Review

Personalized Plasma Medicine for Cancer: Transforming Treatment Strategies with Mathematical Modeling and AI Algorithms

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Personalized Plasma Medicine for Cancer: Transforming Treatment Strategies with Mathematical Modeling and AI Algorithms

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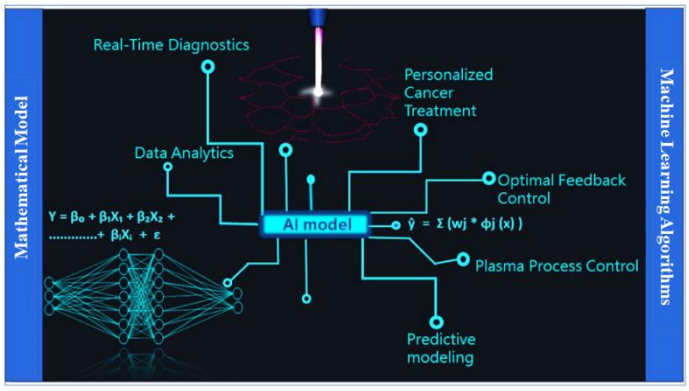
Simple Summary: Complexity, heterogeneity, and treatment resistance of cancers create challenges in achieving successful treatment outcomes. Personalized Cold Atmospheric Plasma (CAP) therapy emerges as a prospective approach, fine-tuning parameters for individual patients. AI-driven self-adaptive CAP optimizes therapy in real-time, promising better outcomes in personalized cancer care.

Abstract: Plasma technology shows tremendous potential for revolutionizing oncology research and treatment. Reactive oxygen and nitrogen species, electromagnetic emissions generated through gas plasma jets, have attracted significant attention due to their selective cytotoxicity towards cancer cells. To leverage the full potential of plasma medicine, researchers have explored the use of mathematical models and various subsets of machine learning, such as reinforcement learning, and deep learning. This review emphasizes the significant application of AI algorithms in the adaptive plasma system, paving the way for precision and dynamic cancer treatment. Realizing the full potential of AI in plasma medicine, requires research efforts, data sharing and interdisciplinary collaborations. Unravelling the complex mechanisms, developing real-time diagnostics, and optimizing AI models will be crucial to harness the true power of plasma technology in oncology. The integration of personalized and dynamic plasma therapies, alongside AI and diagnostic sensors, presents a transformative approach to cancer treatment with the potential to improve outcomes globally.

Keywords: machine learning; reinforcement learning; deep learning; Gaussian process; artificial neural networks; real-time diagnostics.

Graphical Abstract



1. Introduction

Plasma technology, rapidly emerging field at the intersection of plasma physics and medicine holds immense potential for biomedical applications [1,2]. Plasma, known as the fourth state of matter

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is typically formed by heating gas such as inert gases like argon or helium, or air. When heated, the high-speed electrons collide with atoms or molecules causing the removal of electrons and generating highly reactive positive and negative ions. These ions are conductive and can oscillate in response to electric and magnetic fields. The oscillations can give rise to emission of various electromagnetic waves [3]. Additionally, there are also low energy electrons that can only excite particles without causing ionization. These excited particles release energy in the form of photons. Plasma or ionized gas, is a complex mixture comprising electrons, positively and negatively charged ions, radicals, neutral atoms and molecules, atoms at excited state, electromagnetic waves, and electromagnetic fields [4]. The degree of ionization and the specific composition of plasma is dependent on factors such as temperature, pressure, energy supply, nature of the gas, electron density ranges, the devise used and operational conditions utilized to generate the plasma [5,6].

The most common type of low temperature atmospheric pressure plasma is the cold atmospheric plasma jets (CAPJ) has been well established in the field of biology and medicine [7,8]. It has shown great potential for numerous biomedical applications including wound healing [9,10] and skin rejuvenation in dermatology, decontamination, and sterilization [11, 12] biofilm removal [13] in health care-hygiene, periodontal treatment [14], root canal disinfection and tooth bleaching in dental and hygiene [15], surface modifications of orthopedic materials [16]. Furthermore, CAP has demonstrated promising effects in antitumor immunity [17,18] and cancer/tumor therapies [19,20] within the field of oncology.

