health system, not just within departmental silos;

-Champion Interprofessional Education: Redesign clinical education to be team-based, preparing future health professionals to work collaboratively in managing patients with complex, co-occurring conditions;

-Implement Decision Support Systems: Integrate AI-powered, evidence-based clinical decision support tools into workflows to help manage the complexities of multi-morbidity and reduce variability in care.

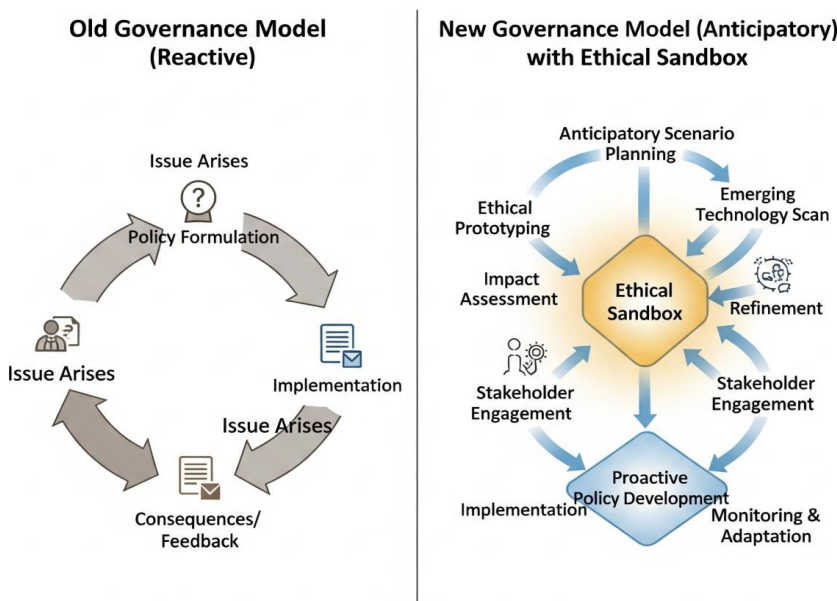


Figure 2. A Comparison of Governance Models. This figure contrasts the traditional, reactive governance cycle (left), which responds to issues after they arise, with the proposed anticipatory model featuring an 'Ethical Sandbox' (right). The new model allows for proactive testing and refinement of policies in a simulated environment before real-world implementation, fostering more responsible and effective governance

8.Implications and Recommendations

The paradigm shift proposed in this paper presents itself as a profound, visceral yet necessary change.

The 20th century model of medicine, focused on the reductionist model for treating specific diseases, has reached the limits of its economic and social sustainability. The challenges brought by the 21st century: aging populations, the burden of chronic multi-morbidity and the need for resilient and equitable systems that are economically viable demand a new approach. We need to move from a system that uses linear models to pursue the goal of a longer lifespan to a new, integrated system that leverages the principles of systems engineering and the power of advanced computational tools to pursue the more holistic goal of longer healthspan and a higher national wellbeing.

The analysed evolution shouldn't be viewed as a departure or alteration of the core medical principles that were built in thousands of years, but a new augmentation and evolution that equips this domain with new tools to tackle the modern complexity. By adopting the theoretical lens of Complex Adaptive Systems and the methodology of Systems Engineering, we can create and manage those systems more efficiently. This shift can be achieved and sustained with a dual layered technological architecture: a high-level "trinity" of population level Digital Twins, Agent Based Modeling and AI models that provide simulation and discovery power, combined with a layer of personal health technologies that provide real-world data to train and adapt the models in a dynamic and relevant manner.

At the same time, this paper argues that a change in theory and technology is not enough, the shift towards a systems paradigm is profound, with practical implications for all actors in the healthcare ecosystem, necessitating fundamental reforms and changes in education, clinical practice, hospital management, research methodologies and governance. This technological and operational evolution must be guided by a robust ethical framework to ensure its success. Introducing the concept of "Ethical Sandbox" allows for policies to be rigorously stress tested for fairness and equity before deployment. This updated model of participatory governance ensures that innovation is steered by societal values and contributes to social sustainability, with participation from the population that is going to be affected by those changes. This is crucial for ensuring that the benefits of digital transformation are distributed equitably, a challenge highlighted in 2025 analyses on the social determinants of health in AI-driven healthcare [90].

