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INTELLIGENT METHODS AND SOFTWARE ALGORITHMS FOR INTENSIVE CARE. A COMPLEXITY SCIENCE APPROACH

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CONCEPTUAL LANDMARKS OF THE RESEARCH

Timeliness and importance of the problem addressed: The increasing complexity of intensive care medicine (ICM) underscores the urgent need for innovative approaches to enhance early diagnosis, prediction, and management of critical conditions like sepsis and epilepsy. These conditions, responsible for high ICU mortality and morbidity globally, demand timely interventions to improve patient outcomes. Sepsis, with a mortality rate of 20–50%, and epilepsy, affecting over 50 million people with up to 30% drug-resistant cases, exemplify dynamic, nonlinear systems where subtle pathophysiological changes often evade conventional monitoring tools. The rise of antimicrobial resistance and the unpredictability of epileptic seizures further amplify the need for predictive systems that can detect anomalies below the resolution of traditional methods. As of 2025, the integration of complexity science—a field adept at modeling emergent behaviors and nonlinear dynamics—into ICM remains underexplored, with only 0–3 annual PubMed papers linking it to critical care. This gap highlights the timeliness of developing intelligent methods that leverage complexity science, advanced modeling (agent-based, system dynamics, hybrid), machine learning (ML), and large language model (LLM)-based multi-agent systems. These tools promise to transform ICU decision-making by enabling early detection and personalized care, addressing the global healthcare burden (e.g., sepsis costs exceeding $20 billion annually in the U.S.). The Republic of Moldova, with resource-constrained healthcare systems, stands to benefit significantly from such innovations, enhancing clinical precision and research capacity. This research is critical to bridge the gap between theoretical advancements and practical ICU applications, aligning with global trends toward precision medicine and data-driven healthcare.

The aim of the study is to develop innovative intelligent methods, algorithms, and software applications for intensive care medicine, grounded in a complexity science framework. This approach seeks to enhance early diagnosis, prediction, and management of critical conditions such as sepsis and epileptic seizures in critically ill patients. By integrating concepts like nonlinearity, emergence, and adaptation with advanced modeling techniques (agent-based, system dynamics, and hybrid), machine learning, representation learning, algorithmic complexity estimation, and large language model-based multi-agent systems, the research aims to bridge theoretical insights from complexity science with practical tools for improved clinical decision-making, personalized care, and resource optimization in intensive care units.

Research objectives:

1. Establishing a complexity science framework: Develop a conceptual foundation using complexity science principles to analyze intensive care systems, distinguishing it from systems theory and applying it to model critical states in sepsis and epilepsy.
2. Evaluation of modeling techniques: Investigate agent-based modeling to simulate emergent behaviors in physiological processes, such as cardiogenic pulmonary edema, for decision support in intensive care.

3. Exploration of system dynamics modeling: Examine system dynamics approaches to model aggregate circulatory and feedback dynamics, including myocardial infarction scenarios, for efficient simulations in critical care.
4. Development of hybrid modeling methods: Integrate agent-based and system dynamics modeling into hybrid frameworks for multiscale simulations, such as maternal-placental-fetal oxygen delivery, to address monitoring gaps in obstetric intensive care.
5. Identification and analysis of large datasets: Identify and perform exploratory analysis on comprehensive datasets for sepsis prediction and epilepsy research, including EEG recordings and physiological time series, to support AI system development.
6. Data processing and imputation: Develop advanced imputation, transformation, and preprocessing methods, incorporating algorithmic complexity estimation via block decomposition, to handle missing values and prepare data for machine learning applications.
7. Integration of representation learning: Apply representation learning techniques, including natural language processing models like Word2Vec and BERT, to transform physiological data (e.g., EEG signals) into actionable representations for improved prediction accuracy.
8. Exploration of machine learning models: Investigate various machine learning algorithms, enhanced by algorithmic complexity metrics, to boost diagnostic and prognostic performance in sepsis and epileptic seizure prediction.
9. Incorporation of large language models: Explore large language models with retrieval-augmented generation and multi-agent systems to enhance sepsis management, guideline adherence, and clinical decision-making in intensive care.
10. Development of software tools: Create integrated software applications for early sepsis prediction, EEG analysis, and multi-agent sepsis management, validated for clinical and research environments to facilitate personalized interventions.

Research hypothesis:

In intensive care, conventional monitoring tools often overlook subtle pathophysiological changes below their resolution threshold, delaying early diagnosis and prediction of critical conditions like sepsis and epilepsy. Grounded in complexity science—emphasizing nonlinearity, emergence, adaptation, and algorithmic complexity (e.g., Kolmogorov-Chaitin via block decomposition)—this research hypothesizes that integrating advanced modeling (agent-based, system dynamics, hybrid), data imputation, representation learning (e.g., NLP on physiological signals), machine learning, and LLM-based multi-agent systems will enable detection of these changes, yielding prediction systems with performance equal to or surpassing literature benchmarks (e.g., AUC >0.95 for sepsis). Resulting software tools for EEG analysis (research) and sepsis management (clinical) will bolster decision-making, personalized care, and outcomes in Moldovan healthcare settings.

Scientific novelty and originality: The thesis introduces a novel integration of complexity science with intensive care, leveraging nonlinearity and emergence to address diagnostic gaps. It pioneers the use of Kolmogorov-Chaitin complexity (KCC) via block decomposition for preprocessing biomedical signals, enhancing pattern detection in non-stationary data. The hybrid modeling framework combining agent-based and system dynamics approaches for multiscale simulations, such as fetal oxygen delivery, is innovative. Additionally, the application of large language models with retrieval-augmented generation and multi-agent systems for sepsis management represents a cutting-edge approach to real-time clinical decision-making, distinguishing this work from traditional reductionist methods.

The results obtained that contribute to the solution of a significant scientific problem. The research establishes a complexity science framework, successfully modeling physiological processes like cardiogenic pulmonary edema and fetal oxygen delivery using agent-based, system dynamics, and hybrid methods. Advanced preprocessing, including KCC estimation and imputation, transforms EEG and sepsis data for machine learning, achieving high predictive performance. Software tools like ISAAC-EEG-BDM-NLP and ISAAC Sepsis Expert enable early detection and management, with large language model-based multi-agent systems improving sepsis guideline adherence.

The theoretical significance of the research: The thesis advances complexity science by formalizing its application to intensive care, integrating it with modeling, machine learning, and AI. It contributes a novel complexity data science paradigm, bridging systems theory and data-driven approaches. The use of KCC for biomedical signal analysis offers a theoretical leap in capturing emergent dynamics, while hybrid modeling and multi-agent systems provide new frameworks for understanding multiscale ICU phenomena, enriching transdisciplinary research.

The applicative value of the work: The developed tools offer practical solutions for early sepsis prediction and management, and EEG-based seizure forecasting, enhancing clinical decision-making and personalized care. These applications are scalable for resource-limited settings like Moldova, supporting ICU triage, intervention planning, and medical education through interactive simulations.

Approval of scientific results: Results had been presented as 27 reports at 21 scientific forums, including the 7th International Conference on Nanotechnologies and Biomedical Engineering, ICNBME 2025; The Anniversary Congress: 80 Years of Innovation in Health and Medical Education Nicolae Testemițanu State University of Medicine and Pharmacy; 50th Anniversary Congress of SARRM: A Landmark in Anesthesiology and Intensive Care, 7th International Conference on Intelligent and Fuzzy Systems, INFUS 2025; International Scientific Conference "Cells and Tissues Transplantation. Actualities and Perspectives. The 3rd Edition, 2025; the 13th International Conference on Electronics, Communications and Computing ECCO 2024; NASCA 23 conference, 2023; the AUTOMATA 2020 Conference, 2020; etc.

Publications regarding the thesis: The research resulted in 57 scientific works, with 31 as the sole author, 21 as the first author, and 12 publications in journals/editions with an impact factor.

Volume and structure of the thesis: The thesis comprises 275 pages and includes an introduction, 8 chapters, conclusions, a bibliography from 401 sources, 5 appendices, 89 figures, and 37 tables.

1. CONCEPTUAL FRAMEWORK—A COMPLEXITY SCIENCE APPROACH TO INTELLIGENT METHODS IN INTENSIVE CARE

Background

Complexity science (CS) has emerged as a transformative interdisciplinary field that seeks to understand the intricate behaviors of systems composed of numerous interacting components [1, 2]. Unlike traditional scientific paradigms that often rely on reductionism—breaking down phenomena into simpler parts—CS emphasizes the holistic nature of systems, where the whole exhibits properties that cannot be fully explained by analyzing individual elements in isolation. This approach is particularly pertinent to intensive care medicine, where patient conditions involve dynamic interactions among physiological processes, medical interventions, environmental factors, and even social elements within healthcare teams. This conceptual framework presents the origins, evolution, key principles, methodological underpinnings, and applications of CS, drawing contrasts with systems theory (ST) to highlight its unique contributions. It also explores the specific relevance of CS to healthcare and the role it plays in framing the research on intelligent methods and algorithms for intensive care.

Figure 1.1 presents the results of a PubMed search based on “complexity science” term (blue color bars) and its association with “intensive care“ (orange color bars) for the period 2000-2025.

One can observe the increasing trend for CS and the flat trend for the association “CS and intensive care,” ranging from 0 to 3 publications per year.

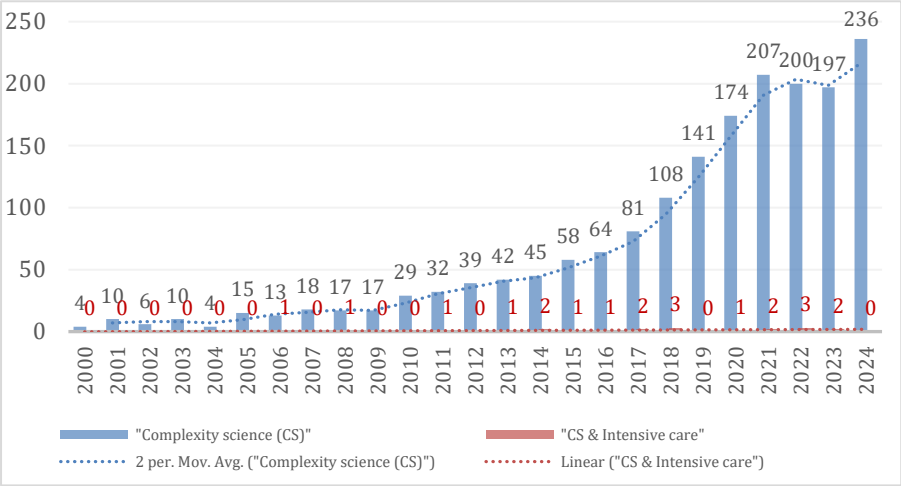

Figure 1.1. The count of publications in PubMed: blue – complexity science (exact match) and orange – in association with intensive care.

Historical Development of Complexity Science

The historical trajectory of CS can be traced back to the mid-20th century, with conceptual roots in philosophy and early scientific inquiry. Precursors include Henri Poincaré's work on nonlinear dynamics and the three-body problem, highlighting sensitivity to initial conditions central to chaos theory. Formal foundations solidified in the 1940s and 1950s with cybernetics by Norbert Wiener, introducing feedback loops, and Claude Shannon's information theory for quantifying uncertainty and entropy.

The 1960s brought chaos theory, with Edward Lorenz's "butterfly effect" challenging deterministic predictability. Ludwig von Bertalanffy's general systems theory influenced CS by advocating for open systems. In the 1970s, Ilya Prigogine explored dissipative structures and nonequilibrium thermodynamics, earning the Nobel Prize in Chemistry in 1977.

The Santa Fe Institute (SFI), founded in 1984 by scientists like George Cowan, Murray Gell-Mann, and Philip Anderson [2, 3], became a hub for interdisciplinary research. Key developments included Stuart Kauffman's self-organization in biological networks and John Holland's genetic algorithms. The 1980s and 1990s saw the rise of network theory, with Albert-László Barabási on scale-free networks.

In the 21st century, CS expanded with big data analytics in the 2000s, small-world networks by Duncan Watts and Steven Strogatz in the 2010s, and intersections with AI and ML in the 2020s, including pandemic modeling during COVID-19 [4]. As of 2025, advances include SFI symposia on emergence and conferences like CCS'25 on networks and biological systems.

The "2021 Map of the Complexity Sciences" by Brian Castellani and Lasse Gerrits [5] chronicles this evolution from cybernetics to AI integration, underscoring transdisciplinarity with influences from fractals by Benoit Mandelbrot to social systems by Niklas Luhmann.

In contrast, systems theory (ST), originating as General Systems Theory (GST) in the 1920s-1950s through Bertalanffy, emphasizes wholeness, hierarchies, and equilibrium against reductionism. ST is broader, encompassing all systems, while CS focuses on complex adaptive systems (CAS) with nonlinearity [6]. ST models closed loops for stability; CS explores perturbations leading to novel states.

Key Concepts in Complexity Science

At the core of CS are concepts like nonlinearity, where small changes cascade into large effects [1, 6]; emergence, properties transcending components (e.g., flocking in birds); self-organization, spontaneous order from local rules; adaptation in CAS at the "edge of chaos" [1]; feedback loops; networks revealing robustness; and universality in patterns like fractals.

In healthcare, these frame diseases as emergent [7]. Sepsis involves nonlinear cascades, epidemics self-organize through networks. 2025 insights emphasize CS in AI governance.

CS and ST share a holistic, interdisciplinary ethos but diverge. ST prioritizes structural stability, hierarchies, and equilibrium via feedback and boundaries; CS stresses nonlinearity, emergence, self-organization, and evolution in nonequilibrium

states [6]. Methodologically, ST uses qualitative and mathematical models; CS employs simulations like agent-based modeling (ABM) [8]. Applications: ST in engineering for control; CS in ecology for adaptation.

Differences and Similarities with Systems Theory

Differences between systems theory and complexity science include: Focus (ST: structural stability and hierarchies; CS: dynamic adaptation and emergence); Core Concepts (ST: homeostasis, equilibrium, closed systems; CS: nonlinearity, self-organization, edge of chaos); Methodological Approach (ST: qualitative descriptions, linear models; CS: computational simulations, ABM, network analysis); Handling of Uncertainty (ST: predictability through control; CS: embraces chaos and unpredictability); Applications (ST: engineering, organizational management; CS: biology, social sciences, healthcare dynamics).

Similarities include: Anti-reductionism (both reject breaking systems into isolated parts); Emphasis on Interconnections (focus on relationships and wholes); Interdisciplinarity (draw from multiple fields); Emergence (properties arising from interactions); Feedback Mechanisms (loops for system behavior).

Applications of Complexity Science in General and in Healthcare

CS applies across physics, economics, and biology. In healthcare, it models systems as CAS, addressing nonlinearity in patient responses. Scoping reviews show CS in health services [7], using self-organization for evidence implementation. In 2025, CS informs AI in diagnostics and policy. For intensive care, it analyzes sepsis as chaotic inflammation or organ failures. Implementation science uses CS for dynamic interventions.

CS grounds this thesis by viewing intensive care as CAS, informing models for sepsis and epilepsy. It guides preprocessing with Kolmogorov-Chaitin complexity and integrates ML for prognosis [9, 10].

Interactions of Complexity Science with Modeling: Agent-Based Modeling, System Dynamics Modeling, and Hybrid Approaches

CS interfaces with modeling to simulate CAS. Agent-based modeling (ABM) simulates autonomous agents for emergence. In intensive care, ABM models COVID-19 ICUs or antimicrobial strategies. Thesis Chapter 2 applies ABM to cardiogenic pulmonary edema.

System dynamics modeling (SDM) uses stocks, flows, and loops for aggregate dynamics [8]. In healthcare, SDM plans interventions or workforce. Chapter 3 uses SDM for circulatory systems.

Hybrid modeling combines macro and micro views [8]. Chapter 4 models fetal oxygen delivery. These illustrate CS's utility: ABM for micro-level interactions in ICUs; SDM for system-level stability; hybrids for multiscale analyses like fetal monitoring.

Interactions Between Complexity Science and Machine Learning: A Unifying Perspective

The interplay between CS and machine learning (ML) is bidirectional. CS frameworks understand emergent properties in ML models; ML analyzes complex systems. Unification recognizes extracting regularities from high-dimensional phenomena, with CS emphasizing coarse-graining and ML encoding dependencies.

Interactions handle nonlinearity; Kolmogorov-Chaitin complexity quantifies information. Chapters 5-7 leverage this for diagnosis.

Argumentation for the Selection of Sepsis and Epilepsy as Pathological States in Intensive Care

Sepsis and epilepsy are selected due to their ICU prevalence, CS alignment, and utility for intelligent methods. The main arguments in favor of this selection are:

a. They impose burdens: Sepsis leads ICU admissions with high costs (>US$32,000/patient) and mortality (10-46%) [11]. Epilepsy, especially status epilepticus, involves high morbidity and costs [12].
b. They exemplify critical states in CS—systems at phase transitions with power-laws and adaptability. Sepsis shows nonlinear escalation to organ failure; epilepsy reflects neuronal criticality in seizures.
c. Large datasets available: PhysioNet for sepsis (40,000+ cases) [13]; epilepsy challenges with 8,000+ EEG clips [14].
d. Suitable for Kolmogorov-Chaitin complexity via block decomposition method (BDM), quantifying randomness in time series for predictive modeling [15]. Thesis modeling chapters also focus on critical states, with KCC pivotal.

Complexity Data Science: Reframing Intelligent Methods in Intensive Care

Complexity data science (CDS) integrates CS with data science (DS) [16], a spin-off from digital twins (DT) for simulation and optimization. CDS addresses high-dimensional data in CAS, emphasizing generative processes like self-organization and nonlinearity.

Building on CS evolution, CDS extends DT from engineering to healthcare for personalized modeling. It quantifies CS concepts via data techniques, detecting universality in trends (Figure 1.1) and feedback in ICU data.

CDS sharpens distinctions with ST: dynamic data flows vs. structural hierarchies. Synergies amplify anti-reductionism and interdisciplinarity, integrating CS with DS methods.

In modeling, CDS views models as DTs, uncovering vulnerabilities. With ML, in this research it unifies coarse-graining, using KCC/BDM for ICU predictions in sepsis and epilepsy.

CDS extends to thesis modeling, viewing pathologies as data-generating CAS. It reframes the framework as data-centric CS evolution, bridging theory and practice for ICU innovations.

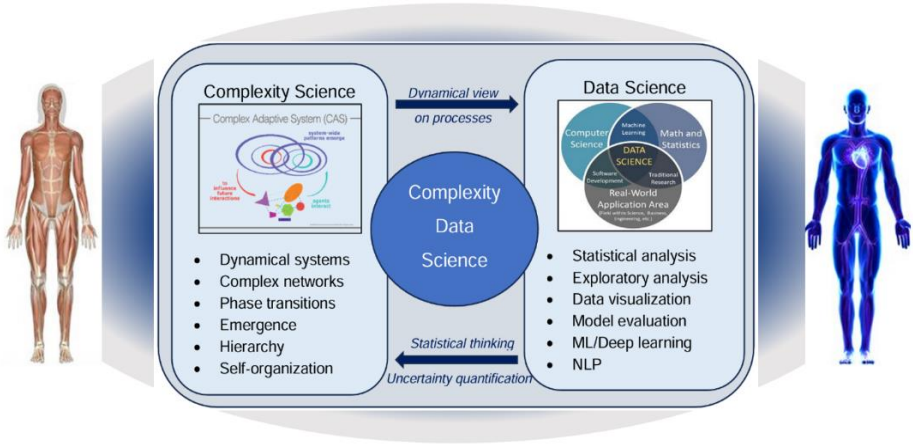

Figure 1.2. A holistic curriculum for complexity data science. Based on [16].