Atmospheric plasma, can self-organize into different patterns with modified plasma compositions in response to various operational parameters and interactions with the target environment [21-22]. This transition from spatially homogeneous state to self-organized patterns in response to various parameters like discharge voltage [23], electrical permittivity of target cells [24] can play an important role in the therapeutic outcome of plasma treatment for cancer [22]. Self-organization might allow an adaptive and self-adaptive plasma system that can dynamically adjust and optimize plasma treatment conditions based on real-time feedback [25]. It aims to maximize the therapeutics on cancer cells while ensuring safety and efficacy.

This review focuses specifically on the recent prominence of cold atmospheric plasma (CAP) in the field of oncology, with special emphasis on the application of various mathematical models and artificial intelligence (AI) algorithms. CAP's potential to revolutionize cancer treatment is explored in this review, drawing attention to its unique adaptive and self-adaptive characteristics and the role of mathematical modelling and advanced algorithms in advancing its application in precision medicine.

2. Mathematical models for CAP treatment response in cancer

In cancer research, mathematical modeling plays a pivotal role in comprehending the intricate dynamics of cancer in response to various treatments [26,27]. It complements cancer research by providing valuable quantitative predictions to unravel the complexity of cancer and open new avenues for developing effective treatments [28]. For instance, a mathematical model of tumor growth and its response to CAP treatment/chemotherapy/radiotherapy might predict the rate at which the tumor size changes over time, the dosage of plasma/drug/radiation in the tumor cells, or the percentage of tumor cells that develop resistance to a treatment. These predictions can then be compared to the actual data collected from the experiments or clinical studies to assess the accuracy and validity of the model. The number of mathematical models developed for various cancer treatment approaches is increasing [29,30-32] (Figure 1).

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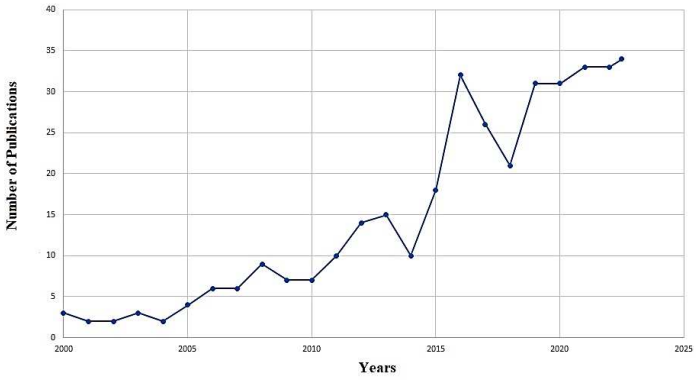

Figure 1. A Graph depicting the rising trend in mathematical modeling to study the response of cancer cells to different treatment strategies, based on search results in PubMed using the search terms, ("mathematical model") AND (cancer treatment response) and after full text screening for better relevancy.

These treatment response models have been developed to predict response of cancer cells to different treatment strategies [33-34]. Additionally, these models aim to optimize treatment schedules by identifying optimal and combination regimens, thus improving treatment outcomes [35–37]. Several mathematical models have been validated in preclinical studies and trials, demonstrating their potential in designing successful clinical trials [38–44]. Leder et al. [45] and Dean et al. [44] developed a novel radiation therapy schedule based on mathematical modeling, which improved survival in preclinical trials using mouse models of glioblastoma (GBM). They then tested this schedule in a clinical trial on recurrent GBM patients, successfully demonstrating its feasibility and safety. While the results suggest improved tumor control, larger trials are needed to confirm its efficacy. These findings highlight the utility of mathematical modeling in optimizing treatment strategies for cancer and provide valuable insights for potential clinical applications.

After the proposal of adaptive and self-adaptive plasma [46,47], an experimental growth model was developed [48] to predict the dynamic response of cancer cells (U-87 MG and MDA-MB-231) to gas plasma treatment [23]. The model successfully captured the response of cancer cells (cell viability data obtained from the luminescence assay) to variations in treatment duration and plasma discharge voltage. The real-time luminescent signals can serve as the feedback signal. Model Predictive Control (MPC), an advanced control algorithm was used to optimize the treatment parameters (treatment duration and plasma discharge voltage) for CAP treatment to minimize cancer cell viability. The optimization is done using the mathematical model of cancer cell response to CAP treatment, and MPC continuously adjusts the treatment parameters based on real-time feedback to achieve the desired treatment outcome.