Combining all the presented elements: a new theoretical lens, a new technological architecture, an updated set of goals, a new operational model for practice and a novel ethical framework we can start to move beyond the reactive medicine model that treats sickness to a proactive science that truly engineers longevity. These systems engineering approach provides the blueprint for building the sustainable, resilient and equitable health systems for the rest of the 21st century, capable of delivering not just longer lives, but more importantly, better ones.

Finally, the 'Engineering Longevity' framework presented in this paper offers a universally applicable blueprint for navigating the global healthcare crisis. Even though healthcare systems are different at many different levels, the fundamental challenges of aging populations, the rise of chronic multi-morbidity burden and the escalating costs there are non-viable from an economic standpoint are worldwide phenomena. The systems engineering approach is not a rigid one size fits all solution, but more of an adaptive methodology that can be tailored to diverse national contexts. By providing the tools to simulate policy in silico and govern AI ethically, this framework empowers any entity to transition from a reactive, cost-prohibitive medical model to a proactive, value-based system that builds a healthier and more prosperous future for its citizens.

REFERENCES

- [1]. Gu, D.; Zhang, Z. *How Does Digital Transformation Affect the Sustainable Development of the Healthcare Industry?* Sustainability **2023**, 15, 10471.
- [2]. Ahn, A.C.; Tewari, M.; Poon, C.S.; Phillips, R.S. The limits of reductionism in medicine: could systems biology offer an alternative? PLoS Med. **2006**, 3, e208.
- [3]. Plsek, P.E.; Greenhalgh, T. *Complexity science: The challenge of complexity in health care*. BMJ **2001**, 323, 625-628.
- [4]. Mitchell, S.D. *Unsimple truths: Science, complexity, and policy*; University of Chicago Press: Chicago, IL, USA, 2009.
- [5]. Joyner, M.J.; Prendergast, F.G. *Chasing unicorns: the deception of personalized medicine*. J. Physiol. **2014**, 592, 2431-2439.
- [6]. Barabási, A.L.; Gulbahce, N.; Loscalzo, J. Network medicine: a network-based approach to human disease. Nat. Rev. Genet. **2011**, 12, 56-68.
- [7]. Bloom, D.E.; Cafiero, E.T.; Jané-Llopis, E.; Abrahams-Gessel, S.; Bloom, L.R.; Fathima, S.; Feigl, A.B.; Gaziano, T.; Mowafi, M.; Pandya, A.; et al. *The Global Economic Burden of Non-communicable Diseases*; World Economic Forum: Geneva, Switzerland, 2011.
- [8]. Centers for Disease Control and Prevention. Health and Economic Costs of Chronic Diseases. Available online: <https://www.cdc.gov/chronicdisease/about/costs/index.htm> (accessed on 29 August 2025).
- [9]. American Cancer Society. Economic Impact of Cancer. Available online: <https://www.cancer.org/research/cancer-facts-statistics/economic-impact-of-cancer.html> (accessed on 29 August 2025).
- [10]. World Health Organization. Dementia Fact Sheet. Available online: <https://www.who.int/news-room/fact-sheets/detail/dementia> (accessed on 29 August 2025).
- [11]. OECD. Health at a Glance 2022; OECD Publishing: Paris, France, 2022.
- [12]. Rokicki, T.; Perkowska, A.; Ratajczak, M. *Differentiation in Healthcare Financing in EU Countries*. Sustainability **2021**, 13, 251.
- [13]. The World Bank. Population Aging. Available online: <https://www.worldbank.org/en/topic/population-aging> (accessed on 29 August 2025).
- [14]. Lee, R.; Mason, A. *Cost of aging*. Finance & Development **2017**, 54, 8-11.
- [15]. Barnett, K.; Mercer, S.W.; Norbury, M.; Watt, G.; Wyke, S. *Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study*. The Lancet **2012**, 380, 37-43.
- [16]. Glynn, L.G.; Valderas, J.M.; Healy, P.; Burke, E.; Newell, J.; Gillespie, P.; Murphy, A.W. *The prevalence of multimorbidity in primary care and its effect on health care utilization and cost*. Fam. Pract. **2011**, 28, 516-523.
- [17]. Boyd, C.M.; Fortin, M.; Mercer, S.W. *The reality of multimorbidity: beyond the single-disease framework*. J. Comorbidity **2014**, 4, 1-2.
- [18]. AlDhaen, E. *Micro-Level CSR as a New Organizational Value for Social Sustainability Formation: A Study of Healthcare Sector in GCC Region*. Sustainability **2022**, 14, 12256.