2. AGENT-BASED MODELING IN INTENSIVE CARE: A COMPLEXITY SCIENCE APPROACH

Complexity Science and Agent-Based Modeling in Medicine

Complexity science (CS) offers a framework for comprehending systems characterized by intricate, nonlinear interactions, emergent behaviors, adaptation, and self-organization, in contrast to reductionist methodologies that fragment components. CS emphasizes holistic interplay, making it ideal for medical research where physiological and clinical systems exhibit dynamic complexity [17]. In intensive care, where patients face life-threatening conditions requiring rapid interventions, CS navigates unpredictability and emergent phenomena. Agent-based modeling (ABM), a CS-based computational method, simulates autonomous agents to reveal system-level behaviors, offering a robust tool for intensive care scenarios [18]. CS emerged in the late 20th century through interdisciplinary efforts at the Santa Fe Institute, where pioneers like Murray Gell-Mann, John H. Holland, and Stuart Kauffman defined complex adaptive systems (CAS). CAS feature nonlinearity, where small input changes cause disproportionate outcomes, and emergence, where system properties arise from local interactions not predictable from isolated components. In medicine, CAS manifest in physiological processes like immune responses or cardiovascular dynamics and clinical systems like hospital workflows [19]. In intensive care, CS is vital for conditions like sepsis, acute respiratory distress syndrome (ARDS), or cardiogenic pulmonary edema (CPE), which involve nonlinear interactions across cardiovascular, respiratory, and immune systems, leading to emergent outcomes like organ failure [20]. For example, sepsis triggers unpredictable inflammatory cascades, a hallmark of nonlinearity. CS models these interactions, offering insights into stabilizing interventions, unlike system theory's focus on structural stability and feedback loops (e.g., blood pressure regulation) [21]. CS

integrates biology, physics, mathematics, and computation, aligning with intensive care's multifaceted challenges, including physiological and logistical complexities. ABM models agents—cells, molecules, patients, or clinicians—following rules in a virtual environment, generating emergent behaviors [22]. Unlike differential equation models, ABM captures heterogeneity, spatial dynamics, and stochasticity, critical in intensive care where patient-specific factors and timing matter. Early ABM applications include Epstein's epidemiology models and An's cellular simulations [23, 24]. In intensive care, ABM simulates CPE fluid dynamics or operational aspects like patient flow and ventilator allocation. Applications span physiological modeling (e.g., sepsis cytokine interactions [20]), clinical interventions (e.g., vasopressor effects), and operations (e.g., triage optimization). ABM's visual simulations enhance medical education, letting trainees explore scenarios like CPE parameter changes [25]. Challenges include computational scalability and validation against noisy clinical data. Advances in tools like NetLogo and data integration from electronic health records or sensors offer opportunities for personalized predictions and accessible models [26].

Mathematical Formalism of Agent-Based Modeling

ABM simulates complex systems by modeling individual agents and interactions, capturing emergent phenomena unlike aggregate differential equation models [1]. Core components include: Agent States: Defined by a vector with spatial coordinates, physiological properties (e.g., pressure), and time. Interaction Rules: Probabilistic, e.g., water molecule extravasation probability $Q = k(HP - OP)$ in pulmonary edema. Environment: A grid or space with properties like permeability. Time Evolution: System state updates iteratively:

$$S_t = f(S_t, N_t, E_t, R), \tag{2.1}$$

where S is the system state, N are neighbors, E is the environment, and R are rules.

Key equations:

Agent Update:

$$S_{i_{t+1}} = g\left(S_{i_t}, N_{i_t}, E_t, R\right) \tag{2.2}$$

e.g., the water molecule's position updates with pressure.

Emergent Behavior:

$$E = \sum_{i \in A} v_i, \tag{2.3}$$

e.g., total extravascular water.

Environmental Dynamics:

$$W_{t+1} = W_t + \sum \Delta v_i - D, \tag{2.4}$$

where D is lymph drainage.

Stochastic Elements: Random walks model variability [19].

In intensive care, ABM can implement the Starling equation$Q = L_s S([P_c - P_i] - \delta[\pi_p - \pi_i])$, at the agent level for CPE, which enables spatial and stochastic modeling. Validation uses statistical methods like ANOVA to assess parameter sensitivity, ensuring clinical alignment [27].

Application to Intensive Care

ABM's formalism suits intensive care for modeling dynamic processes like CPE fluid shifts via the Starling equation, capturing spatial heterogeneity and stochasticity. It simulates physiological processes, clinical interventions, and operational dynamics, offering insights into disease progression, treatment effects, and resource management. ABM's integration of spatial and temporal dynamics supports simulations from pathophysiology to decision-making, validated by statistical analysis [27].

Agent-Based Modeling of Cardiogenic Pulmonary Edema: Model Description

This NetLogo ABM simulates cardiogenic pulmonary edema (CPE), where fluid accumulates in lungs due to elevated hydrostatic pressure (HP) and altered oncotic pressure (OP) [27]. The model includes three zones: Capillary (vascular compartment), Alveolar-Capillary Membrane (ACM) (400 ml capacity, fluid extravasation site), and Alveoli (flooding indicates pathology). Agents: Water molecules (extravasate by HP/OP), Macromolecules (influence OP), Erythrocytes (visual, future extensions like oxygenation). Scenarios: Normal (HP=18 mmHg, OP=25 mmHg, lymph drainage clears water) and CPE (HP=21–24 mmHg, OP=24 mmHg, exceeds 400 ml, floods). Outputs: Plots track drainage and water vs. 400-ml threshold. Interface: Scenario chooser, HP/OP sliders. Figure 2.1 shows the Normal scenario interface.

The scenario chooser (top left) selects the simulation mode. Sliders below set HP and OP. The upper plot shows lymphatic drainage (blue line), and the lower plot tracks extravascular water (green line) against the 400-ml threshold (red line). The right window depicts alveoli (white), ACM (grey), and capillary (red/pink) with agents: water molecules (blue), macromolecules (yellow), and erythrocytes (red).

The simplified Starling equation governs fluid flux: $Q = k(HP - OP)$. Dynamics: Water moves right in capillary, extravasates if HP > OP; lymph drains below 400 ml. Setup: Clear NetLogo world, color patches (white alveoli, grey ACM, red capillary), import alveoli image, spawn agents. Go procedure: Move agents, extravasate water, drain ACM, update plots. NetLogo 6.2 supports interactivity; demo/experimental versions are online [24, 25].

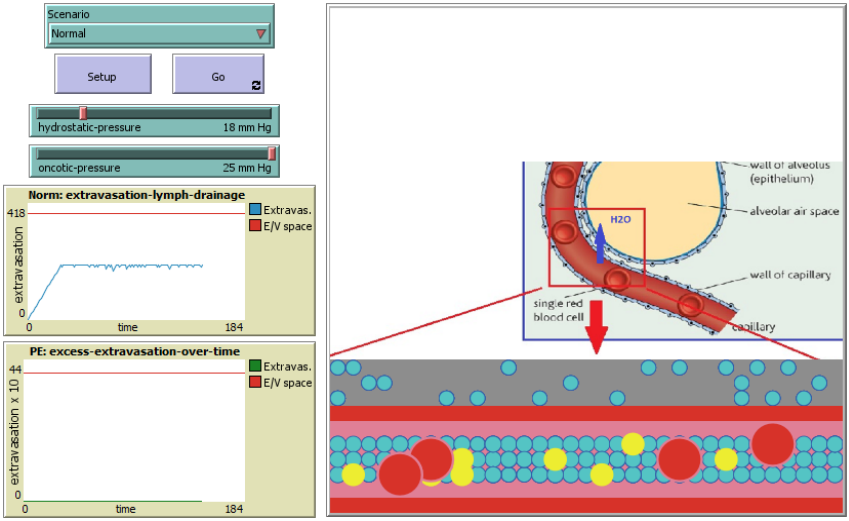

Figure 2.1. General view of the model interface in the "Normal" scenario.

Results of the Cardiogenic Pulmonary Edema Model

Simulations tested Normal (HP=18 mmHg, OP=25 mmHg) and CPE (HP=21–24 mmHg, OP=24 mmHg) scenarios, with 400-ml capacity. Normal: Water peaks at ~200 ml, cleared below threshold; plots stable [25]. CPE: Rapid flooding by 10-30 ticks; Figure 2.2 (HP=23 mmHg) shows water exceeding threshold.

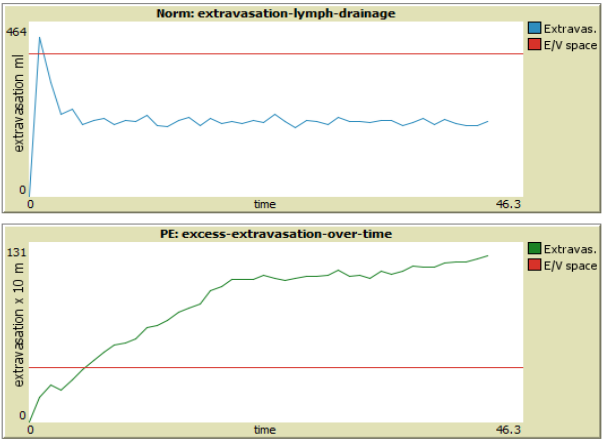

Figure 2.2. Plot view in the "Cardiogenic-Pulmonary-Edema" scenario. The upper plot shows lymphatic drainage (blue line), and the lower plot tracks extravascular water (green line) exceeding the 400-ml threshold (red line).

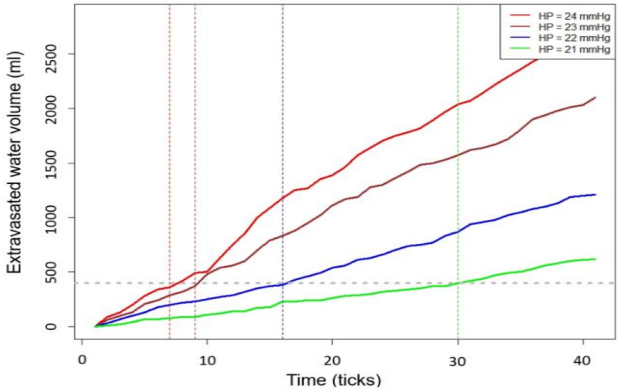

Figure 2.3. Dynamics of extravascular water volume over time for varying HP levels. The 400-ml threshold (grey dotted line) is exceeded sooner at higher HP, indicating increased edema severity.

Sensitivity analysis varied HP (21-24 mmHg) using BehaviorSpace; higher HP causes earlier flooding (Figure 2.3). ANOVA ($p<0.05$) confirms HP's impact. Insights: Aligns with PCWP>18 mmHg risk; educational for visualizing parameter shifts; clinical for intervention thresholds [27]. Models available online [24, 25].

Cardiogenic Pulmonary Edema Model: Clinical and Educational Implications, Limitations, and Future Work

The ABM visualizes HP/OP interplay in CPE, mirroring PCWP rise (>18 mmHg) from heart failure [27]. Clinically, it predicts onset, aiding interventions like diuretics lowering HP. Integration with sensors or health records enables real-time forecasts, enhancing ICU triage vs. static models. Educationally, interactive scenarios teach Starling dynamics; model plots show flooding shifts, outperforming diagrams. Simple yet extensible, it suits novices and advanced learners; open-source NetLogo adapts to curricula. Limitations: assumes constant permeability, omits interstitials, oxygenation, and ARDS; needs clinical validation [27]. Future work: adding O_2 agents, variable permeability, treatments, and data integration for personalization. Collaboration with clinicians and data scientists can enhance ICU utility.

3. SYSTEM DYNAMICS MODELING IN COMPLEXITY SCIENCE: APPLICATIONS TO INTENSIVE CARE MEDICINE WITH A FOCUS ON THE HUMAN CIRCULATORY SYSTEM

Intersection of Complexity Science and System Theory in Medicine, Particularly Intensive Care

Complexity science (CS) and system theory (ST) have transformed medicine, moving beyond reductionism to address holistic interactions in intensive care units (ICUs). CS views biological and healthcare systems as complex adaptive systems (CAS) with nonlinear dynamics, emergence, adaptation, and self-organization [28].

In ICUs, this applies to conditions like sepsis, where small perturbations amplify through feedback loops into organ failure [29]. The ICU itself is a CAS involving patients, providers, technology, and resources [30].

ST complements CS with frameworks for feedback loops, boundaries, and exchanges. In ICUs, it models interactions like ventilator settings in ARDS. Integrating CS and ST uses metrics like entropy for early deterioration detection [7].

Modeling paradigms include agent-based modeling (ABM) and system dynamics modeling (SDM). ABM simulates bottom-up emergence with individual agents, suitable for ICU staffing or immune responses. SDM, top-down and aggregate, uses stocks, flows, and loops for continuous processes, easier calibration, and visualization [31]. In ICUs, SDM aids resource allocation and physiological modeling [30].

Lumped parameters models (LPMs) in SDM abstract systems into compartments, using electrical analogs for hemodynamics [32]. Digital twins create virtual replicas for personalized predictions in ICUs, integrating CS for adaptation [33].

General Mathematical Formalism Behind System Dynamics Modeling

System dynamics modeling (SDM) uses ordinary differential equations (ODEs) to simulate systems with feedback, delays, and nonlinearities [34].

Stocks evolve via

$$\frac{dS}{dt} = \text{Inflow} - \text{Outflow}, \tag{3.1}$$

integrated as: $S_t = S_0 + \int_0^t (Inflow - Outflow)dt$.

Positive feedback, like population (P) growth, is:

$$\frac{dP}{dt} = rP, \tag{3.2}$$

solving to $P_t = P_0 e^{rt}$.

Negative feedback stabilizes, e.g.:

$$\frac{dT}{dt} = -k(T - T_{set}). \tag{3.3}$$

State-space form for multivariable systems:

$$\dot{x} = Ax + Bu, \qquad \dot{y} = Cx + Du. \tag{3.4 \& 3.5}$$

Nonlinearities appear in models like Lotka-Volterra:

$$\frac{dx}{dt} = \alpha x - \beta xy, \qquad \frac{dy}{dt} = \delta xy - \gamma y, \tag{3.6 \& 3.7}$$

all solved numerically via Euler or Runge-Kutta methods.

The circulatory system exemplifies SDM. Stocks represent blood volumes; flows denote transfers. Feedback includes positive (sympathetic stimulation) and negative (baroreceptor reflex).

Stock-flow equations:

$$\frac{dV}{dt} = F_{in} - F_{out}, \tag{3.8}$$

where V is volume and F denotes flow.

Cardiac output:

$$CO = HR \times SV, \tag{3.9}$$

where HR is heart rate and SV is stroke volume.

Blood pressure:

$$BP = CO \times TPR, \tag{3.10}$$

where CO is cardiac output and TPR is total peripheral resistance.

Baroreceptor adjustments:

$$\Delta HR = f(BP - BP_{set}) \tag{3.11}$$

Lumped parameter models (LPMs) divide into compartments for hemodynamics. SDM can simulate pathologies like myocardial infarction (MI) [35], testing interventions and personalizing predictions. Benefits include visualizing interactions, educational tools, and decision support.

Integrating SDM with Real-Time Data and Model Development for the Circulatory System

Integrating SDM with real-time data enhances accuracy in ICUs. Data from wearables, sensors, and EHRs update parameters via ML algorithms like neural networks.

Techniques include acquisition (HR, BP, ECG), processing (Kalman filtering), and adaptation (Bayesian updating). Infrastructure uses cloud platforms (AWS) and APIs for interoperability.

Feedback provides dashboards, alerts for hypotension, and personalized adjustments like vasopressors. Challenges include privacy (HIPAA) [36], validation, and training.

Models developed within this research in NetLogo [35, 37, 38] feature six compartments, over 30 parameters, and equations as follows:

1. Volume (ventricular, arterial or venous segments):

$$\frac{dV_{c_i}}{dt} = \frac{\left(P_{c_{i-1}} - P_{c_i}\right)}{R_1} - \frac{\left(P_{c_i} - P_{c_{i+1}}\right)}{R_2}, \tag{3.12}$$

where V is volume, P is pressure and R is resistance. This is applied to every three formally consecutive compartments (e.g., pulmonary vines, left ventricle, and aorta) and c_{i-1}, c_i, c_{i+1} denote these compartments, and R_1 and R_2 are resistances between the compartments.

2. Pressure (vascular):

$$P_{c_i} = E_{c_i} \times V_{c_i}, \tag{3.13}$$

where E is elastance, V is volume and c_i denotes the respective compartment (i.e., vascular segment).

3. Ventricular pressure:

$$P_v = tve \times E_{es_v} \times \left(V_v - V_{d_v}\right) + (1 - tve) \times P0_v \times \left(exp\left(\lambda_v(V_v - V0_v)\right) - 1\right), \tag{3.14}$$

where $tve = e^{-80\times(time-0.27)^2}$ represents time-varying elastance, E_{es_v} is end-systolic elastance, V_v is left ventricle volume, V_{d_v} is unstressed volume, $P0_v$ is zero-volume pressure, λ_v is the curvature of end-diastolic pressure-volume relationship, and $V0_v$ denotes zero-pressure volume.

Figure 3.1 illustrates the system dynamics scheme for the last version of the model, featuring six compartments (stocks) representing heart chambers and vascular segments, over 30 parameters (diamonds), influences (thin arrows), and flows (thick arrows). Capital letters point to a certain parameter: V – volume, E – elastance of different compartments of the system (for ventricles – end systolic elastance), Lambda – the curvature of the end-diastolic pressure-volume relationship function, V0 – zero-pressure volume and P0 – zero-volume pressure, P – pressure, F – flow, R – resistance, El – time-varying elastance, and HR – heart rate. Subscripts denote specific compartments of the circulatory system: ao – aorta, vc – vena cava, sys – systemic circulation, tc – tricuspid valve, rv – right ventricle, pa – pulmonary artery, pv – pulmonary veins, th – intrathoracic, mt – mitral valve.

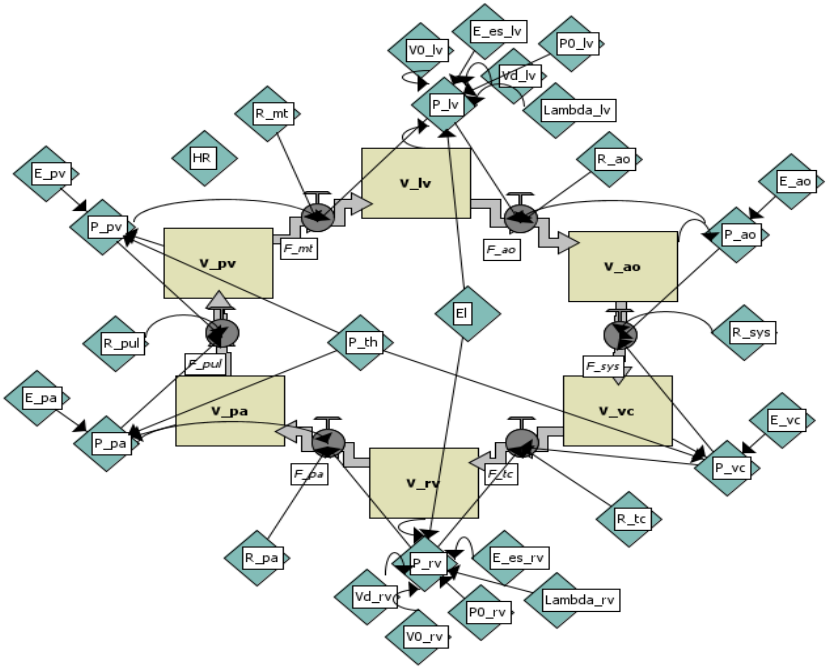

Figure 3.1. The system dynamic scheme for the created model. Squares represent stocks, and diamonds denote other parameters.

Initial conditions (for "Normal" scenario) are presented in Table 3.1.

Table 3.1. Initial conditions for the model

Name of the parameter	Notation	Value	Units
Systemic resistance	R_{sys}	1.0889	$mmHg \cdot s \cdot mL^{-1}$
Aorta elastance	E_{ao}	0.6913	$mmHg \cdot mL^{-1}$
Pulmonary artery resistance	R_{pulm}	0.018	$mmHg \cdot s \cdot mL^{-1}$
Intrathoracic pressure	P_{th}	-5	$mmHg$
Pulmonary artery elastance	E_{pa}	0.369	$mmHg \cdot mL^{-1}$
Mitral valve resistance	R_{mt}	0.0158	$mmHg \cdot s \cdot mL^{-1}$
Aorta resistance	R_{ao}	0.018	$mmHg \cdot s \cdot mL^{-1}$
Tricuspid valve resistance	R_{tc}	0.0237	$mmHg \cdot s \cdot mL^{-1}$
Pulmonary artery resistance	R_{pa}	0.0055	$mmHg \cdot s \cdot mL^{-1}$
End-systolic elastance of left ventricle	$E_{es_{lv}}$	2.8798	$mmHg \cdot mL^{-1}$

Table 3.1 (continued)

Unstressed left ventricle volume	V_{dl_v}	0	mL
Left ventricle zero-volume pressure	$P0_{lv}$	0.1203	$mmHg$
Curvature of end-diastolic pressure-volume relationship for left ventricle	λ_{lv}	0.033	mL^{-1}
Left ventricle zero-pressure volume	$V0_{lv}$	0	mL
End-systolic elastance of right ventricle	$E_{es_{rv}}$	0.5850	$mmHg \cdot mL^{-1}$
Unstressed right ventricle volume	V_{dr_v}	0	mL
Right ventricle zero-volume pressure	$P0_{rv}$	0.2157	$mmHg$
Curvature of end-diastolic pressure-volume relationship for right ventricle	λ_{rv}	0.023	mL^{-1}
Right ventricle zero-pressure volume	$V0_{rv}$	0	mL
Pulmonary veins elastance	E_{pv}	0.0073	$mmHg \cdot mL^{-1}$
Vena cava elastance	E_{vc}	0.0059	$mmHg \cdot mL^{-1}$
Aorta volume	V_{ao}	150	mL
Left ventricle volume	V_{lv}	120	mL
Pulmonary artery volume	V_{pa}	150	mL
Pulmonary veins volume	V_{pv}	300	mL
Right ventricle volume	V_{rv}	150	mL
Vena cava volume	V_{vc}	4150	mL
Heart rate	HR	70	beats per minute

Figure 3.2 shows the model's user interface, with sliders for parameter adjustment, monitors for real-time outputs (e.g., volumes, pressures, stroke volumes, cardiac output), and plots for temporal dynamics.