In recent studies, indirect treatment using plasma treated liquids (PTLs) [49,50] or plasma treated hydrogels (PTHs) [51] has shown enhanced cytotoxicity and anticancer immune responses, attributed to the long-lived reactive oxygen and nitrogen species (RONS) such as H_2O_2, NO_2^-, NO_3^- [52]. These treatments have demonstrated greater effectiveness than direct plasma treatment [53–57]. However, despite their advantages, concerns regarding the lack of consistent molecular-level analysis and precise control over their chemical compositions have been raised, limiting their clinical suitability. Bengston and Bogaerts [58,59] developed a predictive model specifically focused on the kinetics of H_2O_2, NO_2^- in PTLs treatment, considering their interactions with cancer cells and the role of catalase, an enzyme that regulates H_2O_2 concentration (Table 1).

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Table 1. Mathematical models to represent the response of cancer cells to CAP/PTLs.

Mathematical models employed	Response parameter measured/assumed	Parameters influencing cancer treatment	Significance of the model	Reference
Linear model	Cell viability using cell counting kit-8	Treatment duration, liquid surface, thickness of the medium, number of cells	Provides an insight into the relationship between various parameters and the efficiency of PAM in treating cancer cells.	[60]
General mathematical model	Permittivity of the cells by capacitance imaging.	Electron density of CAP bullet with cell lines as targets	Permittivity of cancer cells can influence the behavior (eg. electron density, electric field) of CAPJ. Implies the significance in selective cancer treatment and adaptive plasma control.	[61]
Exponential growth model, Net proliferative rate function together with MPC	Cell viability using Real Time-Glo assay providing real-time feedback	Plasma discharge voltage, treatment duration	Improves the effectiveness and selectivity of CAP treatment on cancer cells by optimizing the treatment parameters.	[48]
Net proliferative rate function, Gaussian process regression model together with MPLC	Electrical properties of cells using EIS/FPR providing real-time feedback	Plasma discharge voltage, treatment duration, flow rate, cell viability	Improves the effectiveness and selectivity by adapting and optimizing the treatment parameters of SACAPJ	[62]

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Phenomenological rate equation model	Lipid peroxidation by measuring MDA, RONS using OES.	Gold nanoparticles, RONS in CAP	CAP treatment enhanced the uptake of gold nanoparticles by the brain cancer cells through clathrin-mediated endocytosis	[63]
A custom mathematical model to analyze the catalase-dependent kinetics	Concentration of hydroxyl radicals	Singlet oxygen exposure, catalase concentration	Demonstrates that catalase inactivation by singlet oxygen would not be sufficient to reactivate the apoptotic pathway. Hence, catalase-dependent apoptotic pathways are unlikely to be the primary cause of the anti-cancer effect of CAP. Needs experimental validations.	[58]
Predictive model	Concentration of H_2O_2 and NO_2^-	Membrane diffusion rate of H_2O_2, intracellular catalase concentration	Predicts how varying properties of PTLs, such as the concentration of H_2O_2 and NO_2^-, influence their anti-cancer efficacy and selectivity.	[59]

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Translating mathematical modeling into clinical reality presents several challenges, including model uncertainty, the complexity of tumor biology, variations in experimental conditions and biological system measures, data sparsity, external disturbances, logistical constraints in treatment administrations, patient-specific factors, variability in the tumor microenvironment, and patient medications [64]. However, to achieve reliable and translational predictions, a systematic and rigorous approach needs to be followed [65]. AI models can significantly improvise mathematical models by enhancing prediction accuracy, automates feature engineering, handles non-linear relationships, deals with noisy, incomplete data, enables real-time adaptability and incorporation of heterogenous data types [66].

3. AI for CAP treatment response in cancer

Artificial intelligence (AI) is about creating "thinking machines" that can make decisions on their own. Machine learning (ML) is the subset of AI that aims at creating "learning machines" in which machines/tools learn from data and perform tasks without explicit programing [67]. Constructing an AI model requires the integration of mathematical models and ML algorithms. Not all mathematical models are ML algorithms but all ML algorithms are mathematical models. A tutorial review on widely used ML methods that can help in discovering patterns and relationships in datasets that may be challenging for human intuition are well described by Bonzanini et al. [68].

Evolution of AI with medicine, particularly with the integration of ML has opened new possibilities in all aspects of oncology, from improving diagnostics to personalized cancer treatment and improved patient care in the ever-evolving health care landscape [69–78]. Although ML has been applied in various treatment approaches in cancer medicine, its use in plasma medicine is relatively limited (Figure 2). The potential of ML in accelerating plasma research towards personalized cancer treatment is well discussed [78–81].