- [19]. Balabel, A.; Alwetaishi, M. *Toward Sustainable Healthcare Facilities: An Initiative for Development of "Mostadam-HCF" Rating System in Saudi Arabia*. Sustainability **2021**, *13*, 6742.
- [20]. Rees, G.H.; James, R.; Samadashvili, L.; Scotter, C. *Are Sustainable Health Workforces Possible? Issues and a Possible Remedy*. Sustainability **2023**, *15*, 3596.
- [21]. Mesteru, E.G. *Sustainability in the Management of the Private Medical Sector in Romania: A European, USA and Japan Comparison*. Sustainability **2025**, *17*, 5360.
- [22]. Cosma, S.A.; Bota, M.; Fleşeriu, C.; Morgovan, C.; Văleanu, M.; Cosma, D. *Measuring Patients' Perception and Satisfaction with the Romanian Healthcare System*. Sustainability **2020**, *12*, 1612.
- [23]. Haldane, V.; De Foo, C.; Abdalla, S.M.; Jung, A.S.; Tan, M.; Wu, S.; Legido-Quigley, H. *Health systems resilience in managing the COVID-19 pandemic: lessons from 28 countries*. Nat. Med. **2021**, *27*, 964-980.
- [24]. Liu, J.; Yu, X. *Social Media as a Catalyst for Sustainable Public Health Practices: A Structural Equation Modeling Analysis of Protective Behaviors in China During the COVID-19 Pandemic*. Sustainability **2025**, *17*, 4642.
- [25]. Kruk, M.E.; Myers, M.; Varpilah, S.T.; Dahn, B.T. *What is a resilient health system? Lessons from the Ebola crisis*. The Lancet **2015**, *385*, 1910-1912.
- [26]. INCOSE. *Systems Engineering Handbook: A Guide for System Life Cycle Processes and Activities*, 4th ed.; John Wiley & Sons: Hoboken, NJ, USA, 2015.
- [27]. Trochim, W.M.; Cabrera, D.A.; Milstein, B.; Gallagher, R.S.; Leischow, S.J. *Practical challenges of systems thinking and modeling in public health*. Am. J. Public Health **2006**, *96*, 538-546.
- [28]. Holland, J.H. *Adaptation in natural and artificial systems: an introductory analysis with applications to biology, control, and artificial intelligence*; MIT press: Cambridge, MA, USA, 1992.
- [29]. Squazzoni, F. *Agent-Based Modeling and Social Simulation in the Era of Big Data*. Sustainability **2020**, *12*, 4293.
- [30]. Epstein, J.M. *Modelling to contain pandemics*. Nature **2009**, *460*, 687.
- [31]. Sterman, J.D. *Business dynamics: Systems thinking and modeling for a complex world*; Irwin/McGraw-Hill: Boston, MA, USA, 2000.
- [32]. Gladwell, M. *The Tipping Point: How Little Things Can Make a Big Difference*; Little, Brown: Boston, MA, USA, 2000.
- [33]. Arthur, W.B. *Competing technologies, increasing returns, and lock-in by historical events*. Econ. J. **1989**, *99*, 116-131.
- [34]. Griesves, M.; Vickers, J. *Digital twin: Mitigating unpredictable, undesirable emergent behavior in complex systems*. In *Transdisciplinary perspectives on complex systems*; Springer: Cham, Switzerland, 2017; pp. 85-113.
- [35]. Björnsson, B.; Borrebaeck, C.; Elander, N.; Gasslander, T.; Gawel, D.R.; Gustafsson, M.; Jönsson, G. *Digital twins to personalize medicine*. Genome Med. **2021**, *13*, 1-5.
- [36]. White, G.; et al. *A Digital Twin for a Smart City: A Case Study of the City of Cambridge*. Sustainability **2021**, *13*, 8299.
- [37]. El Saddik, A. *Digital twins: The convergence of multimedia and big data*. IEEE multimedia **2018**, *25*, 87-92.