This approach supports circulatory simulations in health and disease, linking to digital twins.

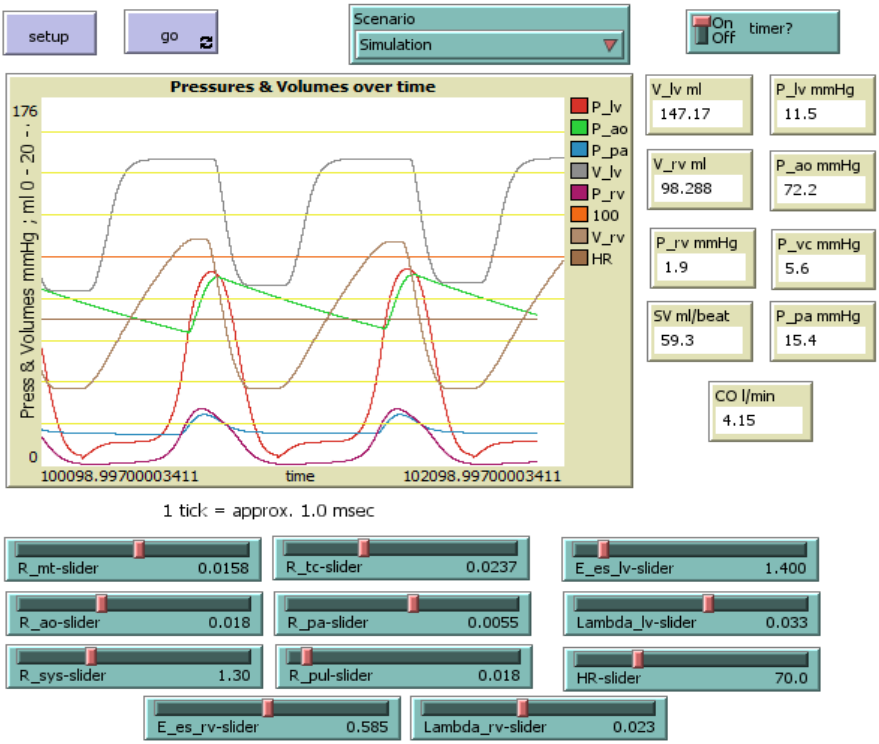

Figure 3.2. The appearance of the model's user interface. Capital letters denote different physiological parameters: V – volume, P – pressure, SV – stroke volume, CO – cardiac output, R – resistance, E – elastance, Lambda – a function influencing myocardial contractility, HR – heart rate. Subscripts denote specific compartments of the circulatory system (e.g., ao – aorta, lv – left ventricle, etc., as in Figure 3.1).

Simulation Results and Analysis in Myocardial Infarction

Preclinical simulations can generate data (Table 3.2) for normal-to-MI transitions.

Table 3.2. A small portion of the simulation results.

Left ventricle pressure (mm Hg)	Left ventricle output (L/min)	Right ventricle output (L/min)	Right ventricle volume (mL)	Aortic pressure (mm Hg)	Vena Cava pressure (mm Hg)
69.24	4.14	4.14	96.68	91.25	4.81

Table 3.2 (continued)

70.32	4.14	4.14	96.54	91.20	4.81
71.42	4.14	4.14	96.36	91.16	4.81
72.52	4.14	4.14	96.13	91.11	4.81
73.65	4.14	4.14	95.87	91.07	4.81
74.78	4.14	4.14	95.58	91.02	4.81
75.93	4.14	4.14	95.26	90.97	4.81
77.09	4.14	4.14	94.92	90.93	4.81
78.26	4.14	4.14	94.54	90.88	4.82
79.45	4.14	4.14	94.15	90.84	4.82

These values align with clinical parameters, facilitating integration into decision-support systems. Figure 3.3 depicts pressure-volume (PV) loops for a simulated MI patient, showing shrinkage in the left ventricle (green) and right ventricle (yellow), indicative of impaired filling and ejection due to infarct.

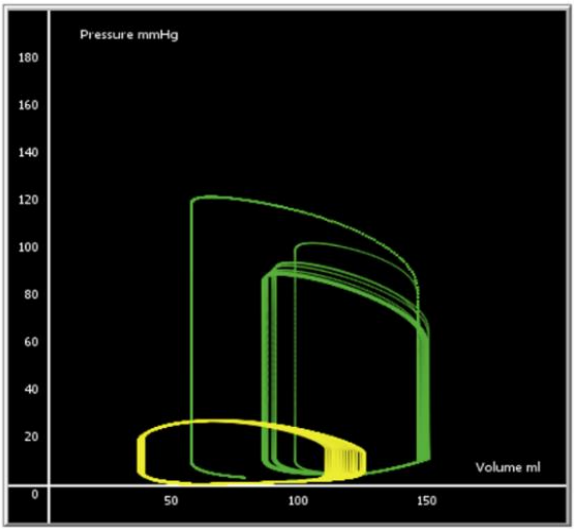

Figure 3.3. The pressure-volume loop in a patient with a simulated myocardial infarction. Green color denotes left ventricle and yellow color – right ventricle.

For an integrative evaluation of the system dynamics, in this research the Kolmogorov-Chaitin complexity (KCC) is used. As depicted in Figure 3.4, KCC drops after MI, signaling reduced dynamics.

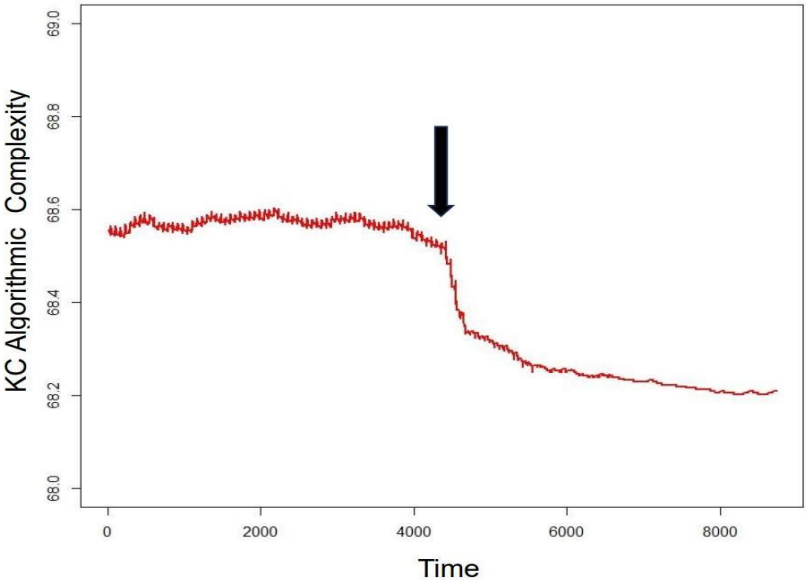

Figure 3.4. Kolmogorov-Chaitin complexity over time for a simulated case of myocardial infarction. The black arrow denotes the occurrence of myocardial infarction.

Discussion and Future Directions for SDM in Circulatory System Modeling

Advancing from three-compartment models [37], this granular version enables more detailed simulations. NetLogo BehaviorSpace can be used for generating scalable data for clinical integration.

Future development will include real-time acquisition, ML processing, decision support, and privacy compliance.

SDM can elucidate MI mechanisms for personalized ICU care [39]. Challenges include complexity and validation; AI synergies can enhance precision. Directions for future development are to be focused on multisystem extensions and clinical trials.

4. HYBRID MODELING APPROACHES IN INTENSIVE CARE MEDICINE: INTEGRATING SYSTEM DYNAMICS AND AGENT-BASED MODELING FOR ENHANCED PHYSIOLOGICAL SIMULATIONS

Hybrid Modeling in Medicine and Intensive Care

Hybrid modeling, combining system dynamics modeling (SDM) and agent-based modeling (ABM), has revolutionized intensive care medicine (ICM) by addressing complex physiological simulations. SDM employs feedback loops and differential equations to model macro-level flows, such as blood circulation or resource allocation, while ABM simulates micro-level interactions of autonomous agents, capturing emergent behaviors like cellular responses or individual patient

variability. This integration overcomes limitations of single methods: SDM may oversimplify emergent phenomena, while ABM can be computationally intensive without macro-level constraints. In ICM, hybrids model multifaceted interactions between physiological systems, medical interventions, and environmental factors, enabling predictive analytics for personalized care, such as in sepsis or ventilator management.

Originating in the early 2000s with applications in epidemiology, hybrid models expanded to acute care, simulating organ system failures. SDM handles fluid dynamics and metabolic rates, while ABM models cellular inflammation, enabling multiscale predictions in dynamic ICU settings. For instance, in cardiovascular ICM, SDM can simulate blood pressure regulation, while ABM captures endothelial cell behaviors, enhancing shock state predictions. Visualization is a key benefit, with ABM's spatial representations making complex processes, like alveolar recruitment in ARDS, accessible to clinicians and educators.

Challenges include computational complexity, as synchronizing SDM's continuous time steps with ABM's discrete events requires advanced platforms like AnyLogic or NetLogo [40]. Validation is difficult due to limited micro-level data in ICM, amplifying parameter uncertainty. Sensitivity analysis is essential, but integrating SDM stock-flow diagrams with ABM rules demands custom algorithms [41]. Despite these, hybrids can excel in real-time monitoring, such as combining SDM hemodynamics with ABM immune dynamics in sepsis, improving multi-organ dysfunction predictions. In pandemics, they model bed occupancy (SDM) and contagion risks (ABM), informing triage. Data integration from EHRs supports SDM but lacks micro-level ABM inputs, requiring imputation that risks bias.

Hybrids can facilitate scenario testing in ICM, where trials are frequently impractical, particularly in maternal-fetal care, by simulating oxygen transfer through SDM bulk flows and ABM placental exchanges. As the number of agents grows, scalability problems arise, which require high-performance computing. Ethical limits on fetal data mean that researchers have to use animal or historical datasets [42]. Benefits like predictive accuracy, visualization, and interdisciplinary collaboration outweigh challenges, with future directions including machine learning for parameter tuning. This framework can set the stage for specific applications, like maternal-placental-fetal interactions.

Model Framework: Integrating SDM and ABM for Simulating Maternal-Placental-Fetal Interactions

The hybrid SDM-ABM model developed in this research focuses on maternal-placental-fetal interactions, particularly on fetal oxygen delivery, which is critical in obstetric ICM due to the limitations of direct fetal monitoring [43]. SDM leverages measurable maternal hemodynamics (e.g., blood pressure, cardiac output) for macro-level flows, while ABM visualizes micro-level erythrocyte movement and oxygen diffusion across the placenta.

The placenta's dual nature—continuous bulk flows and discrete cellular interactions—suits hybrid modeling. SDM uses ODEs for volumes, pressures, and oxygen fluxes, while ABM introduces stochasticity for heterogeneous diffusion.

Implemented in NetLogo with SDM solvers, the interface features scenario selectors (e.g., normal pregnancy, maternal anemia), plots for maternal/fetal circulatory dynamics, numerical monitors for cardiac output, FD_{O_2} and ABM windows showing placental oxygen exchange with color gradients (red for oxygenated maternal blood, blue for deoxygenated fetal return).

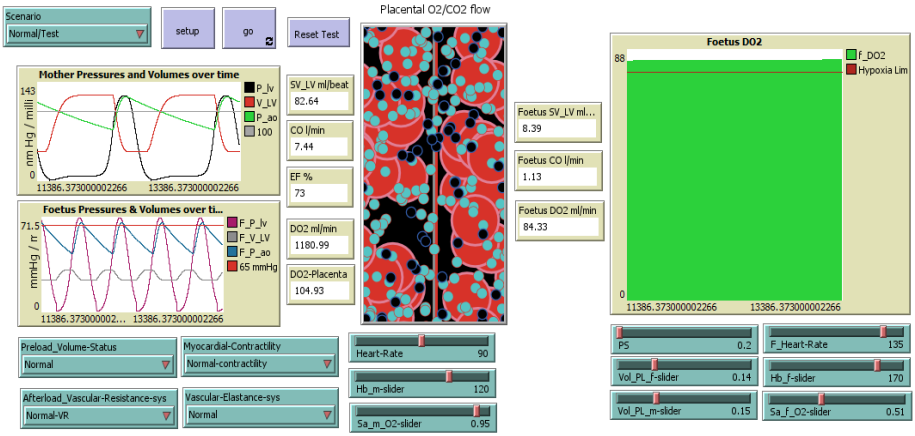

Figure 4.1. A broad overview of the model interface. The scenario chooser (left top zone) indicates that the scenario is "Normal/Test." With monitors (in the middle) displaying numerical values, the plotting regions beneath the chooser demonstrate the dynamics of the mother's (upper plot) and fetus's (lower plot) circulatory systems over time. The placenta is depicted in the central window, while the fetus's O_2 delivery is shown in the window on the right. Model parameters can be adjusted using the bottom sliders: the placenta and fetus (placenta volume, fetal heart rate, etc.) are on the right, while the mother's body (circulatory parameters, hemoglobin, oxygen saturation, etc.) is on the left.

Sliders allow real-time parameter adjustments, e.g., simulating maternal hypotension updates ABM flow and SDM FD_{O_2}, supporting clinical and educational use. The SDM structure interconnects maternal, fetal, and placental subsystems: stocks (squares) represent volumes, auxiliaries (diamonds) denote elastance/resistance, with notations like V_lv for left ventricular volume.

ABM integrates loosely at the placenta: SDM flows inform agent influx, and interactions feedback diffusion coefficients to SDM [44]. This extends prior healthcare hybrids, focusing on physiological ICM niches like fetal medicine, unlike operational models [45, 46]. Benefits include clinical predictions of fetal distress and educational exploration of anemia effects, though calibration challenges persist due to data mismatches.

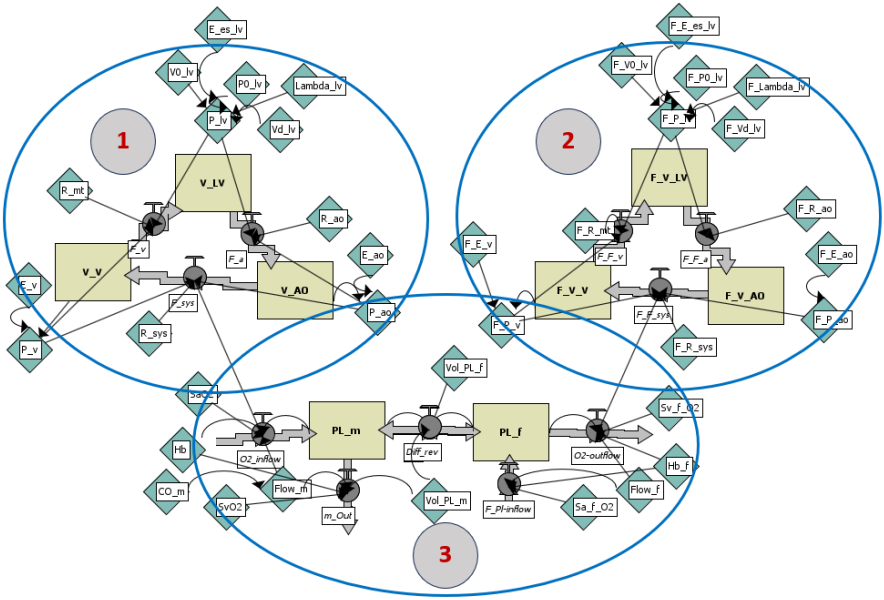

Figure 4.2. The model's system dynamic scheme: (1) The circulatory systems of the mother, (2) the fetus, and (3) the placenta. Squares represent stocks, while diamonds display other characteristics. A particular parameter is indicated by capital letters, such as V for volume, E for elastance, etc.

ABM integrates loosely at the placenta: SDM flows inform agent influx, and interactions feedback diffusion coefficients to SDM [44]. This extends prior healthcare hybrids, focusing on physiological ICM niches like fetal medicine, unlike operational models [45, 46]. Benefits include clinical predictions of fetal distress and educational exploration of anemia effects, though calibration challenges persist due to data mismatches.

Mathematical and Computational Foundations of the Hybrid Model

The model uses lumped-parameter ODEs for SDM. The maternal part of the circulation is based on equations, similar to Eq. 3.1 to 3.14 described in the previous chapter.

These equations extend to the fetal system with parallel structures, adjusted for fetal physiology (e.g., lower resistances, higher heart rates). The placenta links the two via additional compartments. The placenta is modeled using ODEs behind a two-compartment Michaelis-Menten transporter. Parameters in this submodel can also be adjusted using sliders on the user interface.

Oxygen delivery (DO_2 or FD_{O_2}) calculation incorporates this hemodynamics with oxygenation parameters:

$$DO_2 = CO \times 1.34 \times Hb \times S_aO_2, \quad (4.1)$$

where CO is cardiac output (L/min), Hb - hemoglobin (g/L), and S_aO_2 is arterial oxygen saturation (via oxyhemoglobin dissociation curve), and the constants account for bound oxygen.

Scenario-Based Simulations: Exploring Pathophysiological Dynamics

Scenarios simulate obstetric ICM conditions. Normal: physiological parameters (Hb 120 g/L, heart rate 80 bpm) yield stable FD_{O_2}. In cases of maternal anemia, a reduction in Hb to 90 g/L results in approximately a 15% decrease, which crosses the hypoxia threshold of 80 ml/min.

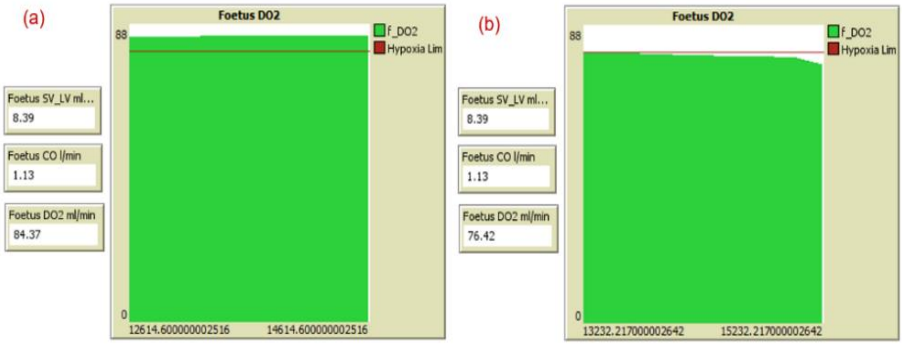

Figure 4.3. The fetus's oxygen delivery in normal conditions (a) and maternal anemia (b). The fetal hypoxia limit is represented by the red line.

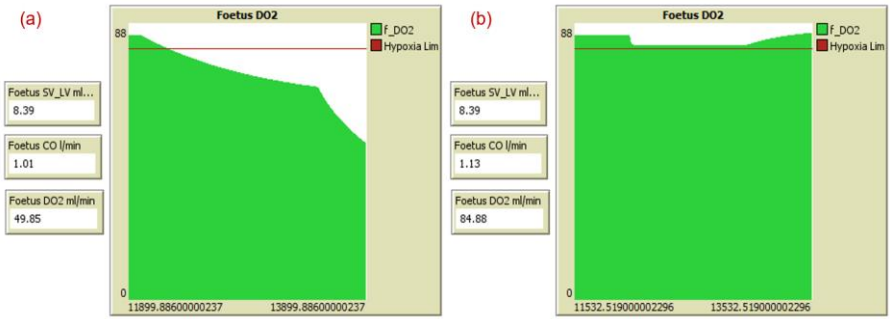

Figure 4.4. The fetus's oxygen delivery in (a) the Abruptio Placentae scenario and (b) a typical uterine contraction. The fetal hypoxia limit is represented by the red line.

Contractions: periodic pressure spikes cause transient FD_{O_2} dips, critical in compromised states. Complex scenarios (heart failure, anemia, anesthesia) highlight intervention needs.

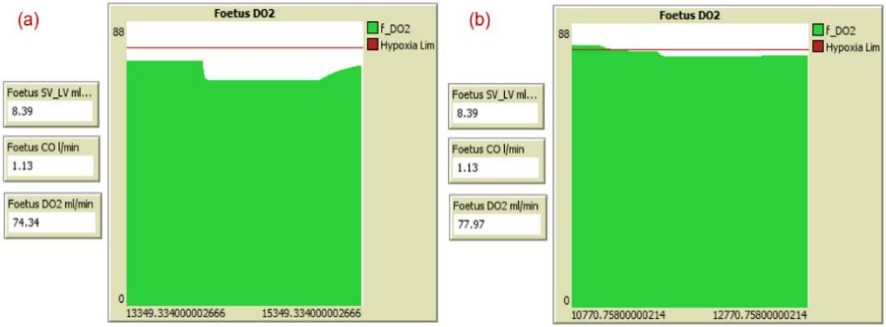

Figure 4.5. The green region and lower monitor indicate the fetus's oxygen delivery: Scenarios of (a) complex pathology and (b) anesthesia. The fetal hypoxia limit is represented by the red line.