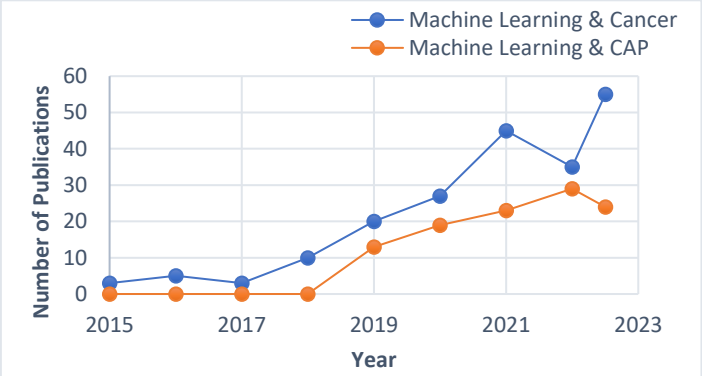

Figure 2. A scatter chart comparing increase in the application of Machine Learning in Cancer and CAP, based on search results in PubMed & Google Scholar using the search terms, ("Machine Learning") AND (Cancer Treatment) & ("Machine Learning") AND ("Cold Atmospheric Plasma").

3.1. Reinforcement learning

In machine learning (ML), algorithms are exposed to large datasets containing relevant information, such as input features (e.g., varying operational parameters of the adaptive plasma system) and target labels (e.g., treatment responses by the cancer cells). The objective is to analyze the datasets, identify patterns and relationships between input features and target labels, and adjust the internal parameters of the model algorithm iteratively to improve its predictive accuracy (e.g., optimizing parameters in the adaptive plasma system for selective cytotoxicity towards cancer cells). The goal is to minimize the difference between the model's predictions and the actual outputs during training, making the model "trained" and capable of making accurate predictions.

Different ML algorithms such as reinforcement learning (RL) and deep learning (DL) have different approaches to update their parameters during training. For example, in RL process, the agent (adaptive plasma system) learns, gets trained and improves its behavior in an environment (cancer cells) through its interaction experience [83]. It takes actions, receives feedback in the form of rewards and penalties based on the effectiveness of its treatment strategies, and uses this feedback to

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update its internal parameters and improve its decision-making. The system aims to find an optimal strategy that maximizes the cumulative reward it receives.

Hou et al. [80], developed an adaptive plasma framework for CAP cancer treatments using integration of empirical dynamic modeling and reinforcement learning. The empirical dynamic model was constructed using data collected from in vitro experiments [23] that provided information on how cancer cell viability changes over time under various CAP treatment conditions (eg. treatment duration from 0 to 180 seconds, and the discharge voltage between 3.16 kV and 3.71 kV). The empirical data obtained from in vitro experiments may represent specific scenarios and treatment conditions. To estimate for a wide range of treatment scenarios, a Gaussian process, a type of statistical modeling tool, that helps the model to capture the variability and uncertainty inherent in real-world clinical settings was incorporated. The CAP cancer treatment was then modelled as a Markov decision process (MDP) and conjugated with safe Q-learning. The MDP represents the sequence of states and actions in the treatment process. Each state corresponds to a specific situation or condition of the cancer cells (eg. cancer cell viability) and each action represents a treatment strategy that the adaptive plasma system can take (eg. treatment duration, discharge voltage). MDP helps in defining the states, actions, and transition probabilities in the treatment process, but it does not inherently provide the optimal policy for selecting actions that lead to the best long-term rewards. Q-learning, a specific algorithm designed for reinforcement learning tasks [84], helps the adaptive plasma system to learn from its interactions with the environment and update its decision-making process by estimating the expected cumulative rewards for different actions in different states. This enables the system to make better decisions and optimize the treatment plan to achieve safer and more personalized cancer treatment (Figure 3).