- [38]. Deng, H.; Zhu, L.; Wang, X.; Zhang, N.; Tang, Y. *Renewal Strategies for Older Hospital-Adjacent Communities Based on Residential Satisfaction: A Case Study of Xiangya Hospital*. Sustainability **2025**, *17*, 4458.
- [39]. Macal, C.M.; North, M.J. *Tutorial on agent-based modeling and simulation*. J. Simul. **2010**, *4*, 151-162.
- [40]. Tracy, M.; Cerdá, M.; Keyes, K.M. *Agent-based modeling in public health: current applications and future directions*. Annu. Rev. Public Health **2018**, *39*, 77-94.
- [41]. Min, L.; Yu, Z. *Intergenerational Information-Sharing Behavior During the COVID-19 Pandemic in China: From Protective Action Decision Model Perspective*. Sustainability **2025**, *17*, 7263.
- [42]. Sutton, R.S.; Barto, A.G. *Reinforcement learning: An introduction*; MIT press: Cambridge, MA, USA, 2018.
- [43]. Park, J.S.; O'Brien, J.C.; Cai, C.J.; Morris, M.R.; Liang, P.; Bernstein, M.S. *Generative agents: Interactive simulacra of human behavior*. In Proceedings of the 36th Annual ACM Symposium on User Interface Software and Technology, San Francisco, CA, USA, 29 October–1 November 2023.
- [44]. Shen, X.; Yang, W.; Sun, S. *Analysis of the Impact of China's Hierarchical Medical System and Online Appointment Diagnosis System on the Sustainable Development of Public Health: A Case Study of Shanghai*. Sustainability **2019**, *11*, 6564.
- [46]. Piwek, L.; Ellis, D.A.; Andrews, S.; Joinson, A. *The rise of consumer health wearables: promises and barriers*. PLoS Med. **2016**, *13*, e1001953.
- [47]. Seshadri, D.R.; Drummond, C.; Craker, J.; Krouse, R.S. *Wearable technology in health care: a paradigm shift in diagnostics and disease management*. IEEE Pulse **2019**, *10*, 18-24.
- [48]. Swan, M. *The quantified self: Fundamental disruption in big data science and biological discovery*. Big data **2013**, *1*, 85-99.
- [49]. Yoon, K.; Park, G.; Lee, M. *Priority Analysis of Right Remedies of Basic Living Recipients in Korea*. Sustainability **2020**, *12*, 2205.
- [50]. Noah, B.; Keller, M.S.; Mosadeghi, S.; Stein, L. *The impact of remote patient monitoring on clinical outcomes: a systematic review*. J. Med. Internet Res. **2018**, *20*, e10019.
- [51]. Kim, N.; Shin, K.M.; Seo, E.S.; Park, M.; Lee, H.Y. *Electroacupuncture with Usual Care for Patients with Non-Acute Pain after Back Surgery: Cost-Effectiveness Analysis Alongside a Randomized Controlled Trial*. Sustainability **2020**, *12*, 5033.
- [52]. Appolloni, L.; Giretti, A.; Corazza, M.V.; D'Alessandro, D. *Walkable Urban Environments: An Ergonomic Approach of Evaluation*. Sustainability **2020**, *12*, 8347.
- [53]. Marcolino, M.S.; Oliveira, J.A.Q.; D'Agostino, M.; Ribeiro, A.L.; Alkmim, M.B.M.; Novillo-Ortiz, D. *The impact of mHealth interventions: systematic review of systematic reviews*. JMIR mHealth uHealth **2018**, *6*, e23.
- [54]. Whittaker, R.; McRobbie, H.; Bullen, C.; Rodgers, A.; Gu, Y. *Mobile phone-based interventions for smoking cessation*. Cochrane database syst. rev. **2016**, *4*.