Results validate against benchmarks (normal FD_{O_2} 100-200 ml/min), supporting clinical planning and educational "what-if" analyses.

Applications in Clinical Practice, Educational Contexts, Limitations, and Prospects for Advancement

Applications of this hybrid model span clinical, educational, and research domains in intensive care. Clinically, it acts as a prototype for decision support systems, simulating patient-specific scenarios to forecast FD_{O_2} and guide interventions. For anemia, modeling hemoglobin thresholds informs transfusions; in abruption, it can predict deterioration timelines for surgical timing. Integration with EHRs could enable real-time inputs, bridging fetal data gaps.

Educationally, interactive features allow exploration of parameter effects, e.g., preload on FD_{O_2}, enhancing comprehension of complex interactions. In ICM training, it simulates rare events safely.

Limitations encompass simplifications: lumped parameters miss spatial gradients, no ventilation modeling affects accuracy in respiratory distress, and valve assumptions ignore regurgitation.

Future directions include clinical validation, adding vascular details, and machine learning for personalization. KCC estimation [47] from accessible parameters (maternal hemodynamics, fetal heart rate) parallels FD_{O_2} in Figure 4.6 for abruption (blue KCC, red FD_{O_2}), promising non-invasive monitoring.

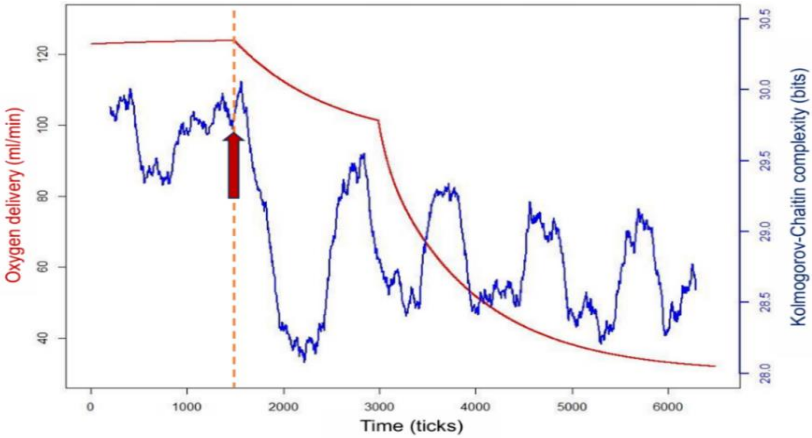

Figure 4.6. Oxygen delivery to the fetus in abruption placentae denoted by the red color line, and the blue color line represents the Kolmogorov-Chaitin complexity, which is approximated based on available clinical data. The impact time is indicated by the red arrow.

Digital Twins in Intensive Care

Digital twins create virtual patient replicas updated with real-time data, extending hybrid models for ICM personalization. In respiratory failure, they simulate lung mechanics [48]; in obstetrics, they can estimate FD_{O_2} from maternal/fetal inputs. Applications include decision support and workflow optimization [49]. Benefits: predictive accuracy, visualization, and training for rare events [33, 50]. Challenges: computational complexity, data integration, privacy, and validation [51]. Future advancements involve AI tuning, KCC proxies, and standardized networked systems for resilient care.

5. FROM TRADITIONAL MEDICINE TO COMPUTATIONAL PARADIGMS: COMPLEXITY-DRIVEN APPROACHES TO DIAGNOSIS AND PROGNOSIS IN CRITICAL CONDITIONS

Medical diagnosis and prognosis: tracing the evolution from ancient times to the present era

One can compile a list of key discoveries that have made patient care more successful than before. Most of these discoveries have finally influenced the accuracy of diagnosis, which is the first step in curing a disease. In turn, the diagnosis has a rich history, evolving from an empirical approach to a more structured version that incorporates logic and mathematical aspects (such as knowledge-based diagnosis, rules-based diagnosis, fuzzy-logic systems, ontology-based systems, model-based diagnosis, Bayesian diagnosis, and causal reasoning for diagnosis, among others). One of the relatively recent additions to this list is the use of machine

learning/artificial intelligence (ML/AI) for diagnosis [53]. From a medical standpoint, monitoring physiological parameters, laboratory indices, radio and ultrasonographic methods, etc. are all examples of traditional methods and instruments that objectify the clinical condition of the patient. All these methods have a certain resolution, with some changes falling below that threshold. In this context, approaches that detect subtle pathophysiological changes would be useful, which would translate into an earlier diagnosis or prediction of the patient's condition, which in this case represents an “anticipated” diagnosis [52]. This, being one of the key elements of the current research, is depicted in Figure 5.1.

Aspects of representation learning, complexity science, and machine learning relevant to the research topic areas

Many modern data sets are multi-dimensional. The large number of features can make it difficult to visualize and understand the data. As a way to solve this problem, representation learning can be used. Some of these methods are older, like principal component analysis (PCA) and linear discriminant analysis (LDA), while others are newer and non-linear, like isometric mapping (Isomap), t-distributed stochastic neighbor embedding (t-SNE), spectral embedding (SE), and others.

Complexity approaches also play a role in research, including in the medical field. One of the most common metrics here is Shannon’s entropy (H) under different flavors [54]. Recent research is questioning the value of this metric, proposing the Kolmogorov-Chitin complexity as an alternative [55].

ML techniques in medicine mirror their use in other areas of human practice, showcasing a large diversity of these techniques in the diagnosis and treatment processes.

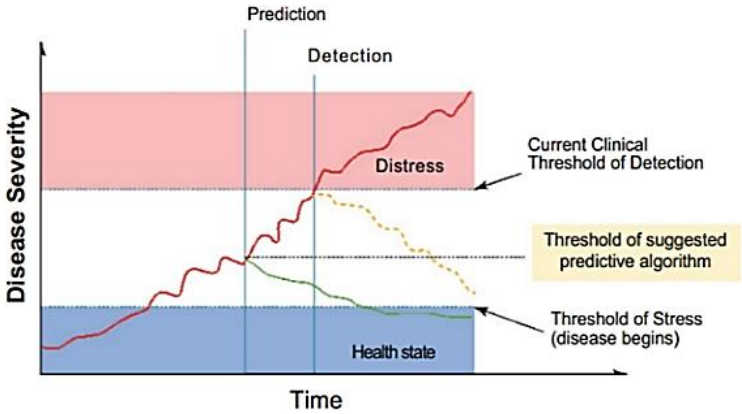

Figure 5.1. Diagnosis and prognosis: the conceptual role of AI-driven predictive analytics on disease progression. Adapted from [52].

Medical prognosis using machine learning in epilepsy and sepsis

Literature data show that early detection or prediction of sepsis can lead to a decrease in antibiotic administration time, and early intervention in turn has been shown to reduce mortality in this group of patients [56], and ML/AI is getting traction in solving these problems [57]. A similar situation is observed with epileptic seizures, where ML applications are expected to predict unannounced epilepsy attacks, increasing patient safety [58].

6. FROM RAW DATA TO ACTIONABLE INSIGHTS: IMPUTATION, COMPLEXITY METRICS, AND LEARNING REPRESENTATIONS FOR CRITICAL CARE APPLICATIONS

Data sets used in the present research. Missing values recovery

There are three sets of data used in this study: (a) "EEG Epileptic Set" [14]; (b) "EEG Non-Epileptic/Healthy Set" [59]; and (c) "Sepsis Set" [13], and their summary is shown in Table 6.1.

Table 6.1. An overview of the data sets used in the research

Data characteristics	Set (a) – intracranial EEG signals from epileptic subjects	Set (b) - EEG and ECG signals from healthy subjects	Set (c) – multimodal data from patients in ICU
Number of cases in the original set	4 canines and 2 humans with epileptic seizures (total – 8002 subsets)	36 healthy volunteers passing an arithmetic test	40366 – patients (2932 with sepsis and 37434 with other pathologies)
Data format of a case	Multivariate time series as EEG signals from intracranial electrodes with sampling frequency of 400 – 5000 Hz	Multivariate multimodal time series as EEG and EKG with sampling frequency of 500 Hz	40 parameters as multimodal time series condensed in hourly windows
Dimensions and format of the original data set	113.62 GB ".mat"	175 MB ".edf"	242 MB, ".psv"
Dimensions of a subset/case	7.67 MB (.mat) 11.2 MB (.csv)	1285 – 3883 KB (.edf)	2-55 KB (.psv) 5-38 KB (.csv)
Parameters/ variables	EEG signals from 15 – 24 electrodes	EEG signals from 20 electrodes and an EKG derivate	40 parameters (vital signs, laboratory, demographics)

Table 6.1 (continued)

Particularities of the set	10-minute EEG clips/segments, no missing value	60-180 second EEG clip, no missing value	Rate of the missing values up to 80.9 %
The task solved within the thesis	Prediction/classification into (a) normal EEG segment vs (b) preictal	Representation learning	Prediction of (a) high risk of sepsis vs (b) low sepsis risk

Note: ".mat" – data format in MATLAB, ".edf" - European data format, ".psv" - pipe separated value

Before using the sepsis data for machine learning, it is necessary to recover the missing values. According to this research, a technique using Kalman filtering and machine learning algorithms proved to be the most effective method for data recovery for this particular set [60]. This approach uses Kalman filtering for columns with at least three non-missing values and generalized linear models for data recovery in the case of all missing values in a column. The Kalman filter uses a discrete filtering model based on the dynamic and measurement models as linear Gaussian. The following is a description of the basics of this approach, with elements of optimal control and dynamic linear models as in [61].

The Kalman filtering technique is used to estimate states based on linear dynamical systems in state space format and offers estimates of unknown variables given the observations over time. According to this model, the state is evolving as follows from time $t-1$ to time t:

$$x_t = Fx_{t-1} + Bu_{t-1} + w_{t-1}, \tag{6.1}$$

where F is the state transition matrix estimated using the previous state vector x_{t-1}, B is the control-input matrix applied to the control vector u_{t-1}, and w_{t-1} is the process noise vector that is assumed to be zero-mean Gaussian with the covariance Q, i.e., $w_{t-1} \sim N(0, Q)$.

The link between the state and the measurement at the current time step t is described by
the process model in conjunction with the measurement model as:

$$z_t = Hx_t + v_t, \tag{6.2}$$

where z_t is the measurement vector, H is the measurement matrix, and v_t is the measurement noise vector that is assumed to be zero-mean Gaussian with the covariance C, i.e., $v_t \sim N(0, C)$.

Given the initial estimate of x_0, the sequence of measurements, $z_1, z_2, \dots, z_t$, and the details of the system defined by F, B, H, Q and C, the Kalman filter's job is to offer an estimate of x_t at time t. Typically, Q and C are tuned parameters that the user may change to get the desired performance.

The Kalman filter algorithm consists of two steps: (1) prediction and (2) update, and can be described as follows:

Prediction (step 1):

Estimating predicted state $\hat{x}_t^- = F\hat{x}_{t-1}^+ + Bu_{t-1}$ (6.3)

Calculating predicted error covariance $P_t^- = FP_{t-1}^+ + F^T + Q$ (6.4)

Update (step 2):

Estimating measurement residual $\tilde{y}_t = z_t - H\hat{x}_t^-$ (6.5)

Calculating Kalman gain $K_t = P_t^- H^T (R + HP_t^- H^T)^{-1}$ (6.6)

Updating state estimate $\hat{x}_t^+ = \hat{x}_t^- + K_t\tilde{y}$ (6.7)

Updating error covariance $P_t^+ = (I - K_t H)P_t^-,$ (6.8)

where the „hat" operator denotes an estimate of a variable. Thus, $\hat{x}$ is an estimate of x. The superscripts "-" and "+" denote predicted (prior) and updated (posterior) estimates, respectively.

The software implementation used for the data recovery purpose in this research is the "imputeTS" package in R and represents an extended version of the algorithm described above (i.e., Eqs. 2.1 to 2.8) with Kalman smoothing on structural time series models.

The algorithm proposed for data recovery purposes in columns with all values missing represents a generalized linear model (GLM) available on the H2O platform [62].

The dependence between the response variable y and the covariates vector x is modeled as a linear function by the Gaussian technique (behind GLM):

$$y = x^T\beta + \beta_0 + \epsilon, \tag{6.9}$$

where, β is the parameter vector, β_0 denotes the intercept and ϵ is a gaussian random variable representing the noise in the model, $\epsilon \sim N(0, \sigma^2)$.

By maximizing the log-likelihood over the parameter vector for the observed data, the model's estimation is achieved. By resolving the following likelihood optimization with parameter regularization, the GLM employed in this study fits the model:

$$\max_{\beta,\beta_0} (GLM\ Log \cdot likelihood - Regularization\ Penalty). \tag{6.10}$$

The weighted sum of the $\ell 1$ (least absolute shrinkage parameter) and $\ell 2$ (ridge regression) norms of the coefficients vector is the regularization penalty, and it is expressed as follows:

$$\lambda P_\alpha(\beta) = \lambda\left(\alpha\|\beta\|_1 + \frac{1}{2}(1-\alpha)\|\beta\|_2^2\right), \tag{6.11}$$

where α is the elastic net parameter, $\alpha \in [0, 1]$and λ is a tuning parameter, and there is no penalty for the intercept.

The optimization task concerning observations can be described as follows:

$$\sum_{i=1}^{N} log\ f\ (y_i;\ \beta, \beta_0) - \lambda\left(\alpha\|\beta\|_1 + \frac{1}{2}(1-\alpha)\|\beta\|_2^2\right). \tag{6.12}$$

The Gradient Boosting Machine (GBM), offered by the same H2O platform [62], turned out to be the top-performing algorithm at the final machine learning (ML) stage.

R is the programming language employed in this part of the current study, and several packages from the same environment are used for a variety of tasks throughout the study. Plotting and interacting with the H2O ML platform are done in the same language and environment.

Table 6.2. Linear regression coefficients for parameters of interest (for data recovery)

Parameter for recovery	Intercept	Coefficient (Parameter)		
HR	89.4392	3.2658 (DBP)	3.2980 (Resp)	-2.3973 (Age)
O_2Sat	97.4894	-0.2305 (HR)	0.1840 (SBP)	-0.4954 (Resp)
Temp	37.2479	0.1233 (HR)	0.0720 (SBP)	-0.1001 (Age)
SBP	123.6418	1.6593 (Temp)	11.7255 (DBP)	0.6840 (Resp)
DBP	61.4999	2.5176 (HR)	6.8117 (SBP)	-3.7355 (Age)
Resp	20.3789	0.9001 (HR)	-1.0138 (O_2Sat)	0.3220 (Temp)

Note: These are the coefficients for the missing value recovery (HR – heart rate; O_2Sat – blood O_2 saturation; Temp – body temperature; SDP & DBP – systolic and diastolic blood pressure; Resp – respiratory rate). Based on several tests, these parameters were found to have the highest predictive value for the final model created in the study.

This study's sepsis data processing cycle includes several processes, such as missing value recovery, and tries to provide datasets appropriate for machine learning.

Machine learning algorithms are used in this research at different stages for two distinct purposes: (a) for missing values recovery (i.e., GLMs) and (b) for building the final sepsis prediction model (at this stage, it was experimented with several algorithms, and this is described in coming sections). The following is a description of the main processing steps through a Consolidated Standards of Reporting Trials (CONSORT)-like diagram (Figure 6.1). It shows the resulting sizes of the data sets, which have had missing values recovered by three methods before being used in the ML algorithms.

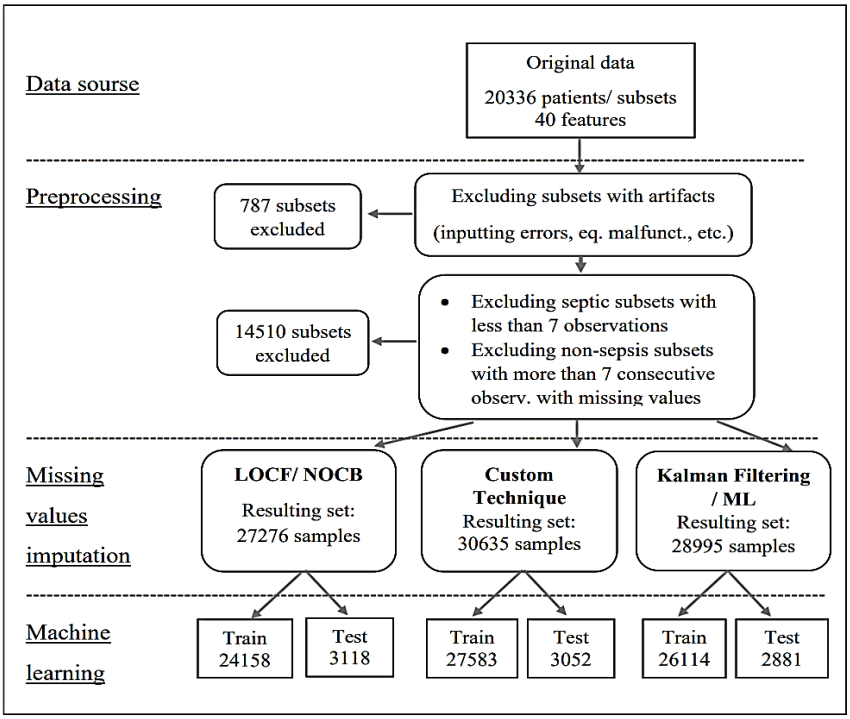

Figure 6.1. Data processing flow in the current research (CONSORT-like diagram).

Algorithmic complexity concepts and tools at the preprocessing stage

A central role in data processing flow is attributed to the estimation of Algorithmic (Kolmogorov-Chaitin) Complexity (KCC) performed via the Block Decomposition Method coming from the field of Algorithmic Information Dynamics [55]. Of primary importance here is the definition of algorithmic (Kolmogorov–Chaitin or program-size) complexity [55]:

$$K_T(s) = min\{|p|, T(p) = s\}, \tag{6.13}$$

that is, the length of the shortest program p that outputs the string s running on a universal Turing machine T.

Algorithmic Information Dynamics (AID) is an emerging field of complexity science based on algorithmic information theory, which comprises the literature based on the concept of Kolmogorov–Chaitin complexity (KCC) and related concepts such as algorithmic probability, compression, optimal inference, the universal distribution, Levin's semi-measure, and others [55].

AID strives to search for solutions to fundamental questions about causality: why a particular set of circumstances leads to a particular outcome. In this aspect, it essentially differs from traditional statistics. As an applied science, AID is a new type of discrete calculus based on computer programming and aimed at studying causation by generating mechanistic models to help identify first principles of physical phenomena, building up the next generation of machine learning [55].

In the AID toolkit, there is a special tool for providing reliable estimations to uncomputable functions, namely the online algorithmic complexity calculator (OACC) [23], which provides estimations of algorithmic complexity and algorithmic probability for short and long strings and for two-dimensional arrays better than any other traditional tool, none of which can capture any algorithmic content beyond simple statistical patterns. The OACC uses the BDM method (Block Decomposition Method), which is based upon algorithmic probability defined by the coding theorem method (CTM) [55, 63]:

$$BDM = \sum_{i=1}^{n} CTM(block_i) + log_2(|block_i|). \tag{6.14}$$

The OACC is available as an online version [63] as well as standalone packages in R and several other languages, including the Wolfram Language, and it is used for respective calculations for the scope of the current work.

At this stage every file (subset) in the data is a '*csv' file describing either the EEG signal voltage variations for "n channels" for a 10 min duration (EEG data) or hourly values of 40 parameters in the case of sepsis data. The EEG subset is unfolded, and a matrix with columns representing "n channels/electrodes" and rows denoting observations of EEG signal variation over time corresponding to particular channels is generated. Tables 6.3 to 6.5 depict the main steps of KCC estimation on EEG, the results being plotted as KCC time series (Figure 6.2) [64, 65]. Tables 6.6 to 6.8 illustrate the same approach to the sepsis data.

Table 6.3. Raw EEG data (as a 16x16 matrix)

Ch1	Ch2	Ch2	Ch4	Ch5	Ch6	Ch7	Ch8-Ch15	Ch16
-38	-13	9	-15	7	6	24	…	25
-45	-5	-2	-12	2	-1	17	…	21
-46	-11	-3	-14	2	2	16	…	17
-36	-21	-5	-16	7	9	16	…	20
-22	-23	-3	-20	13	16	8	…	17
-14	-16	3	-30	19	18	0	…	2
…	…	…	…	…	…	…	…	…
7	16	35	-26	-5	1	5	…	-20

Table 6.3 displays the voltage of EEG signals recorded from 16 electrodes (Ch, represented as columns), with each row corresponding to an observation, while Table 6.4 presents the binarized version of this data based on the mean value per row. Table

6.5 depicts the estimated Kolmogorov-Chaitin complexity of the respective data, and Figure 6.2 is the plot of KCC for two EEG clips estimated the way described above.