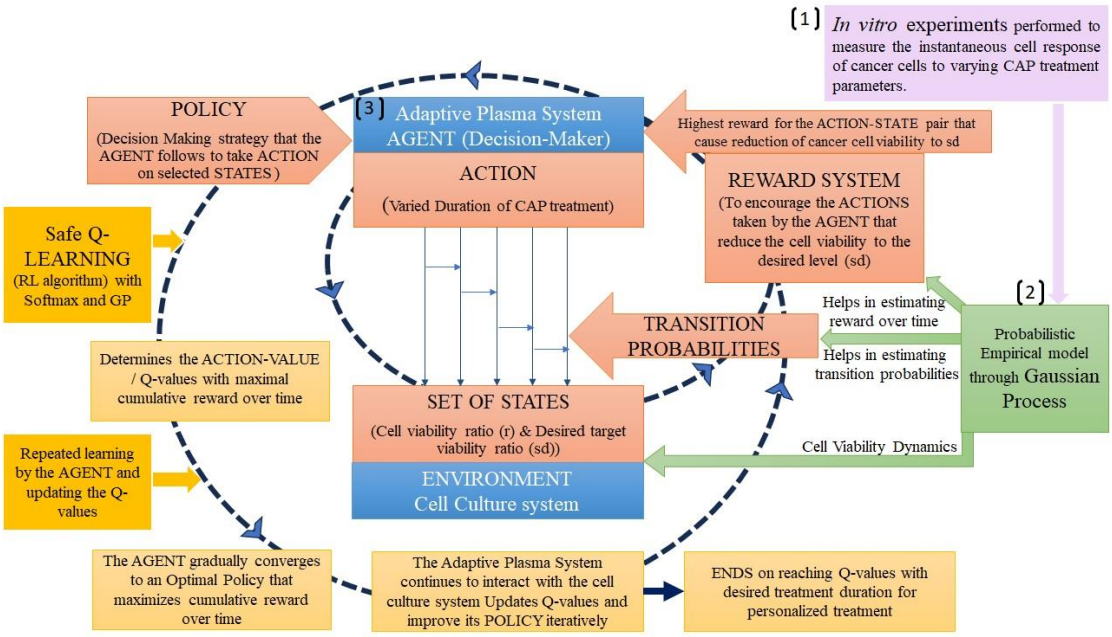

Figure 3. Adaptive Plasma Framework for Precision Cancer Treatment: Integration of GP, MDP, Safe Q-Learning and Softmax[80].

Despite its limitations in capturing all treatment scenarios, handling higher-dimensional inputs, ensuring complete safety, and requires in vivo validation, further research, and advancements in real-time diagnostics in vivo, deep learning and clinical experiments can address some of these limitations and enhance the model's performance and safety in clinical applications.

3.2. Gaussian process

Lin et al. [62] used Model Predictive Learning Control (MPLC), an extension of MPC that incorporates machine learning techniques for improved performance and adaptation. While MPC typically uses a fixed mathematical model and optimization algorithm-based control strategy [48],

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MPLC integrates machine learning models to capture system dynamics and adapt the control strategy based on real-time data. In the study, MPLC is implemented by using Gaussian Process (GP) regression, a statistical machine learning technique, to model the dynamic behavior of cancer cell viability in response to CAP treatment. The GP model is continuously updated with real-time feedback from the actual cancer cell responses, measured using real-time electrochemical impedance spectroscopy (EIS), after each treatment. This real-time feedback enables the MPLC algorithm to adapt and improve its predictions and treatment plans over time (Figure 4).

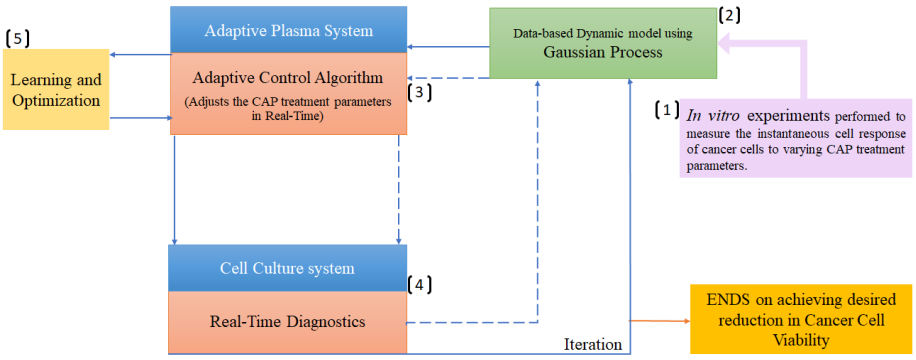

Figure 4. Model Predictive Learning Control (MPLC) framework: Merging Real-Time data with Adaptive Plasma Control System to modify the treatment parameters online, making treatment more effective and personalized to each cancer cell's response [62].

By dynamically adjusting the plasma treatment parameters based on actual system responses, the self-adaptive plasma jet can optimize its treatment strategy for a wide range of biomedical applications and variations in the system. This adaptive approach enhances the effectiveness and efficiency of the CAP treatment, making it more adaptable to different situations and treatment objectives. The integration of machine learning with control algorithms allows the system to learn from data and refine its decisions, leading to more robust and successful treatments.