- [55]. Chen, X.; Valdmanis, V.; Yu, T. *Productivity Growth in Chinese Medical Institutions during 2009-2018*. Sustainability **2020**, 12, 3080.
- [56]. Stiglitz, J.E.; Sen, A.; Fitoussi, J.P. *Mismeasuring our lives: Why GDP doesn't add up*; The New Press: New York, NY, USA, 2010.
- [57]. Fioramonti, L. *Gross domestic problem: The politics behind the world's most powerful number*; Zed Books Ltd.: London, UK, 2014.
- [58]. Lee, M.; Yoon, K. Effects of the Health Promotion Programs on Happiness. Sustainability **2020**, 12, 528.
- [59]. Cooke, M.; Irby, D.M.; O'Brien, B.C. *Educating physicians: a call for reform of medical school and residency*; John Wiley & Sons: San Francisco, CA, USA, 2010.
- [60]. Poroşnicu, C. *The Role of Education in Promoting Sustainable Development*. Sustainability **2023**, 15, 3330.
- [61]. Sweeney, K.; Griffiths, F. *Complexity and healthcare: an introduction*; Radcliffe medical press: Abingdon, UK, 2002.
- [62]. de Savigny, D.; Adam, T., Eds. *Systems thinking for health systems strengthening*; World Health Organization: Geneva, Switzerland, 2009.
- [63]. Frenk, J.; Chen, L.; Bhutta, Z.A.; Cohen, J.; Crisp, N.; Evans, T.; Zurayk, H. *Health professionals for a new century: transforming education to strengthen health systems in an interdependent world*. The Lancet **2010**, 376, 1923-1958.
- [64]. Sturmberg, J.P.; Martin, C.M. *Handbook of systems and complexity in health*; Springer Science & Business Media: New York, NY, USA, 2013.
- [65]. Tucker, A.; Zsurka, G.; Wallace, I. *Machine learning and systems biology in medicine and health*; Springer: London, UK, 2013.
- [66]. Marmot, M. *Social determinants of health inequalities*. The Lancet **2005**, 365, 1099-1104.
- [67]. Braithwaite, J.; Runciman, W.B.; Merry, A.F. *Towards safer, better healthcare: harnessing the natural properties of complex adaptive systems*. BMJ Qual. Saf. **2009**, 18, 37-41.
- [68]. Kim, C.S.; Spahlinger, D.A.; Bria, W.F.; Bilimoria, K.Y. *A systems approach to improving the value of inpatient care*. Am. J. Med. **2006**, 119, 600-605.
- [69]. Yoon, K.; Park, G.; Lee, M. *Effects of the Health Promotion Programs on Happiness*. Sustainability **2020**, 12, 528.
- [70]. Victora, C.G.; Habicht, J.P.; Bryce, J. *Evidence-based public health: moving beyond randomized trials*. Am. J. Public Health **2004**, 94, 400-405.
- [71]. Peters, D.H.; Adam, T.; Alonge, O.; Agyepong, I.A.; Tran, N. *Implementation research: what it is and how to do it*. BMJ **2013**, 347.
- [72]. Cargo, M.; Mercer, S.L. *The value and challenges of participatory research: strengthening its practice*. Annu. Rev. Public Health **2008**, 29, 325-350.
- [73]. Innes, J.E.; Booher, D.E. *Planning with complexity: An introduction to collaborative rationality for public policy*; Routledge: London, UK, 2010.
- [74]. Obermeyer, Z.; Powers, B.; Vogeli, C.; Mullainathan, S. *Dissecting racial bias in an algorithm used to manage the health of populations*. Science **2019**, 366, 447-453.
- [75]. Ji, Z.; Lee, N.; Frieske, R.; Yu, T.; Su, D.; Xu, Y.; Fung, P. *Survey of hallucination in natural language generation*. ACM Comput. Surv. **2023**, 55, 1-38.