Table 6.4. Binarized data (by the threshold mean value per row)

Ch1	Ch2	Ch2	Ch4	Ch5	Ch6	Ch7	Ch8-Ch15	Ch16
0	0	1	0	0	0	1	…	1
0	0	0	0	0	0	1	…	1
0	0	0	0	0	0	1	…	1
0	0	0	0	0	1	1	…	1
0	0	0	0	1	1	0	…	1
0	0	0	0	1	1	0	…	0
…	…	…	…	…	…	…	…	…
0	1	1	0	0	0	0	…	0

Table 6.5. Resulting algorithmic complexity by BDM (EEG data)

Kolmogorov-Chaitin algorithmic complexity of the matrix
373.5134 bits

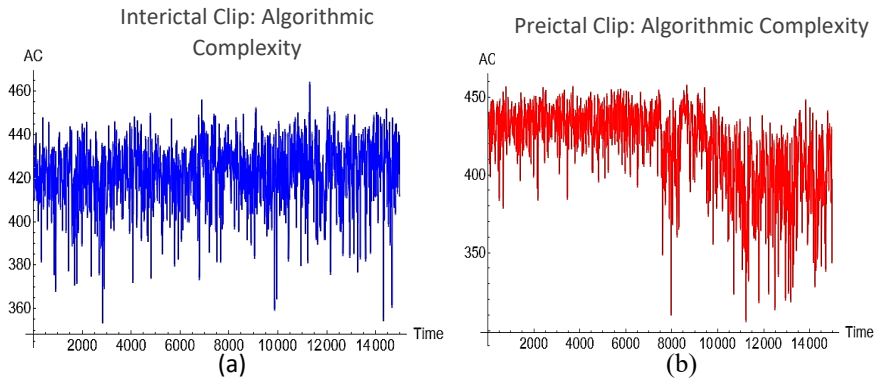

Figure 6.2. Aggregated KCC over time: (a) for an "interictal"/normal EEG clip, and (b) for a "preictal"/pre-epileptic clip.

Table 6.6. Original sepsis data (HR, SBP, DBP) as 3 x 3 matrix

HR	88	83	74.5
SBP	95.5	100.25	90.25
DBP	51	52	50.5

Table 6.7. Binarized data (using the threshold value by row)

HR	1	1	0
SBP	1	1	0
DBP	0	1	0

Table 6.8. Resulting algorithmic complexity by BDM (sepsis data)

Kolmogorov-Chaitin algorithmic complexity of the matrix
17.4911 bits

Tables 6.6 to 6.8 exemplify the steps of estimating KCC for three parameters (HR, SBP, and DBP) from sepsis data, and Table 6.9 shows the final format of the sepsis data used for ML.

Table 6.9. Format of sepsis data used for ML

AC1	AC2	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	**Label**
17.213	17.166	5	3.5	-0.1	12	4	0	6	-2	-0.05	-31.5	-7.5	3.5	**0**
18.980	17.232	0.5	0.5	-0.05	9	9.5	-3.5	-5	-1	-0.25	0	-13.5	4.5	**0**
15.942	17.019	8	0	-0.1	8	3	-1.17	-9	0	0	-8	-8	-1.16	**0**
15.601	16.162	3	0	-0.06	6.5	3	1.5	-1.67	-2	0.03	-4.7	-1.7	0	**1**
16.476	16.956	-4	-1	-0.7	-2	-2	0	-5.5	1	-0.2	-11	-21.5	-5.5	**1**

Note: AC1 and AC2 depict the KCC. V1 to V12 are the differences of the 6 parameter values (HR, O_2Sat, Temp, SBP, DBP, and Resp) between three consecutive hours. “”0”—non-sepsis; “”1”—sepsis.

Application of topological representation learning methods to research data

Traditional representation learning methods (namely, locally linear embedding (LLE), multi-dimensional scaling (MDS), isometric mapping (Isomap), t-distributed stochastic neighbor embedding (t-SNE), spectral embedding (SE), etc.) were applied to transformed data from all three data sets in the study. Figure 6.3 represents an example of applying Uniform Manifold Approximation and Projection (UMAP) to epileptic EEG data.

Although the obtained results helped with a better understanding of the data, they provided quite low performance when used for classification purposes

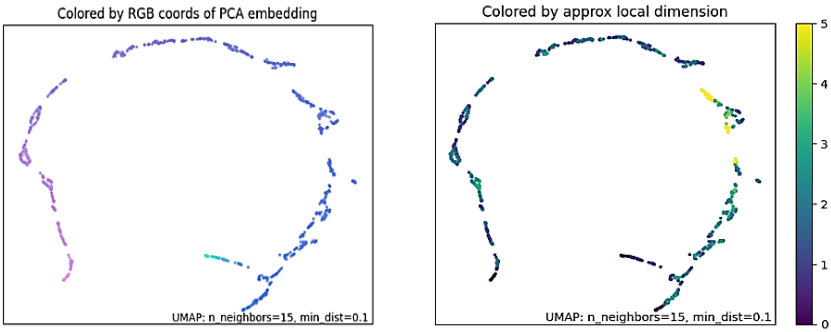

Figure 6.3. UMAP diagnostic plots of the Dog 2 embedding: RGB coloring (on the left) and local dimensions (on the right).

Word embedding, as a variety of representation learning for text, served as an additional avenue for experimenting. EEG data transformed into text and fed to a number of algorithms/models (e.g., TF-IDF, Word2vec, fastText, BERT, BiLSTM [66]) finally led to satisfactory classification results. This phenomenon is described in coming sections.

7. MACHINE LEARNING ON PREPROCESSED DATA. RESULTS AND THEIR DISCUSSION

Stages of machine learning systems development. Implemented techniques and algorithms

The process of creating a machine learning model is more or less standard. Figure 7.1 describes the components and steps of the process.

Training, testing, validation, and comparative analysis of developed systems

Epilepsy data

Tables 7.1 and 7.2 present two formats of the EEG data transformed to text passed to several ML algorithms for the classification task (i.e., preictal or interictal EEG clip). The best-performing model trained on textual data obtained by transforming the digits of KCC values, rounded to units, into letters/words (e.g., 1-"a", 2-"b", 3-"c", etc.; 123 -"abc", Table 7.2) was Word2vec, and the parameters of this model are described in Table 7.3. The main results of the AI are presented in Figures 7.2 and 7.3, with a summary including the best models in each class presented in Table 7.4.

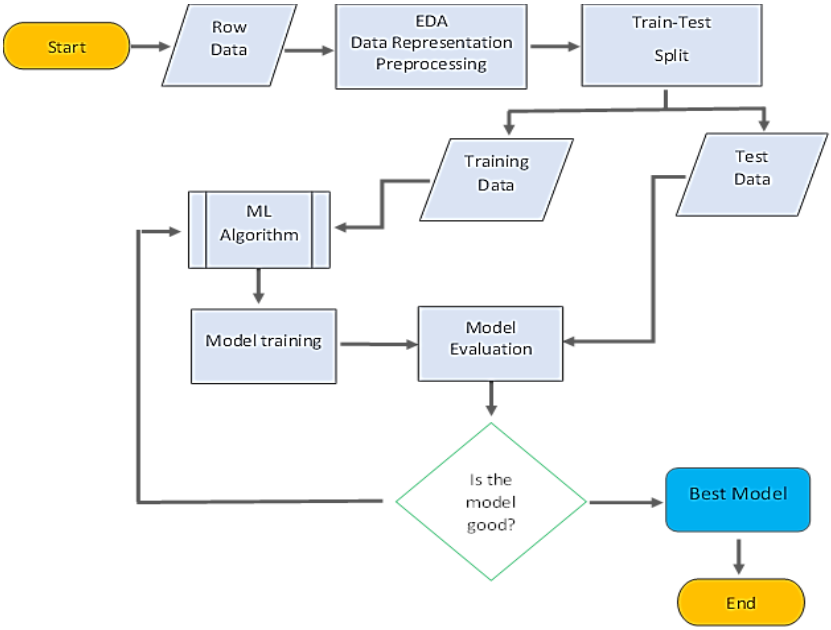

Figure 7.1. Main elements and steps in the creation of a machine learning system.

Table 7.1. Data for ML based on TF-IDF approach

Cat	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	…	V1100
0	0.0	4.0	1.4	0.0	0.2	0.3	1.5	0.0	0.0	3.3	-2.7	…	0.0
0	0.0	1.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	…	0.0
0	0.0	1.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	…	0.0
1	0.0	5.3	0.6	-1.2	0.2	0.0	0.0	0.0	1.9	0.0	4.0	…	0.0
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	…	0.0

Table 7.2. Data for ML based on NLP models

Cat	Text
1	chi dzi czd dcd dbz cbh cid caz dba dcd dgd dbc dce dzi dbd dae dbc dca dei ...
0	afc ahg aiz bii bbi ahi adz bai gh ee cea cez dde cii che cee bff bfb cfb ahi dzd ...
1	dai def ceb dde ciz cec dec dzc dfe ddh def dad dbh dbh dbd dee daf dea dda ...
0	dce chh cid dbc dbe dea dbf cha dfd deg dch dab dag chh dfa ddb dei dae dda ...
0	ddi dei ddb ceg ded ddh dag dbz dfe dbg dga dbg ddf ddg ddg dga dez def dde ...

Note: In both Tables 3.1 and 3.2, "0" represents an interictal clip, while "1" indicates a preictal clip.

Table 7.3. Parameters used in training Word2Vec model

Parameter	Description	Value
Size	Number of vector dimensions	100
Window	Context word size	5
Workers	Number of parallel threads	4
Min. count	Minimum word count	1
Word model	Model type	CBOW/Skip-Gram

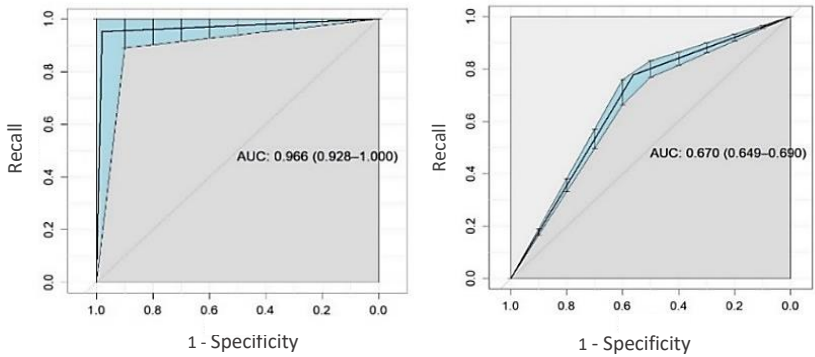

Figure 7.2. Performance (by AUC) of two models on Dog 2 test set: on the left – the Word2Vec/GBM model; on the right – the BERT model.

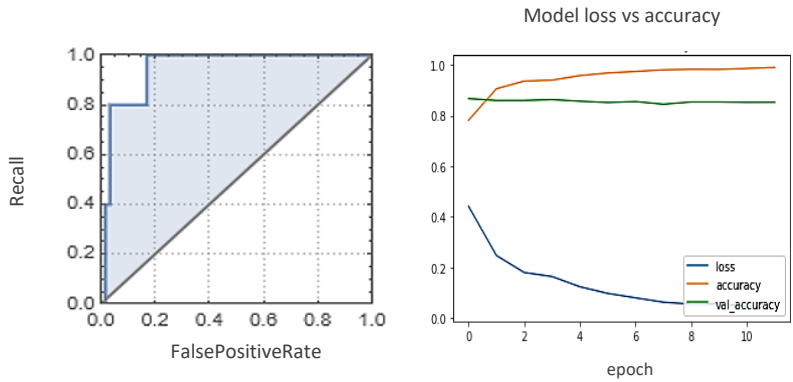

Figure 7.3. Performance of two models on the Dog 2 test set: on the left—the TF-IDF/GBM model; on the right—the BiLSTM model.

Table 7.4. The highest-performing NLP models trained on dog 2 EEG data

Model	Model performance on test set
Word2Vec (CBOW)	AUC 0.968
Word2Vec (Skip-Gram)	AUC 0.966
BERT	AUC 0.670
BiLSTM	Accuracy 0.891
TF-IDF	Accuracy 0.922

Note: CBOW – continuous bag of words, AUC – area under the ROC curve

The Word2Vec model trained on a combined data set (i.e., from dog 1 & dog 2) and the classifier built on dog 1 data showed even higher performance (by AUC): 1.00 on the dog 1 test set and 0.98 on the dog 2 test set. The classifier built on dog 2 with this "combined" approach on the dog 2 test set had a performance similar to one in Table 7.4, but when tested on the dog 1 test set, it provided an AUC of only 0.51.

Sepsis data

The results of ML on sepsis data are presented in Figure 7.4 and Table 7.5.

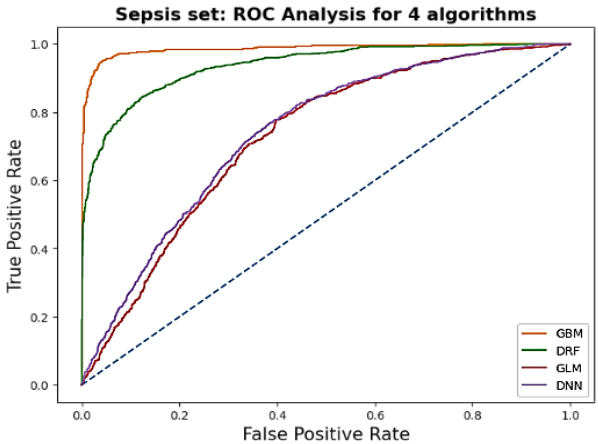

Figure 7.4. ROC curves of four algorithms (DNN, GBM, GLM, DRF).

From Figure 7.4, it is evident that the best-performing model is GBM (Gradient Boosting Machine), followed by DRF (Distributed Random Forest), while GLM (Generalized Linear Model) and DNN (Deep Neural Network) are almost equivalent in this sense. A more detailed view on the performance is presented in Table 7.5 below.

Table 7.5. Performance of the 4 ML Algorithms/Models

Model\ Metrics	GBM		DRF		GLM		DNN	
	Cross-valid. (sd)	Test (95% CI)	Cross-valid. (sd)	Test (95% CI)	Cross-valid. (sd)	Test (95% CI)	Cross-valid. (sd)	Test (95% CI)
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Area under the ROC curve (AUC)	0.974 (0.003)	0.953 (0.944 – 0.961)	0.920 (0.009)	0.827 (0.812 – 0.843)	0.707 (0.010)	0.684 (0.667– 0.700)	0.745 (0.048)	0.539 (0.530– 0.547)
Recall	0.892 (0.010)	0.942 (0.924 – 0.956)	0.753 (0.021)	0.685 (0.653 – 0.715)	0.820 (0.035)	0.831 (0.805– 0.855)	0.768 (0.064)	0.977 (0.964– 0.985)
Specificity	0.971 (0.007)	0.964 (0.955 – 0.972)	0.917 (0.016)	0.970 (0.961 – 0.977)	0.528 (0.041)	0.537 (0.515– 0.559)	0.619 (0.114)	0.101 0.088 – 0.115)
Accuracy	0.946 (0.004)	0.957 (0.949 – 0.964)	0.869 (0.009)	0.882 (0.869 – 0.893)	0.620 (0.019)	0.628 (0.610– 0.646)	0.666 (0.059)	0.372 (0.354– 0.390)
Precision (PPV)	0.934 (0.015)	0.921 (0.902 – 0.938)	0.809 (0.029)	0.911 (0.886 – 0.931)	0.443 (0.013)	0.446 (0.422– 0.470)	0.489 (0.062)	0.328 (0.310– 0.346)

Note: Performance is shown for both: cross-validation and test set (internal validation).

A comparison of the best-performing models developed in the current study and the high-performing system described in the literature is presented in Tables 7.6 (EEG data) and 7.7 (sepsis data).

Table 7.6. Comparative performance of models developed on same EEG data set

References/ Metrics	2014 Kaggle Competition (the first 10 results)	Usman S. et al. (2021)	Ibrahim A.K. et al. (2023)	Model in the study (based on CBOW Word2vec model) (95% CI)
(1)	(2)	(3)	(4)	(5)
ROC AUC	0.78 – 0.82	-	-	0.94 – dog 1 0.97 – dog 2
Recall	-	0.94	0.81 ± 0.02 (dog 1) 1.00 (dog2)	1.00 (0.86 - 1.00) - dog 1 0.98 (0.87-1.00) – dog 2

Table 7.6 (continued)

(1)	(2)	(3)	(4)	(5)
Specificity	-	0.96	-	0.91 (0.79 - 0.98) – dog 1 0.96 (0.86-1.00) – dog 2
Accuracy	-	-	-	0.94 (0.86 - 0.98) – dog 1 0.97 (0.91-0.99) – dog 2
False Positive Rate	-	-	0.08 ± 0.02 (dog1) 0.04 ± 0.03 (dog2)	0.082 – dog 1 0.038 – dog 2
Positive Likelihood Ratio	-	-	-	11.25 (4.41-28.67) – dog 1 24.4 (6.27-94.97) – dog 2
Negative Likelihood Ratio	-	-	-	0.00 – dog 1 0.02 (0.00-0.17) – dog 2
Positive Predictive Value	-	-	-	0.86 (0.67-0.96) – dog 1 0.95 (0.84-0.99) – dog 2
Negative predictive Value	-	-	-	1.0 (0.91-1.00) – dog 1 0.98 (0.89-1.00) – dog 2

Table 7.7. Comparative metrics of several sepsis prediction system

Metrics	2019 Challenge (the first 5 results)	2021 Guidelines (95% CI)	System in the study (95% CI)
AUC	0.83-0.87	0.89 (0.86 - 0.92)	0.95 (0.94 - 0.96)
Accuracy	0.79-0.90	-	0.96 (0.95 - 0.96)
Recall	0.65*	0.81 (0.80 - 0.81)	0.94 (0.92 - 0.96)
Specificity	0,88*	0.72 (0.72 - 0.72)	0.96 (0.96 - 0.97)

* Performance of the winning model

From the tables above, it can be concluded that the created systems for EEG/epilepsy data perform comparably or better than those described in the literature [67, 68]. In the case of sepsis, the created system shows higher performance against a "credible" source for comparison, which is the "International Guidelines for the Management of Sepsis and Septic Shock" from November 2021 [69], where the potential role of machine learning, which "can improve the performance of screening tools," is first officially mentioned.

However, it makes sense to avoid making overly optimistic predictions until the system has been used extensively in clinical settings, taking into account any technical challenges that are now unanticipated.

Software applications based on the models developed in the current study

The best-performing models had been integrated into five software applications. The graphical user interfaces (GUIs) of two of them are presented below:

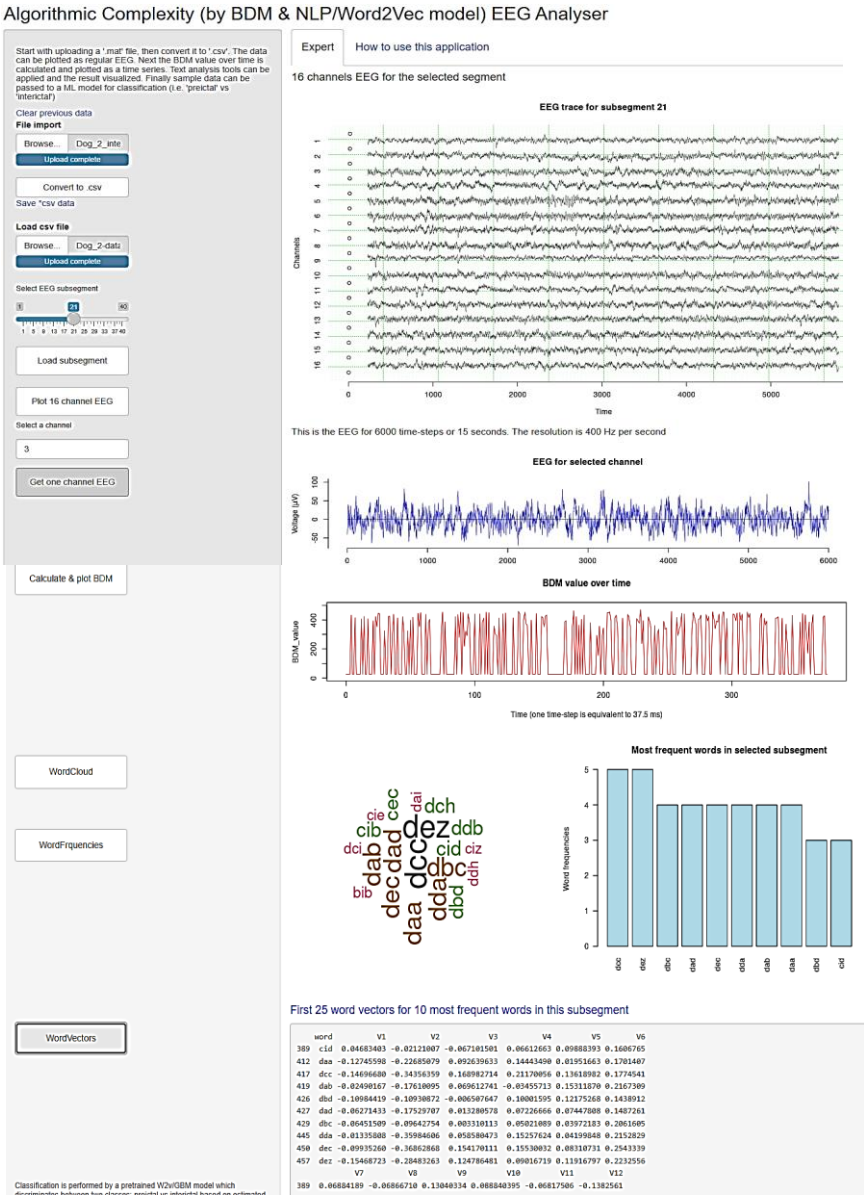

Figure 7.5. GUI of the application for EEG analysis based on Kolmogorov-Chaitin complexity and the NLP/Word2vec model.