Despite the promising potential of the model, it faces challenges such as data noise and uncertainty, computational complexity, and optimization difficulties. To address these challenges, researchers can employ strategies such as data preprocessing, uncertainty estimation, approximation techniques, parallel computing, advanced optimization algorithms.

3.3. Deep learning

Deep learning uses artificial neural networks (ANNs) with multiple layers (deep neural networks) to make predictions from the labeled data (for instance real-time spectra from Optical Emission Spectroscopy). The self-adaptive plasma system empowered with AI holds great promise for advancing precision medicine and improving cancer treatment outcomes [85]. The self-adaptive plasma system is a plasma control system that can dynamically and autonomously diagnose plasma chemistry, adjust its operating parameters (eg. Gas and power inputs) to control and optimize plasma chemical composition in real-time according to the required species/dosage to kill cancer cells. This system typically employs artificial neural networks and Gradual-Mutation algorithms (GMA), to continuously monitor, analyze the datasets, control, and optimize plasma chemistry and thus make real-time decisions on how to modify the plasma conditions. The real-time spectra of plasma chemical composition and temperatures are obtained using spontaneous emission spectroscopy and processed by a diagnostic ANN. The diagnostic ANN provides valuable outputs on plasma chemistry, which are then used by a control ANN as inputs to adjust plasma parameters like gas injections and energy levels. The control ANN is trained by GMA to adjust the production of specific RONS associated with apoptosis of cancer cells. It receives feedback from the diagnostic ANN and dynamically adjusts the gas and power inputs to optimize the concentration of these species using in the plasma. GMA is used to train both the diagnostic and control ANNs effectively, allowing the self-adaptive plasma system to diagnose, control and optimize the plasma chemistry in real-time based on the OES data and specific objectives. Such an AI empowered self-adaptive plasma system allows for personalized treatments tailored to the specific characteristics of the patient's cancer

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The integration of diagnostic ANN, chemical process network (CPN), and control ANN creates an adaptive and intelligent system for effective and personalized cancer treatment [86] (Figure 5).

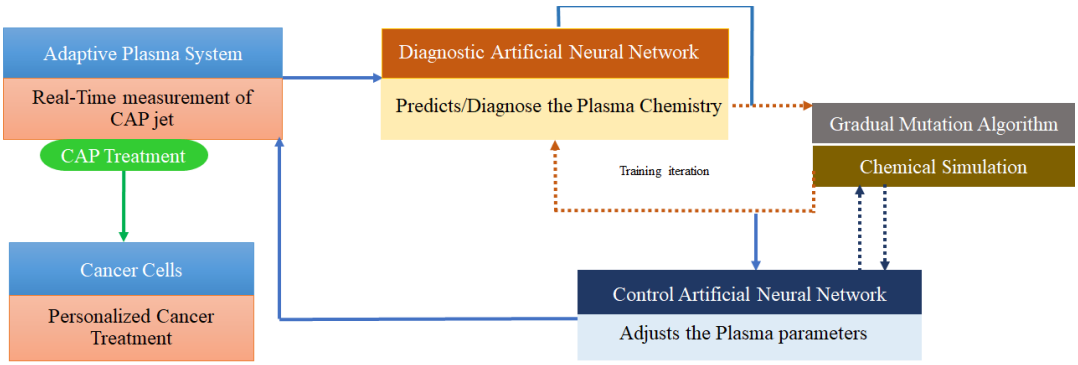

Figure 5. Artificial Neural Networks (ANNs) in Real-Time diagnostics of plasma composition and Real-time control of plasma parameters to achieve optimized composition for personalized cancer treatment [85].

AI-driven gas plasma can continuously learn from treatment outcomes, adapt to changing conditions, and optimize treatment plans. This personalized and dynamic approach has the potential to improve the efficacy of cancer therapies, reduce side effects, and advance precision medicine. The combination of self-adaptive gas plasma with AI technologies has the potential to revolutionize cancer treatment, making it more personalized, efficient, and adaptable to individual patients' needs. This research area holds promise for high-impact advancements in cancer therapy and precision medicine.