- [76]. Bainbridge, L. *Ironies of automation*. Automatica **1983**, 19, 775-779.
- [77]. Mandelblatt, J.S.; Cronin, K.A.; Bailey, S.; Berry, D.A.; de Koning, H.J.; Draisma, G.; Feuer, E.J. *Effects of mammography screening under different screening schedules: model estimates of potential benefits and harms*. Ann. Intern. Med. **2009**, 151, 738-747.
- [78]. Forman, R.; Shah, S.; Jeurissen, P.; Jit, M.; Mossialos, E. *COVID-19 vaccine challenges: What have we learned?* Health Econ. Policy Law **2021**, 16, 385-396.
- [79]. Al-Shorbaji, N.; Hashmi, R. The role of digital health in the post-COVID-19 era. JMIR Med. Inform. **2021**, 9, e29234.
- [80]. Financial Conduct Authority. Regulatory Sandbox Lessons Learned Report; London, UK, 2017.
- [81]. Infocomm Media Development Authority of Singapore. AI Governance Framework; Singapore, 2020.
- [82]. Morley, J.; Machado, C.C.; Cowls, J. *The ethics of AI in health care: A mapping review*. Soc. Sci. Med. **2021**, 289, 114426.
- [83]. European Commission. Proposal for a Regulation on the European Health Data Space; Brussels, Belgium, 2022.
- [84]. Adadi, A.; Berrada, M. *Peeking inside the black-box: a survey on explainable artificial intelligence (XAI)*. IEEE access **2018**, 6, 52138-52160.
- [85]. Iliuță, M.-E.; Moisesescu, M.-A.; Caramihai, S.-I.; Cernian, A.; Pop, E.; Chiș, D.-I.; Mitulescu, T.-C. *Digital Twin Models for Personalised and Predictive Medicine in Ophthalmology*. Technologies **2024**, 12, 55.
- [86]. Min, L.; Yu, Z. *Intergenerational Information-Sharing Behavior During the COVID-19 Pandemic in China: From Protective Action Decision Model Perspective*. Sustainability **2025**, 17, 7263.
- [87]. Caramihai, S. I., Dumitrache, I., Moisesescu, M. A., & Sacala, I. S. (2022). *Decision Support Collaborative Platform for e-Health Integration in Smart Communities Context*. Procedia Computer Science, Volume 214, **2022**, 1152-1159.
- [88]. Al-Thaqeb, A.A.; Al-Salloum, K.A.; Al-Yahya, A.S.; Al-Turki, A.M.; Al-Otaibi, A.F. *The Effectiveness of Remote Patient Monitoring in Managing Chronic Diseases: A Systematic Review of Systematic Reviews*. Healthcare **2024**, 12, 697.
- [89]. Filippas, A.; Horton, J.J.; Manning, B.S. *Large Language Models as Simulated Economic Agents: What Can We Learn from Homo Silicus?* In Generative AI and Economic Research; University of Chicago Press: Chicago, IL, USA, **2024**; pp. 43-66.
- [90]. Deng, H.; Zhu, L.; Wang, X.; Zhang, N.; Tang, Y. *Renewal Strategies for Older Hospital-Adjacent Communities Based on Residential Satisfaction: A Case Study of Xiangya Hospital*. Sustainability **2025**, 17, 4458.