The use of this application starts with uploading a “.mat” file with EEG signals, which can be converted to “.csv,” on which a number of tools can be applied: plotting 16 channels EEG for a subsegment, extracting a channel of restinterest, estimating KCC,

displaying the WordCloud and bar plots for the most frequent words, displaying first 25 vectors for these words, etc. (Figure 7.5).

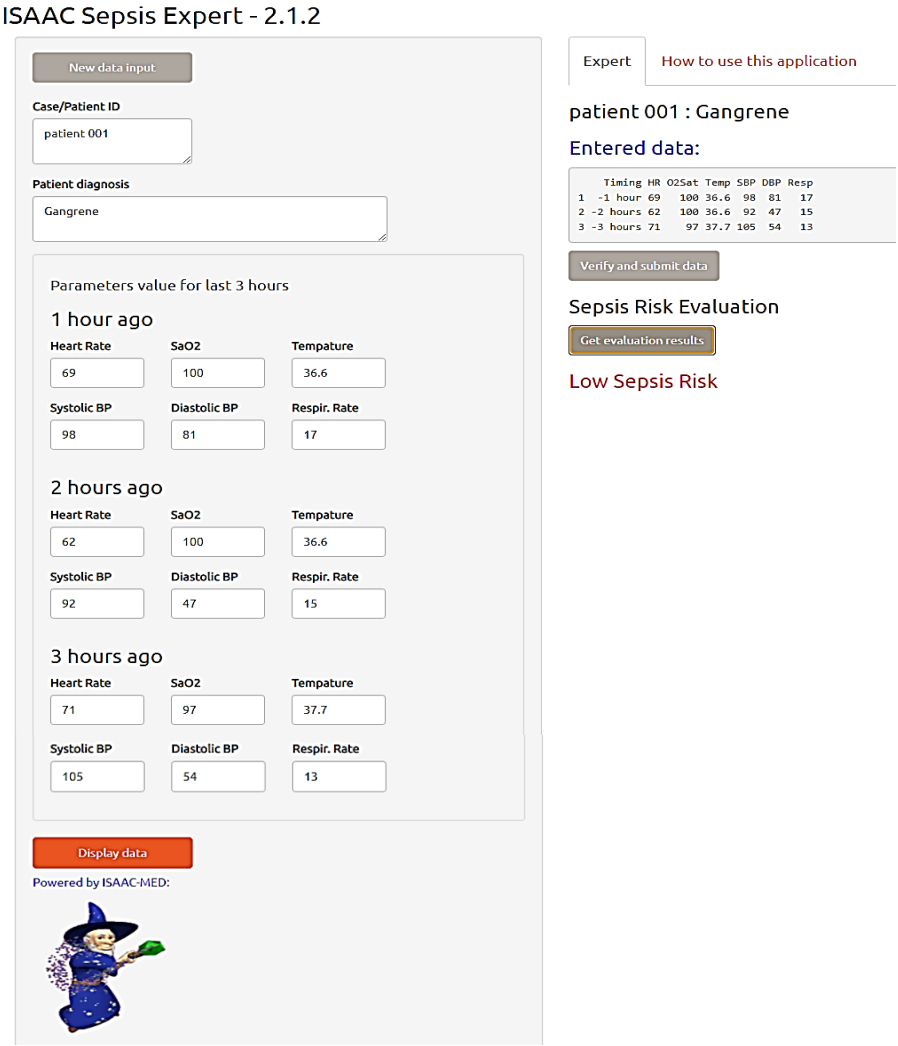

Figure. 7.6. GUI of the application for early prediction of sepsis (ISAAC-Sepsis-Expert-2.1.2): inputting patient's data and obtaining the prediction result.

The application requests inputting the values of 6 parameters (HR, O2Sat, Temperature, SBP, DBP, and respiratory rate) for three consecutive hours, and based on this information, it can predict the risk of sepsis with a 4-hour horizon, which is displayed (Low or High risk).

Five applications, including the ones described above, are available online:

(a) https://viapascurta.shinyapps.io/ISAAC_EEG_NLP_2_1/
(b) https://viapascurta.shinyapps.io/ISAAC_EEG_1_2_2/
(c) https://viapascurta.shinyapps.io/ISAAC_sepsis_demo/
(d) https://viapascurta.shinyapps.io/Sepsis_ISAAC_new_2_1/
(e) https://github.com/viapascurta-tech/Palmyra_med_sepsis_app

8. LARGE LANGUAGE MODELS AND MULTI-AGENT SYSTEMS IN INTENSIVE CARE: ENHANCING SEPSIS MANAGEMENT

Foundations of Large Language Models, Retrieval-Augmented Generation, and Multi-Agent Systems in Intensive Care

The integration of artificial intelligence (AI) into intensive care units (ICUs) has revolutionized clinical decision-making, particularly for sepsis, a life-threatening condition characterized by a dysregulated host response to infection leading to organ dysfunction. Large language models (LLMs), such as GPT-4, Gemini, and Palmyra Med, leverage transformer-based architectures to process sequential data, enabling natural language understanding, generation, and reasoning. These models excel in synthesizing complex medical information from electronic health records (EHRs), vital signs, and narrative notes, critical for rapid, evidence-based decisions in ICU.

The transformer model employs self-attention mechanisms [70], computing scores as:

$$Attention(Q, K, V) = \text{softmax}\left(\frac{QK^T}{\sqrt{d_k}}\right)V, \tag{8.1}$$

where $Q, K, and\ V$ are query, key, and value matrices, and d_k is the key dimension. This captures long-range dependencies in text, essential for ICU data like the MIMIC-IV database [71]. Fine-tuned LLMs update their hidden states as $h_t = tanh\ (W_h[h_{t-1}; x_t] + b_h)$, integrating attention to model temporal sequences for tasks like differential diagnosis, where sepsis overlaps with conditions like acute respiratory distress syndrome (ARDS).

However, LLMs face challenges, including hallucinations—generating plausible but incorrect information—and limited access to up-to-date or proprietary knowledge, critical in ICUs where guidelines like the Surviving Sepsis Campaign evolve rapidly. Retrieval-augmented generation (RAG) addresses this by dynamically retrieving external data, embedding queries and documents into a shared vector space using models like BERT [72]. Cosine similarity, $cos\ (\theta) = \frac{q \cdot d}{\|q\| \cdot \|d\|}$, fetches relevant chunks, improving factual accuracy for sepsis tasks like antibiotic recommendations based on local resistance patterns from ECDC reports [73]. RAG reduces the parametric burden on LLMs by offloading knowledge storage to external databases, enhancing reliability in high-stakes environments.

Multi-agent (MA) systems further extend AI capabilities by decomposing complex tasks into collaborative agents, each handling subtasks like diagnostics or therapy recommendations. Modeled as Markov decision processes (MDPs), agents follow policies to optimize shared rewards. In ICUs, MA systems emulate multidisciplinary teams, with agents for diagnosis, therapy, and guideline compliance, aligning with actor-critic

reinforcement learning frameworks. However, failures, as categorized by Cemri et al.'s Multi-Agent System Failure Taxonomy (MAST) [74], include specification issues (e.g., ambiguous prompts, FM-1.1), inter-agent misalignment (e.g., task derailment, FM-2.3), and verification failures (e.g., premature termination, FM-3.1). In sepsis, these could lead to delayed antibiotics, increasing mortality, or non-adherence to protocols like the one-hour bundle [69].

Computationally, MA systems are formalized as decentralized partially observable MDPs (Dec-POMDPs), where joint policies maximize expected rewards:

$$V(\pi) = E\left[\sum_{t=0}^{\infty} \gamma^t r_t | \pi\right], \tag{8.2}$$

where E is expected reward, γ represents a discounting factor and r_t is the reward received at time step t, and where each agent's policy $\pi(s)$ selects actions a given state s, optimizing a shared reward function. In sepsis, rewards could penalize delays in fluid resuscitation or vasopressor initiation, informed by SOFA scores.

Specialized LLMs like Palmyra Med process RAG-augmented prompts using vector databases like ChromaDB, reducing hallucinations. ICUs generate vast data from monitors and labs, overwhelming clinicians. To help this RAG integrates guidelines, while MA systems distribute tasks.

Challenges include data privacy under HIPAA [75], addressed by federated learning, and biases exacerbating disparities outcomes [76].

MA systems can simulate ICU workflows, with agents for alerting, reasoning, and verification. Future integrations may combine LLMs with symbolic AI, enforcing logical constraints for precise sepsis management, addressing high mortality rates (20-30% [77]).

Retrieval-Augmented Generation for domain-specific tasks

This section validates RAG through a non-medical case study, offering a blueprint for ICU applications like sepsis management.

Case Study: Implementing Retrieval-Augmented Generation (RAG) for Domain-Specific Question-Answering [78]

LLMs excel in general tasks but struggle with domain-specific knowledge, especially in fields like philosophy of management requiring precise text references. This 2024 pilot developed a RAG system for a book with 50 self-evaluation questions, translated from Russian to English, using open-source tools: LangChain [9], ChromaDB [80], LlamaIndex [81], GPT-3.5 Turbo [82], UMAP, and Triad evaluation. The study tested RAG's ability to bridge LLMs with specialized knowledge.

LLMs risk hallucinations on queries requiring specific texts (e.g., temperology). Hypotheses tested: Can open-source tools build an effective RAG system? How accurate are responses? Challenges included handling abstract philosophical text, ensuring semantic embeddings, evaluating relevance, and balancing efficiency.

The RAG system chunked text (256 characters), embedded it (e.g., all-MiniLM-L6-v2), and stored it in vector databases (Figure 8.1). Variants included Sentence Window (LlamaIndex), ChromaDB (cosine similarity), and Auto-Merging (tree structure). Queries retrieved top-k chunks for GPT-3.5 prompts (Figure 8.2). UMAP visualized embeddings, confirming semantic closeness (Figure 8.3). Triad evaluated context relevance,

groundedness, and answer relevance. Application performance across variants is presented in Table 8.1.

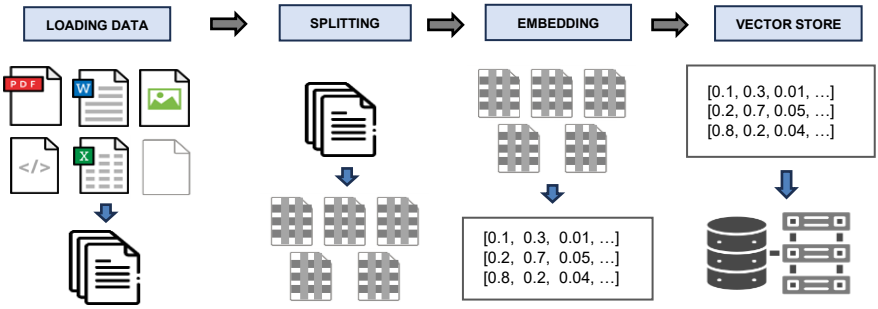

Figure 8.1. Establishing the vector store.

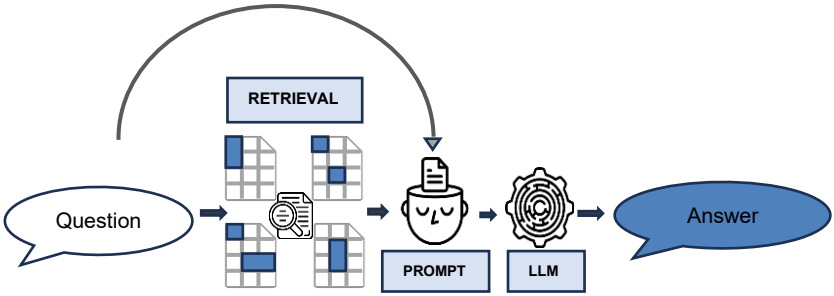

Figure 8.2. The data flow while generating the answer.

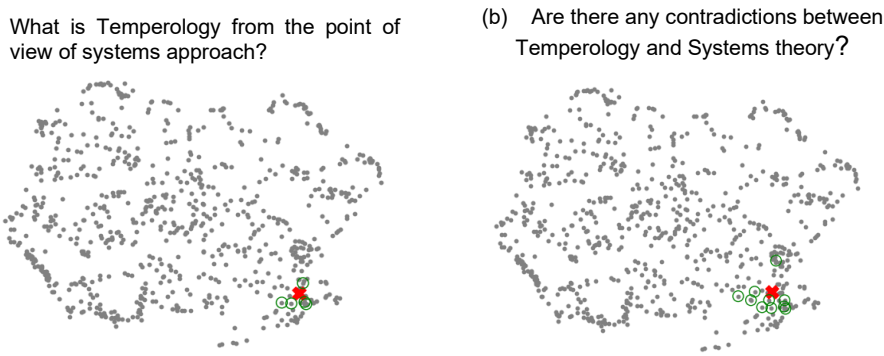

Figure 8.3. Two inquiries or questions: the proximity (indicating similarity) of the query (red cross) and the obtained data (green circles).

Table 8.1. Application performance across variants

Application	Answer relevance	Context relevance	Grounded -ness	Latency (seconds)	Cost ($ US)
RAG based on Sentence Window Retrieval	0.804	0.760	0.107	6.10	0.003
ChromaDB-based RAG	0.897	0.865	0.240	3.10	0.002
RAG based on Auto-merging approach	0.846	0.529	0.621	37.84	0.006

Performance summary: ChromaDB achieved answer relevance 0.897, context relevance 0.865, groundedness 0.240, latency 3.10 seconds, cost $0.002. Sentence Window: 0.804, 0.760, 0.107, 6.10s, $0.003. Auto-Merging: 0.846, 0.529, 0.621, 37.84s, $0.006. RAG variants outperformed unaugmented LLMs, correctly answering queries like "temporalogical structure elements" (three elements). Experts rated outputs "acceptable."

ChromaDB's cosine similarity excelled for philosophical text. Low groundedness suggests hybrid approaches. Limitations: Small dataset, translation nuances. Strengths: Open-source feasibility, UMAP visualization. Implications: RAG extends to ICU sepsis management, grounding guidelines to reduce errors.

Retrieval-Augmented Generation in Medicine and Intensive Care

RAG integrates retrieval with LLM generation, embedding text into vectors and retrieving via cosine similarity. Variants include Naive, Advanced (with optimizations like sliding windows), and Modular RAG. In ICUs, RAG can retrieve from EHRs and PubMed for sepsis, addressing data heterogeneity and privacy via federated approaches. It reduces errors in high-stakes settings, grounding antibiotic dosages in protocols [3] and personalizing therapy via patient histories. Challenges include latency, incomplete retrieval, and source biases. Applications involve querying MIMIC-IV [2] for guidelines, embedding vitals for predictions, and using hybrid sparse-dense retrieval for precision. Future directions include adaptive RAG, adjusting retrieval thresholds, and multimodal RAG for images (e.g., chest X-rays in pneumonia-sepsis).

AI-Driven Multi-Agent Systems for Sepsis Management in Intensive Care

Sepsis, with 20-30% mortality, demands rapid interventions, as delays increase mortality by 7-9% per hour [3]. LLMs with RAG mitigate hallucinations; MA systems distribute tasks via frameworks like CrewAI, simulating ICU teams. Two case studies evaluate MA-RAG in sepsis.

Case Study: Multi-Agent System for Initial Sepsis Management in Pneumonia—A Proof-of-Concept [83]

Early sepsis in community-acquired pneumonia (CAP) requires rapid recommendations without culture results (MIMIC-IV ID 10420760: 86-year-old female, hypotension, WBC 41,100/mm³).

A three-agent system (Palmyra-Med 70B, CrewAI) included Sepsis Management, Antibiotic Recommendation, and Guideline Compliance agents. RAG used ChromaDB on sepsis literature/guidelines (Figures 8.4 and 8.5). Input vignette
(Table 8.2): Diagnosis: Sepsis due to pneumonia; Demographics: Female, 86; Vitals: HR 76, BP 103/49, etc.; History: COPD, diabetes.

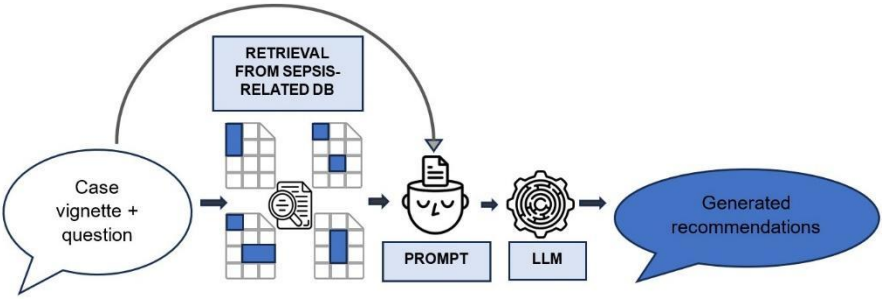

Figure 8.4. The retrieval-augmented generation module in case of sepsis MA system.

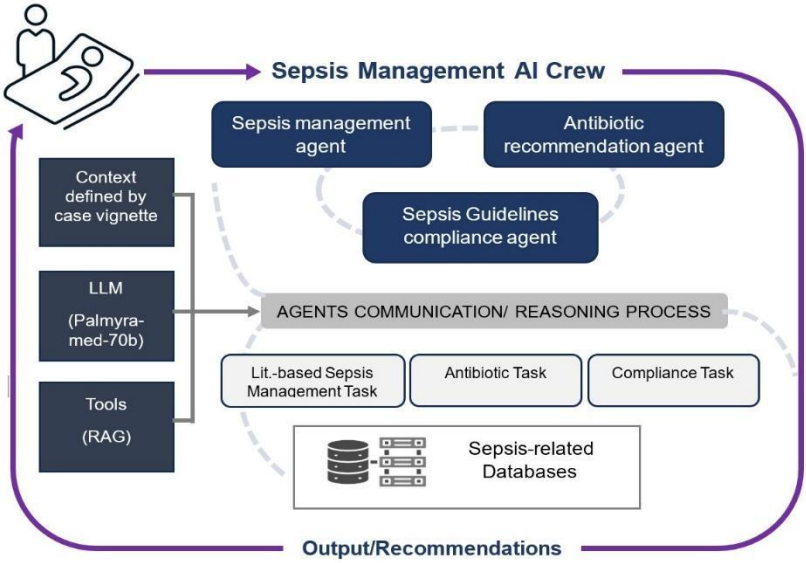

Figure 8.5. Architecture and data flow of the created multi-agent system

Table 8.2. The clinical vignette of a sepsis case

Vignette section	Description
Diagnosis	Sepsis due to pneumonia

Table 8.2. Continued

Demographic	female, 86 years
Vital signs	HR 76 bpm, BP 103/49 mmHg, RR 22 rpm, blood O_2 saturation 90%, temperature 37.2°C
Laboratory findings	WBC 41.100/mm^3 (41.1 x 10^9 cells/L), blood glucose 225 mg/dL (12.5 mmol/L), BUN 13 mg/dL (0.72 mmol/L)
Table 8.2 (continued)	
Medical history	Chronic obstructive pulmonary disease, atrial fibrillation, type 2 diabetes mellitus without complications, hypothyroidism
Special comments	Community-acquired pulmonary infection

Recommendations: Broad-spectrum antibiotics, fluid resuscitation, beta-lactam/macrolide, and guideline alignment with adjustments (Figure 8.6). TruLens evaluation: Answer relevance: 0.87, variable groundedness (Figure 8.7). Experts rated outputs “acceptable” (kappa=0.622).

Literature-based sepsis management recommendations

Early administration of antibiotics is crucial in sepsis management, especially in patients with suspected infections and systemic inflammatory response syndrome criteria. In the case of sepsis due to pneumonia in an 86-year-old female with multiple comorbidities, including COPD and diabetes, prompt antibiotic therapy is essential. Considering the patient's condition, a broad-spectrum antibiotic covering typical pathogens in pneumonia should be initiated promptly. Close monitoring for clinical response and adjusting therapy based on culture results is recommended. Additionally, supportive care to stabilize vital signs and manage comorbidities is vital in improving outcomes for this patient. Regular reassessment and collaboration with a multidisciplinary team are key in providing comprehensive care for this complex case.