The models mentioned above have shown substantial advancements in optimizing treatment strategies for safer and personalized cancer treatment. Their current usage primarily remains limited to research-oriented formats, impeding their practical implementation in real-world clinical settings. However, for these models to be deployed in clinical practice, they must undergo rigorous validation testing, including clinical trials and regulatory approval. As artificial intelligence gains broader acceptance in clinical applications, we foresee the imminent emergence of an artificial intelligence-driven adaptive plasma system for personalized cancer treatment, revolutionizing medical practice and paving the way for transformative advancements in oncology.

4. AI in Real-Time diagnostics

To exploit the adaptive and self-adaptive properties of CAP in developing personalized treatment protocols, it is important to estimate the operational parameters of the CAP sources and measure the cell response to CAP treatment in real-time.

4.1. Real-time diagnosis of operational parameters of CAP sources

Traditional diagnostics (eg. Laser induced fluorescence, mass spectrometry, spontaneous Raman scattering) of the different operational parameters of CAP sources are complex and expensive requiring sophisticated instrumentation setups and specialized analysis making them impractical for real-time use [87,69] and makes it challenging to control the plasma consistently and effectively. Using information-rich datasets collected from simpler diagnostic methods like optical emission spectroscopy (OES) [88], electro-acoustic emission and enabling fast, automated data processing and analysis using AI algorithms in real-time monitoring and control, improves the feedback control, ensuring effective and optimal performance of CAP sources [69,87]. Simulated data [89,90], although not capturing all the complexities in real-world scenarios, complements real data by providing a controlled environment for analysis and experimentation.

Analysis of the datasets manually with traditional methods can be challenging due to complex relations and patterns in the data. ML algorithms and other AI algorithms (Table 2) are designed to handle such complexity and can identify patterns and trends that may not be apparent to human analysis [68].

Table 2. Selected parameters of the CAP sources for real-time diagnostics and AI algorithms employed.

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Selected Parameters of the CAP sources for Real-Time diagnostics	Input Data obtained from	AI algorithms employed	Reference
Rotational and Vibrational temperatures	OES	Linear regression (Supervised ML)	[87]
Substrate characteristics	OES	k-Means Clustering (Unsupervised ML)	[87]
Separation distance between the electrodes	Electro-Acoustic Emission	Gaussian Process Regression (Supervised probabilistic ML)	[87]
Electron energy distribution function (EEDF)	OES	Genetic Algorithm (metaheuristic algorithm)	[91]
EEDF	OES, Momentum-transfer cross section	Visible Bremmsstrahlung Inversion (Supervised ML)	[92,93]
Time-series current signals from APPJ (discharge type and working gas)	Sensors/Probes	Convolutional neural networks (DL)	[94]
Plasma Plume length	Video frames of the plasma plume captured using a camera (iPhone 11)	Computer Vision algorithms	[95]
Temperature setpoint	Simulated data from thermal dynamics model of plasma-substrate interactions	Reinforcement learning	[89]
Self-Adaptive Plasma Chemistry Gas input densities and Energy levels	OES	Artificial Neural Networks (DL), Gradual Mutation Algorithm	[85]
Pulse Discharge characteristics (current density and gap voltage)	Simulated fluid model data of time and pulse rise rate	Deep neural networks (DL)	[90]
Plasma chemistry (tokamak)	FTIR	Physics Informed Neural Networks	[96]

ML algorithms can be trained on the operational parameters and their corresponding data, allowing them to learn and generalize their knowledge for making predictions on new, unseen data. As new data is received the algorithms rapidly process and analyze data, enabling quick estimation of critical operational parameters from the spectral data or other input data in real-time. ML offers promising solutions by developing input-output models that enable real-time computations allowing for more advanced feedback control strategies [81,97]. Building multivariable non-linear prediction models to describe the intricate behavior of CAP interacting with cancer cells are essential for guiding efficient cancer treatment strategies [86]. AI models can thus be used for real-time monitoring and diagnostics [87,91–93], detecting any deviations from the normal behavior [94,95,98], and predicting when maintenance or adjustment is required [85] for maintaining optimal real-time control of the operational parameters. Thus, AI based approaches, specifically ML can significantly improve the reliability and performance of CAP by adapting to dynamic and uncertain environments.

4.2. Real-time diagnosis of the cell responses to CAP treatment

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Collecting real-time data on cancer cell responses to different CAP treatment modalities is challenging. Studies discussed in section 3.1 and 3.2 have utilized real-time EIS measurements [62,80] (Table 3) and has focused on incorporating automated feedback control systems into adaptive plasma system to optimize performance and safety (Figure 6).

Table 3. Cancer cell response measured in Real-time *in vitro* studies.