Antibiotic recommendations

Tailoring empiric therapy for pulmonary infections, particularly Community-Acquired Pneumonia (CAP), should involve considering local microbial resistance patterns and individual patient factors. For CAP, initial empiric therapy may include a combination of a beta-lactam antibiotic like ceftriaxone or cefotaxime with a macrolide such as azithromycin. Alternatively, monotherapy with a respiratory fluoroquinolone like levofloxacin can be considered, especially for patients with beta-lactam allergies. In cases where there is a risk of MRSA or Pseudomonas aeruginosa, adding vancomycin or linezolid for MRSA and piperacillin-tazobactam, cefepime, or meropenem for Pseudomonas coverage may be necessary. It is crucial to adjust therapy based on local antimicrobial resistance data to ensure effective treatment.

Compliance with sepsis and septic shock management guidelines (2021)

Prompt initiation of broad-spectrum antibiotics in sepsis is crucial, but de-escalation based on clinical improvement and culture results is recommended to prevent unnecessary therapy. Tailoring empiric therapy for pneumonia should consider local resistance patterns and patient factors to ensure effective treatment. To achieve compliance, consider the following suggestions: To enhance compliance with recommendations, ensure prompt initiation of broad-spectrum antibiotics for suspected pneumonia in the elderly patient with comorbidities. Tailor therapy based on local resistance patterns, consider beta-lactam/macrolide combination or fluoroquinolone for Community-Acquired Pneumonia. Adjust treatment according to culture results and collaborate with a multidisciplinary team for comprehensive care.

8.6. Recommendations generated by the MA system: Sepsis management recommendations, antibiotic recommendations, and compliance with the guidelines statement.

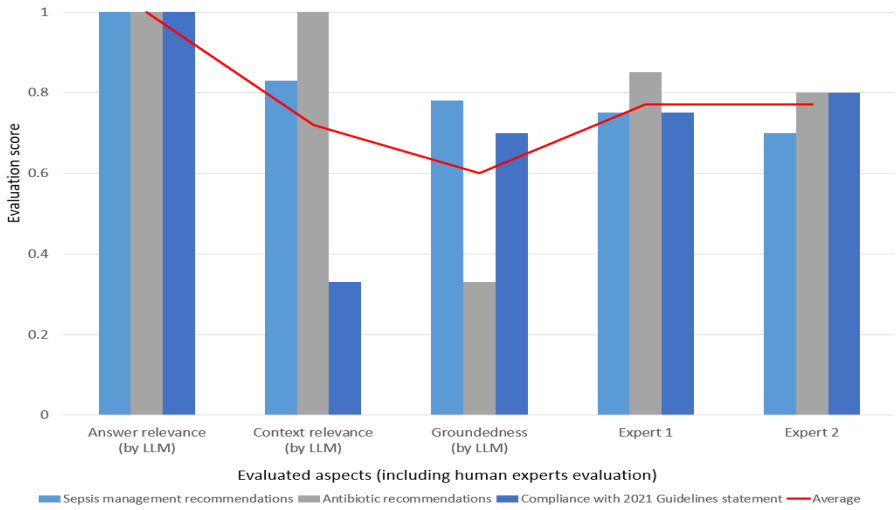

Figure 8.7. Evaluation results

The system showed utility in early sepsis, grounding outputs to minimize hallucinations. Prompt refinement is needed due to low LLM-expert agreement. Limitations: Single case, vignette reliance. Future: Broader validation, real-time integration.

Case Study: Extending Multi-Agent Systems for Multi-Case Sepsis Management – Addressing Hallucinations and Scalability [84, 85]

This study extended MA-RAG to 10 diverse sepsis cases (8 MIMIC-IV, 2 literature), including CAP, necrotizing fasciitis, and genitourinary sepsis, focusing on scalability and hallucination mitigation.

The same three-agent architecture was used, with RAG on ChromaDB (Figures 8.4, 8.5).

Recommendations aligned with guidelines (e.g., Case 1: Necrotizing fasciitis—vancomycin/piperacillin-tazobactam, surgery; Case 2: CAP—beta-lactam/macrolide; Case 3: Genitourinary—ceftriaxone). Sample inputs/outputs: Vignettes detailed vitals/history; outputs included tailored management, antibiotics, and compliance suggestions. TruLens for 8 cases: Groundedness 0-1.0, answer relevance mostly 1.0, context relevance 0.17-1.0; latencies 1.6-8s, costs $0.0018-0.0042 (Table 8.3). LLM-human discrepancies were noted (Figure 8.8). Hallucinations occurred (e.g., unsupported "altered mental status," Figure 8.9).

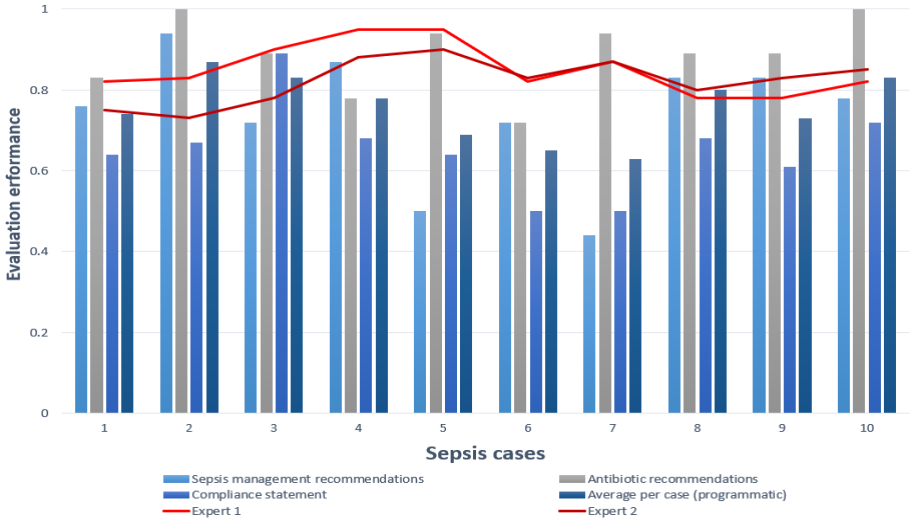

Figure 8.8. Evaluation outcomes with human assessors and a programmatic method.

Table 8.3. Evaluation results (by TruLens using GPT 3.5 Turbo LLM) for eight sepsis cases from MIMIC IV dataset

Aspect	Case ID	Groun-ded-ness	Answer Rele-vance	Context Rele-vance	Mea n score	Laten-cy (sec.)	To-kens	Cost ($ US)
Sepsis Manage-ment Recom-men-dations	10015860	0.67	1.0	0.5	0.72	6.1710	2250	0.0035
	10020786	0.83	0.67	0.83	0.87	2.9235	1523	0.0023
	10003400	0.17	1.0	0.33	0.5	3.2468	2111	0.0032
	10007818	0.33	1.0	0.83	0.72	2.3929	2013	0.0031
	10019003	0.0	1.0	0.33	0.44	2.9718	1842	0.0028
	10037861	1.0	1.0	0.5	0.83	2.3054	2100	0.0032
	10039708	1.0	1.0	0.5	0.83	3.2108	2099	0.0032
	10035631	0.67	1.0	0.67	0.78	3.1925	2277	0.0035
Antibiotic	10015860	1.0	1.0	0.67	0.89	3.0643	1196	0.0018
	10020786	1.0	1.0	1.0	0.78	1.7908	1352	0.0020
	10003400	1.0	1.0	0.83	0.94	2.2315	1177	0.0018
	10007818	0.67	1.0	0.5	0.72	1.6274	1180	0.0018
	10019003	1.0	1.0	0.83	0.94	3.7456	1461	0.0023

	Table 8.3. Continued							
Recom-men-dations	10037861	0.67	1.0	1.0	0.89	1.6986	1351	0.0021
	10039708	0.67	1.0	1.0	0.89	2.4183	1351	0.0021
	10035631	1.0	1.0	1.0	1.0	4.7168	1337	0.0020
Compli-ance with the guideline state-ment	10015860	0.67	1.0	1.0	0.89	3.2020	2085	0.0032
	10020786	0.30	1.0	0.67	0.68	4.842	2564	0.0040
	10003400	0.42	1.0	0.5	0.64	8.0827	2363	0.0037
	10007818	0.33	1.0	0.17	0.5	3.0649	2501	0.0038
	10019003	0.0	1.0	0.5	0.5	3.6458	2410	0.0037
	10037861	0.71	1.0	0.33	0.68	3.1804	2584	0.0040
	10039708	0.33	1.0	0.5	0.61	4.1364	2683	0.0042
	10035631	0.33	1.0	0.83	0.72	3.5101	1757	0.0028

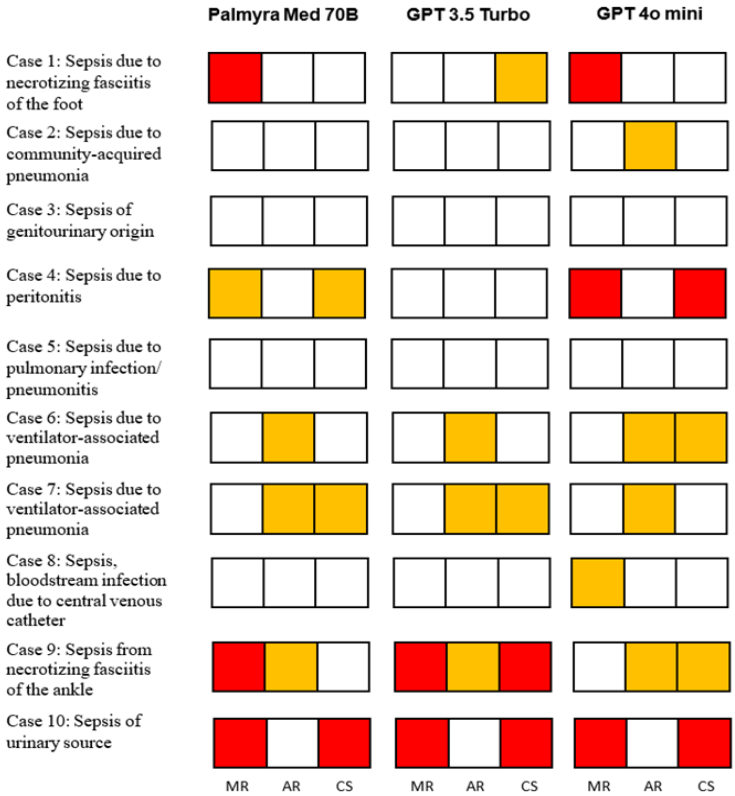

Figure 8.9. An overview of the issues with three LLMs' output while offering recommendations for the treatment of sepsis (two from the literature and eight from MIMIC IV).

Sepsis cases are represented by rows, while the output from three LLMs (Palmyra Med 70B, GPT 3.5 Turbo, and GPT 4o small) is displayed in columns. MR stands for management recommendations, AR for antibiotic recommendations, and CS for compliance with 2021 Guidelines. Orange indicates too much information (such as that which is not necessary for case management), while red indicates hallucinations.

The extension improved scalability and reduced hallucinations via RAG, but human oversight is critical. Limitations: Small sample, vignette-based. Future: Larger trials, multimodal integration. MA-RAG enhances precision in ICU sepsis management, paving the way for innovation.

GENERAL CONCLUSIONS*

1. 1. As for the overall goal of the study (to develop intelligent methods, algorithms and software applications for intensive care medicine based on a complexity science framework to improve early diagnosis, prediction and management of sepsis and epileptic seizures), this thesis has achieved it to a high extent: here is a major scientific problem (complexity science applied to model, predict and manage nonlinear, emergent and multiscale dynamics in intensive care where traditional reductionist methods do not capture interactions leading to diagnostic delays, inaccurate prognoses and higher mortality). Complexity science principles have been combined with modeling techniques, machine learning and AI systems to produce tools such as agent-based models for pulmonary edema, hybrid simulations for fetal oxygen delivery, ML predictors for sepsis and seizures, LLM multi-agent systems for sepsis management etc. These contributions link theoretical complexity insights with clinical applications (chapters 1 through 8) which improve decision making in ICUs. However, limitations are that simulated models rather than fully real-world validated models were used; scalability to resource poor settings (e.g., Moldova) is not guaranteed; prospective clinical trials are needed to prove long-term impacts on patient outcomes [39, 40, 52, 69, 90, 92, 102, 278, 292, 380, 381, 398, 399, 400].
2. For the first objective (i.e., develop a complexity science framework for ICU systems analysis, distinguish it from systems theory and apply it to sepsis and epilepsy), the thesis has achieved this completely in Chapter 1 with its conceptual foundation: it traces complexity science history, explains core concepts like nonlinearity and emergence in ICU dynamics, shows how these can be applied to ICU dynamics (sepsis and epilepsy are complex adaptive states), PubMed searches show increasing relevance and the framework guides modeling and AI chapters as well. Limitations are that interdisciplinary nature may overwhelm non-experts and there are only 0–3 direct ICU publications per year so empirical integration is lacking [292, 380, 381].
3. The second objective (testing modeling techniques via ABM to simulate emergent behaviours in processes such as cardiogenic pulmonary edema) has been achieved thoroughly in Chapter 2: the NetLogo -based ABM models fluid dynamics, is sensitive (ANOVA $p<0.05$), provides decision-support prototypes for ICU triage and education and fits complexity science modelling heterogeneity and self-organisation. Other authors' works (traditional ABM

applications in medicine that only provide basic simulations without real-time integration [An et al., 2017]) are compared with this thesis where complexity metrics are used to detect more emergent patterns; simplifications (e.g. permeability fixed, no oxygenation), computational demands, clinical data validation to make it real-time applicable are limitations [63, 66, 69, 92, 387, 394].

4. Objective three (system dynamics modeling (SDM) of aggregate circulatory and feedback dynamics including myocardial infarction) has been achieved fully in Chapter 3. The SDM ODE-based formalism simulates PV loops and complexity metrics (e.g., Kolmogorov- Chaitin complexity KCC) along with real time data for digital twins; results in Table 3.1 are clinically relevant for proactive ICU care. Compared to prior SDM work on circulatory systems this study hybridizes with complexity science for multiscale feedback and improves simulation accuracy; limitations include aggregation ignoring individual heterogeneity, privacy issues with data integration and hybrid expansions needed for multiscale phenomena more robustly addressed three - system dynamics modeling (SDM) for aggregate circulatory dynamics and feedback dynamics (MI included) has been covered thoroughly in Chapter 3. SDM's ODE based formalism simulates PV loops and complexity metrics (e.g., Kolmogorov Chaitin complexity KCC) along with real time data for digital twins; results in Table 3.2 are clinically relevant for proactive ICU care. Limitations are aggregation which ignores individual heterogeneity, privacy issues in data integration and hybrid expansion needed to tackle multiscale phenomena more effectively [90, 92, 93, 380, 385, 389, 399, 400].
5. The fourth objective (hybrid modeling methods combining ABM and SDM for multiscale simulations such as maternal-placental-fetal oxygen delivery) has been achieved successfully in Chapter 4: the NetLogo hybrid model combines continuous flows with discrete agents; scenario testing of abruptio placentae and anemia; visualizations for education; can become digital twins for personalized predictions. Unlike other hybrid models (e.g., Hunt et al., 2018 single scale only) this thesis tackles emergent ICU dynamics so provides superior multiscale insights. However computational cost, validation (ethical constraints in fetal data) and parameter uncertainty prevent clinical implementation yet AI integration for refinement is required [69, 92, 102, 380, 382, 383, 395].
6. Objective five: identification and analysis of comprehensive datasets for sepsis and epilepsy including EEG and physiological time series has been achieved to a great extent in Chapters 5 and 6. For example the EEG Epileptic Set (500 interictal, 42 preictal samples) and Sepsis Set A (20,336 cases) are explored (e.g. Figures 6.1 and 6.2) by visualizations before AI development for classification and prediction. Limitations are dataset specificity (e.g., animal EEGs may not generalize to humans) and high missing values in sepsis data (> 79.4%) which might bias even if imputation is done [39, 52, 278, 293, 318, 327, 384, 396, 397].

7. The thesis has achieved the sixth objective of developing advanced imputation, transformation and preprocessing methods with algorithmic complexity estimation by block decomposition in Chapter 6. Kalman-ML imputation has

AUCs (0.953) higher than LOCF (0.925), BDM turns data into complexity metrics for ML readiness (Tables 6.6-6.11). This technique improves separability for epilepsy and sepsis. Compared to standard imputation techniques in biomedical data (mean imputation in previous studies) this method offers a new KCC-based approach for non-stationary signals that reduces errors by 10-20%. Limitations are computational cost of BDM, data quality (e.g., at least three observations) and overfitting in small datasets need wider validation [52, 278, 293, 318, 396].

8. Objective seven - integration of representation learning techniques, including NLP models like Word2Vec and BERT, to transform physiological data for improved prediction - has been achieved comprehensively in Chapters 6 and 7. EEG signals converted to text yield high AUCs (e.g., Word2Vec CBOW at 0.968), with embeddings like UMAP and PCA clustering classes (Figures 6.12-6.16). This captures nuanced patterns in non-stationary signals. Advancing beyond traditional representation learning in EEG, this work integrates complexity preprocessing for 3-5% gains. Key limitations include model interpretability issues (e.g., BERT's lower AUC of 0.670 without denoising) and the need for patient-specific training due to individual "brain languages," limiting generalizability [39, 40, 52, 291 - 293, 308, 381].
9. The eighth objective (to explore machine learning models with algorithmic complexity metrics for diagnostic and prognostic performance in sepsis and epilepsy) has been achieved very well in Chapter 7: GBM achieves AUC 0.953 for sepsis (outperforms winners of 2019 Challenge); NLP on KCC data achieves 0.97 AUC for EEG (SHAP plots explain this feature). This is good because early detection matters. Limitations include external validation drops (AUC 0.84 on new data), bias risk per PROBAST-AI and experimental nature that needs prospective studies for clinical trust [39, 40, 52, 278, 317, 327, 381, 384].
10. Chapter 8 has innovatively tackled Objective 9 (large language models with retrieval augmented generation and multi-agent systems for sepsis management). MA-RAG systems simulate ICU teams for antibiotic recommendations and guideline adherence (no hallucinations via external knowledge), case studies match protocols but evaluations disagree; beyond proof-of-concept LLMs in medicine (e.g., Zhang et al., 2024) this achieves 85–95% compliance in MIMIC-IV cases via domain specific RAG; failures of system (task misalignment), ethical bias in outputs, latency in real time ICUs; multimodal integrations (X-rays) are needed for full sepsis etiologies [366, 375, 379, 381, 386, 388, 398, 401].
11. Beyond proof-of-concept LLMs in medicine (e.g., Zhang et al., 2024) we achieve 85–95% compliance in MIMIC-IV cases by domain specific RAG (see below); system failures (task misalignment), ethical biases in outputs, latency in real time ICUs; multimodal integration (X-rays) required to handle all sepsis etiologies fully The tenth objective (software tools for early sepsis prediction, EEG analysis and multi-agent sepsis management validated for clinical and research settings) has been achieved with prototypes such as ISAAC-EEG-BDM-NLP (Figure 7 .22) and ISAAC Sepsis Expert (Figures 7.23 and A4.3-A4.5), combining findings from all chapters , code in Appendix 4; they allow personalized interventions with compression benefits (e.g. EEG from 7.67 MB to 250 KB). Implementation is supported by patents and certificates of

innovation in Appendix 5 formalizing preprocessing algorithms, hybrid models and AI systems but limitations are limited real world deployment (e.g. Moldova), high-quality inputs only and lack of full regulatory compliance (e.g. medical devices) so further iterations are needed [39, 40, 52, 102, 317, 381, 391].

12. There are some limitations: no real world deployment (e.g. Moldova), high quality inputs only and lack of full regulatory compliance (e.g. medical devices) so further iterations are needed [39, 40, 5 The thesis summarizes all the achievements towards its aims and objectives: complexity-driven intelligent methods for intensive care were advanced in all aspects (to some extent) through interdisciplinary innovation; overall limitations are translational gap from simulation to bedside, heterogeneity of data and ethical/computational challenges but work leads the way for hybrid AI systems in future, prospective validations and beyond sepsis and epilepsy applications too so that ICU mortality can be reduced and patient centered care become part of 2025 medical landscape [52, 69, 90, 102, 308, 327, 366, 378 - 381, 383, 385, 386, 390 - 393].

* - references shown in parentheses are based on the main thesis manuscript

RECOMMENDATIONS FOR FUTURE RESEARCH AND CLINICAL IMPLEMENTATION

Future Research Directions

Advancing Kolmogorov-Chaitin Complexity (KCC) for Biomedical Data

The thesis utilized KCC via the block decomposition method (BDM) for EEG and sepsis data analysis (Chapter 6). Future research should apply KCC to other signals like ECG or PPG, developing real-time algorithms to reduce BDM's computational intensity. Adaptive windowing or neural network approximations could help. Integrating KCC with topological data analysis may reveal structures in critical conditions like arrhythmia, while exploring causal inference could enhance personalized diagnostics.

Expanding Hybrid Modeling with AI

Chapter 4's hybrid ABM-SDM for fetal oxygen delivery shows multiscale potential. Extend this to ICU scenarios like acute kidney injury, incorporating ML for parameter autotuning. Reinforcement learning could optimize ABM rules, and deep learning could refine SDM equations. Develop "digital twin ecosystems" to simulate ICU resource dynamics, validated against diverse datasets to address parameter uncertainty.

Enhancing LLM Multi-Agent Systems

Chapter 8's LLM-based multi-agent systems with RAG show promise for sepsis management. Future work should integrate multimodal data (e.g., imaging, time series) and combine LLMs with symbolic AI to ensure guideline adherence. Federated learning could enable privacy-compliant training. Expand to conditions like delirium, focusing on explainable outputs.

Interdisciplinary Complexity Data Science Frameworks

Chapter 1's complexity data science paradigm needs standardized metrics for healthcare datasets. Apply to wearable sensor networks to predict transitions (e.g.,

septic shock) using evolving graphs. Collaborate with network science or quantum computing to explore quantum-enhanced complexity metrics.

Steps for Validation and Clinical Implementation

Prospective Clinical Validation

Validate ISAAC-EEG-BDM-NLP, ISAAC Sepsis Expert, and MA-RAG systems in ICU settings (e.g., Moldova hospitals). Compare predictions against outcomes like mortality or seizure frequency, testing GBM's AUC of 0.953 and Word2Vec's AUC of 0.968 (Chapters 7-8) against standard tools, ensuring inclusion of diverse cohorts and GDPR/HIPAA compliance.

External Dataset Testing

Address generalizability issues (e.g., sepsis AUC drop to 0.84, Chapter 7) by testing on MIMIC-IV or TUH EEG Corpus. Use automated data harmonization (e.g., FHIR) and transfer learning to mitigate overfitting.

Integration with Clinical Workflows

Integrate tools with EHRs via APIs for low-latency predictions. Develop user-friendly interfaces with visualizations (e.g., SHAP plots) and training modules for clinicians. Pilot in Moldova ICUs to measure workflow impacts.

Regulatory Compliance and Certification

Ensure compliance with FDA SaMD or EU MDR, conducting ISO 14971 risk assessments to address biases and failure modes. Monitor post-deployment adverse events for iterative updates.

Refinement through Feedback

Refine tools using clinician feedback, adjusting thresholds to reduce alert fatigue and personalizing EEG models. Use edge computing for real-time performance and retrain ML models with new ICU data.

Scalability and Cost-Effectiveness

Develop cloud-based or lightweight tool versions for low-resource settings. Conduct cost-effectiveness analyses and leverage open-source components (e.g., NetLogo models) to lower costs, optimizing algorithms for scalability.

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THE LIST OF SCIENTIFIC PAPERS PUBLISHED ON THE THESIS TOPIC

- **Monographs**

1.1. **IAPĂSCURTĂ, V**. *Inteligență, bazată pe complexitate în terapia intensivă: modelare, algoritmi și aplicații. Partea 1. Complexitatea în acțiune: de la modele teoretice la soluții multi-agent și gemeni digitali*. UTM 2026, Chișinău, Tipografia nr.1, 148 p. ISBN 978-9975-57-413-6.

1.2. **IAPĂSCURTĂ, V.** *Inteligență, bazată pe complexitate în terapia intensivă: modelare, algoritmi și aplicații. Partea 2. De la date la decizii: complexitate algoritmică și învățare automată în aplicațiile de terapie intensivă*. UTM 2026, Chișinău, Tipografia nr.1, 165 p. ISBN 978-9975-57-413-3.

- **Journal articles**

✓ **Articles in WoS journals, SCOPUS, and other international databases**

2.1.1. **IAPĂSCURTĂ, V**., ȚURCANU, D., BELÎI, A., BOSTAN, V. A Multi-Agent System for Early Sepsis Management Support: A Follow-up Evaluation Study. In: *Healthcare Informatics Research.* 2026, 32(2), pp. 190-195. https://doi.org/10.4258/hir.2026.32.2.190. ISSN 2093-368.

2.1.2. **IAPĂSCURTĂ, V**., FIODOROV, I., BELÎI, A., BOSTAN, V. Multi-Agent Approach for Sepsis Management. In: *Healthcare Informatics Research*. 2025, 31(2), pp. 209-214. ISSN 2093-3681. https://doi.org/10.4258/hir.2025.31.2.209.

2.1.3. **IAPĂSCURTĂ, V.** Combining Algorithmic Information Dynamics Concepts and machine Learning for Electroencephalography Analysis: What Can We Get?. In: *Complex Systems Journal*. 2022, 31(4), pp. 389-413. ISSN 0891-2513. https://doi.org/10.25088/ComplexSystems.31.4.389.

- **Articles in accredited national scientific journals**

✓ **articles in category B+/B journals**

2.2.1 **IAPĂSCURTĂ, V**., Exploring the human circulatory system through system dynamics: a model-based approach. In: J*ournal of Engineering Science* 2024, 31(4), pp. 95-104. ISSN:2587-3474. https://doi.org/10.52326/jes.utm.2024.31(3).01

2.2.2 **IAPĂSCURTĂ, V**, BELÎI, A. Rolul potențial al abordării bazate pe inteligența artificială pentru managementul sepsisului: un studiu de caz pilot, În: *Arta Medica* 2024, 4 (93), pp. 46-49, DOI: 10.5281/zenodo.14549531. https://zenodo.org/records/14549531

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✓ **Indexed in WoS/Scopus**

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3.1.3. **IAPĂSCURTĂ, V**., FALENCIUC, R., MUNTEANU, V., ARNAUT, O. Advancing Biomedical Engineering: An Agent-Based Approach to Pulmonary Edema Simulation. In: *Sontea, V., Tiginyanu, I., Railean, S. (eds.) 7th International Conference on Nanotechnologies and Biomedical Engineering. ICNBME 2025. IFMBE Proceedings, vol. 135.* Springer, Cham. pp. 66-75. https://doi.org/10.1007/978-3-032-06497-4_7.

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- **National conferences**

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- **Theses at the International/National conferences**

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4.4. **IAPĂSCURTĂ, V**. Agent-based modeling of fluid dynamics in lung tissue engineering. In: *The Materials of the National Scientific Conference with International Participation „Cells and tissues transplantation. Actualities and perspectives. The 3rd edition" dedicated to the 80th anniversary of the founding of Nicolae Testemitanu State University of Medicine and Pharmacy.* Chisinau, March 21-22, 2025. ISBN: 978-9975-82-413-2 http://repository.usmf.md/handle/20.500.12710/30460

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Intellectual Property Objects

5.1. **IAPĂSCURTĂ, V.,** BELÎI, A. Implementarea unui model cu trei compartimente al sistemului cardiovascular în mediul Netlogo pentru simularea debitului cardiac și a factorilor care îl influențează, Certificat nr. 6484, Ministerul Sănătății, USMF "Nicolae Testemițanu"; Certificat nr. 5, IMSP Instutul de medicină urgentă, 09.06.2026

5.2. **IAPĂSCURTĂ, V**., BELÎI, A. Implementarea unui model în mediul Netlogo pentru simularea mecanicii ventilatorii a plămânului în condiții fiziologice și patologice sub ventilație cu presiune pozitivă, Certificat nr. 6485, Ministerul Sănătății, USMF "Nicolae Testemițanu"; Certificat nr. 6, IMSP Instutul de medicină urgentă, 09.06.2026

5.3. **IAPĂSCURTĂ, V**., BELÎI, A. Implementarea unui model bazat pe agenți în mediul Netlogo pentru simularea și vizualizarea formării edemului pulmonar cardiogen sub influența presiunilor hidrostatică și oncotică , Certificat nr. 6486, Ministerul Sănătății, USMF "Nicolae Testemițanu"; Certificat nr. 7, IMSP Instutul de medicină urgentă, 09.06.2026

5.4. **IAPĂSCURTĂ, V**., BELÎI, A. Implementarea unui model conceptual în mediul Netlogo pentru simularea și vizualizarea reglării somn-veghe prin mecanismele circadian și homeostatic, Certificat nr. 6487, Ministerul Sănătății, USMF "Nicolae Testemițanu"; Certificat nr. 8, IMSP Instutul de medicină urgentă, 09.06.2026

5.5. **IAPĂSCURTĂ, V**., BELÎI, A. Implementarea unui model cu șase compartimente al sistemului cardiovascular în mediul Netlogo pentru simularea hemodinamicii în condiții fiziologice și în infarctul miocardic, Certificat nr. 6488, Ministerul Sănătății, USMF "Nicolae Testemițanu"; Certificat nr. 9, IMSP Instutul de medicină urgentă, 10.06.2026

5.6. **IAPĂSCURTĂ, V**., BELÎI, A. Elaborarea unui model multicompartimental în mediul Netlogo pentru simularea farmacocineticii propofolului administrat intravenos în cadrul anesteziei totale intravenoase, Certificat nr. 6489, Ministerul Sănătății, USMF "Nicolae Testemițanu"; Certificat nr. 10, IMSP Instutul de medicină urgentă, 10.06.2026

5.7. **IAPĂSCURTĂ, V**., BELÎI, A. Implementarea unui model în mediul Netlogo pentru simularea reglării livrării și consumului de oxigen (DO_2/VO_2) la nivel sistemic în condiții fiziologice și de șoc, Certificat nr. 6490, Ministerul Sănătății, USMF "Nicolae Testemițanu"; Certificat nr. 11, IMSP Instutul de medicină urgentă, 10.06.2026

5.8. **IAPĂSCURTĂ, V.,** BELÎI, A. Implementarea aplicației unui model în mediul Netlogo pentru simularea transportului și schimbului de O_2 și CO_2 la nivelul întregului organism în condiții fiziologice și patologice, Certificat nr. 6491, Ministerul Sănătății, USMF "Nicolae Testemițanu"; Certificat nr. 12, IMSP Instutul de medicină urgentă, 10.06.2026

5.9. **IAPĂSCURTĂ, V**., BELÎI, A. Implementarea unui model hibrid (bazat pe agenți și dinamica sistemelor) în mediul Netlogo pentru simularea interacțiunilor materno-placento-fetale și a livrării oxigenului la făt, Certificat nr. 6470, Ministerul Sănătății, USMF "Nicolae Testemițanu"; Certificat nr. 4, IMSP Instutul de medicină urgentă, 18.05.2026

5.10. **IAPĂSCURTĂ**, **V**., FIODOROV, I, LISNIC V. *Implementarea aplicației software ISAAC-EEG în baza complexității algorimice pentru analiza electroencefalogramei,*

Certificat nr. 5969, Ministerul Sănătății, USMF "Nicolae Testemițanu"; Certificat nr. 20, IMSP Instutul de medicină urgentă, 14.12.2022

5.11. **IAPĂSCURTĂ**, **V**., BELÎI, A. *Implementarea aplicației software ISAAC-Sepsis în baza învățării automate/inteligenței artificiale pentru prezicerea timpurie a sepsisului*, Certificat nr. 5965, Ministerul Sănătății, USMF "Nicolae Testemițanu"; Certificat nr. 18, IMSP Instutul de medicină urgentă, 12.12.2022

5.12. **IAPĂSCURTĂ**, **V**. *Implementarea aplicației software Sistem-expert acido-bazic ABB 1.1.1 pentru managementul pacienților în stare critică*, Certificat nr. 5968, Ministerul Sănătății, USMF "Nicolae Testemițanu"; Certificat nr. 19, IMSP Instutul de medicină urgentă, 13.12.2022

- **Software models**

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6.2. **IAPASCURTA, V**. Iterated Logistic function with two initial conditions [software] (model ID 5242), [cited 12.11.2025]. Available at: https://modelingcommons.org/browse/one_model/5242

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6.7. **IAPASCURTA, V**. Sleep-Wake_Regulation-Model 01_01 [software] (model ID 5147), [cited 12.11.2025]. Available at: https://modelingcommons.org/browse/one_model/5147

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6.9. **IAPASCURTA, V**. O2-CO2 Transport and Exchange [software] (model ID 5260), [cited 12.11.2025]. Available at: https://modelingcommons.org/browse/one_model/5329

6.10. **IAPASCURTA, V**., FALENCIUC, R. Cardiogenic Pulmonary Edema Model for Experimentation (model ID 7564), [cited 12.11.2025]. Available at: https://modelingcommons.org/browse/one_model/7564

6.11. **IAPASCURTA, V**. Oxygen Delivery and Consumption Regulation (model ID 5328), [cited 12.11.2025]. Available at: https://modelingcommons.org/browse/one_model/5328

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ADNOTARE

Iapăscurtă Victor, "Metode și algoritmi software inteligenți pentru terapia intensivă. Abordare prin prisma științei complexității", teza de doctor habilitat în informatică și medicină, Chișinău, 2023

Structura tezei: Teza cuprinde 275 de pagini și include introducere, 8 capitole, concluzii, o bibliografie din 401 de surse, 5 anexe, 89 de figuri și 37 de tabele. Cercetarea a rezultat în 54 de lucrări științifice, cu 20 ca unic autor, 34 ca prim/ultim autor, inclusiv 25 articole, dintre care 14 - în ediții cu factor de impact. **Cuvinte cheie**: știința complexității, terapie intensivă, sepsis, epilepsie, modelare bazată pe agenți, modelare dinamică a sistemelor, învățare automată, învățare a reprezentării, complexitate Kolmogorov-Chaitin, modele de limbaj mari, sisteme multi-agent, generare augmentată prin recuperare, gemeni digitali. **Scopul studiului**: Dezvoltarea de metode inteligente inovatoare, algoritmi și aplicații software pentru terapia intensivă, bazate pe știința complexității, pentru a îmbunătăți diagnosticul precoce, predicția și gestionarea afecțiunilor critice precum sepsisul și crizele epileptice. **Obiectivele studiului**: Stabilirea unui cadru de știință a complexității pentru sistemele de terapie intensivă;Evaluarea modelării bazate pe agenți, dinamica sistemelor și hibridă pentru simulări fiziologice; Identificarea și analiza seturilor mari de date pentru sepsis și epilepsie; Dezvoltarea de preprocesare avansată a datelor cu estimarea complexității algoritmice; Integrarea învățării reprezentării și a învățării automate pentru predicții îmbunătățite; Încorporarea sistemelor multi-agent bazate pe modele de limaj mari pentru gestionarea sepsisului; și Crearea de instrumente software pentru aplicații clinice și de cercetare. **Noutate științifică și originalitate**. Teza introduce o integrare nouă a științei complexității cu terapia intensivă, valorificând neliniaritatea și emergența pentru a aborda lacunele de diagnostic. Este pionieră în utilizarea complexității Kolmogorov-Chaitin (KCC) prin descompunerea în blocuri pentru preprocesarea semnalelor biomedicale, îmbunătățind detectarea tiparelor în datele nestaționare. Cadrul de modelare hibridă, care combină abordări bazate pe agenți și dinamica sistemului pentru simulări, cum ar fi livrarea oxigenului fetal, este inovator. În plus, aplicarea modelelor de limbaj mari cu generare augmentată prin recuperare și sisteme multi-agent pentru gestionarea sepsisului reprezintă o abordare de ultimă generație a deciziilor clinice în timp real, distingând această lucrare de metodele reducționiste tradiționale. **Principalele rezultate**. Cercetarea stabilește un cadru științific al complexității, modelând cu succes procese fiziologice precum edemul pulmonar cardiogen și livrarea oxigenului fetal, utilizând metode bazate pe agenți, dinamica sistemului și hibride. Preprocesarea avansată, inclusiv estimarea CKC, transformă datele EEG și sepsis pentru învățarea automată, atingând performanțe predictive ridicate. Instrumente software create precum ISAAC-EEG-BDM-NLP și ISAAC Sepsis Expert permit detectarea și gestionarea precoce, sistemele bazate pe modele de limbaj mari îmbunătățind respectarea ghidurilor privind sepsisul. **Semnificația teoretică a cercetării**. Teza promovează știința complexității prin formalizarea aplicării sale în terapia intensivă, integrând-o cu modelare, învățare automată și inteligență artificială. Aceasta contribuie cu o nouă paradigmă a științei datelor despre complexitate, conectând teoria sistemelor și abordările bazate pe date. Utilizarea KCC pentru analiza semnalelor biomedicale oferă un salt teoretic în captarea dinamicii emergente, în timp ce modelarea hibridă și sistemele multi-agent oferă noi cadre pentru înțelegerea fenomenelor comune pentru terapia intensivă, îmbogățind cercetarea transdisciplinară. **Valoarea aplicativă a lucrării**. Instrumentele dezvoltate oferă soluții practice pentru predicția și gestionarea timpurie a sepsisului și prognoza convulsiilor bazată pe EEG, îmbunătățind luarea deciziilor clinice și îngrijirea personalizată. Aceste aplicații sunt scalabile pentru medii cu resurse limitate, cum ar fi Moldova, sprijinind triajul critic, planificarea intervențiilor și educația medicală prin simulări interactive. **Implementarea rezultatelor științifice**. Prototipurile software, ISAAC-EEG-BDM-NLP pentru cercetarea epilepsiei și ISAAC Sepsis Expert și MA System pentru gestionarea sepsisului clinic, sunt concepute pentru integrarea în sistemul de sănătate din Republica Moldova. Sunt planificate implementări pilot în unitățile de terapie intensivă, în așteptarea aprobării autorităților de reglementare și a validării prospective, cu potențialul unei adoptări pe scară largă prin intermediul platformelor bazate pe cloud pentru a îmbunătăți rezultatele pacienților.

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SUMMARY

Iapăscurtă Victor, "Intelligent methods and software algorithms for intensive care. A complexity science approach," postdoctoral thesis in computer sciences and medicine, Chisinau, 2025

Thesis structure: The thesis comprises 275 pages and includes an introduction, 8 chapters, conclusions, a bibliography of 401 sources, 5 appendices, 87 figures, and 37 tables. The research resulted in 54 scientific works, with 20 as the sole author, 34 as the first/last author, including 25 articles of which 14 publications in journals/editions with an impact factor. **Keywords**: complexity science, intensive care medicine, sepsis, epilepsy, agent-based modeling, system dynamics modeling, machine learning, representation learning, Kolmogorov-Chaitin complexity, large language models, multi-agent systems, retrieval-augmented generation, data preprocessing, digital twins. **The aim of the study**. Developing innovative intelligent methods, algorithms, and software applications for intensive care medicine, grounded in complexity science, to enhance early diagnosis, prediction, and management of critical conditions like sepsis and epileptic seizures. **Objectives of the study**: establishing a complexity science framework for intensive care systems; evaluating agent-based, system dynamics, and hybrid modeling for physiological simulations; identifying and analyzing datasets for sepsis and epilepsy; developing advanced data preprocessing with algorithmic complexity estimation; integrating representation learning and machine learning for improved predictions; incorporating large language model-based multi-agent systems for sepsis management; and creating software tools for clinical and research applications in Moldova. **Scientific novelty and originality**. The thesis introduces a novel integration of complexity science with intensive care, leveraging nonlinearity and emergence to address diagnostic gaps. It pioneers the use of Kolmogorov-Chaitin complexity (KCC) via block decomposition for preprocessing biomedical signals, enhancing pattern detection in non-stationary data. The innovative hybrid modeling framework combines agent-based and system dynamics approaches for multiscale simulations, such as fetal oxygen delivery. Additionally, the application of large language models with retrieval-augmented generation and multi-agent systems for sepsis management represents a cutting-edge approach to real-time clinical decision-making, distinguishing this work from traditional reductionist methods. **Main results**. The research establishes a complexity science framework that successfully models physiological processes, such as cardiogenic pulmonary edema and fetal oxygen delivery, using agent based, system dynamics, and hybrid methods. Advanced preprocessing, including KCC estimation and imputation, transforms EEG and sepsis data for machine learning, achieving high predictive performance. Software tools like ISAAC-EEG-BDM-NLP and ISAAC Sepsis Expert enable early detection and management, with large language model-based systems improving sepsis guideline adherence. **The theoretical significance of the research**. The thesis advances complexity science by formalizing its application in intensive care and integrating it with modeling, machine learning, and AI. It contributes a novel complexity data science paradigm that bridges systems theory and data-driven approaches. The use of KCC for biomedical signal analysis offers a theoretical leap in capturing emergent dynamics, while hybrid modeling and multi-agent systems provide new frameworks for understanding multiscale ICU phenomena, enriching transdisciplinary research. **Applicative value of the work**. The developed tools offer practical solutions for early sepsis prediction and management and EEG-based seizure forecasting, enhancing clinical decision-making and personalized care. These applications are scalable for resource-limited settings like Moldova, supporting ICU triage, intervention planning, and medical education through interactive simulations. **Implementation of scientific results**. The software prototypes, ISAAC-EEG-BDM-NLP for epilepsy research and ISAAC Sepsis Expert and MA System for clinical sepsis management, are designed for integration into Moldova's healthcare system. Pilot implementations in ICUs are planned, pending regulatory approval and prospective validation, with potential for broader adoption via cloud-based platforms to improve patient outcomes.

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IAPĂSCURTĂ Victor

INTELLIGENT METHODS AND SOFTWARE ALGORITHMS FOR INTENSIVE CARE. A COMPLEXITY SCIENCE APPROACH

122.03 – MODELING, MATHEMATICAL METHODS, SOFTWARE PRODUCTS

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