Input data	Real-time diagnostics	Algorithms used	Reference
CAP treatment duration and Discharge voltage applied	Cell viability Luminescence Assay	Model Predictive Control (MPC)	[48]
Cancer Cell viability ratio	Electrochemical Impedance Spectroscopy (EIS), operational parameters	Gaussian Process (GP), MPLC	[62]
Cancer Cell viability ratio	EIS, Cell viability assays, operational parameters	GP Regression (Supervised probabilistic ML), Safety Q – Reinforcement learning	[80]
Voltage applied, irradiation time, frequency of the plasma and flow rate of the feed gas on the extent of DNA damage	Agarose gel electrophoresis, UV fluorescence Imaging	Artificial Neural Networks (supervised DL) Physics Guided Neural Network (supervised DL	[99]

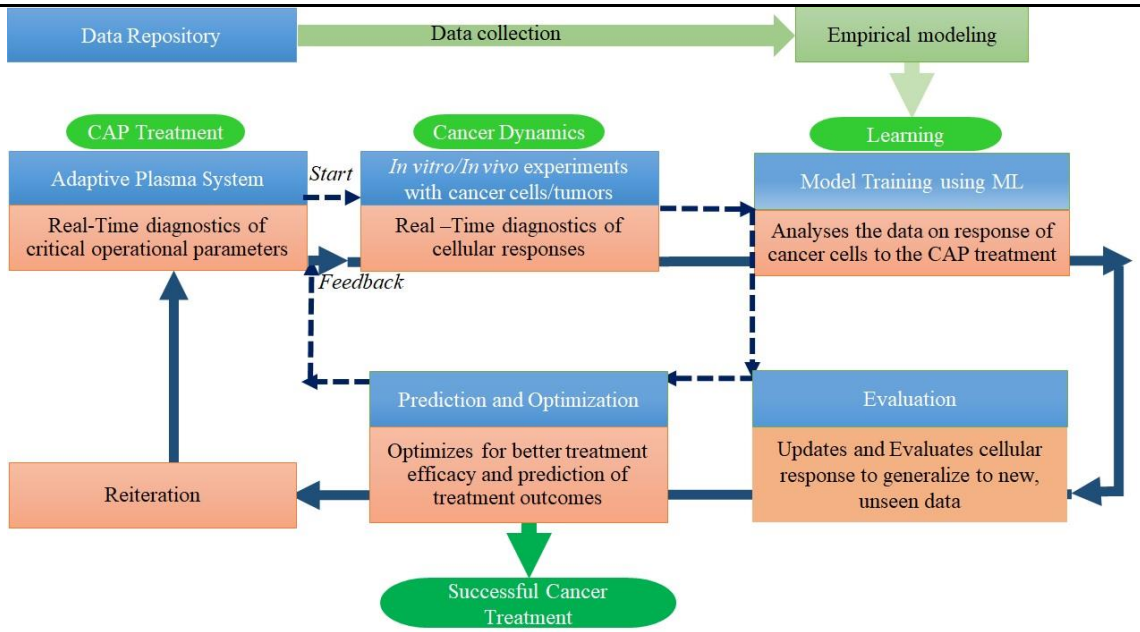

Figure 6. Incorporating automatic real-time feedback control strategy into Adaptive Plasma system.

Yet, advanced real-time diagnostic systems are still needed to provide sensitive, accurate, and reproducible data for these feedback control systems. To achieve optimal results, sophisticated diagnostic systems with high sensitivity, accuracy, and reproducibility are imperative. These systems should seamlessly integrate with the biological target and have minimal interference with the plasma treatment process. By fulfilling these criteria, the feedback control loop can make well-informed and precise adjustments, optimizing treatment outcomes for diverse cancer cells and individual patients [100].

Developing electronic and optical sensors suitable for addressing this technological gap and to integrate these sensors into autonomous plasma systems must be focused. Bridging this gap could lead to the development of next-generation medical plasma technologies, offering superior healthcare outcomes.

The applications of ML in modeling and simulating different aspects of CAP processing are well reviewed by Treischmann et al. [101]. Future advancements for CAP modelling and simulation promises precise control, pattern discovery, and transformative insights, advancing plasma science and technology. Open data access and collaboration are pivotal for breakthroughs [68,101].

5. Conclusions

Cancer is a challenging disease to treat due to its complexity, heterogeneity, invasion (metastasis), and resistance to treatments. The intricate nature of cancer manifests in the variability of responses to therapies among patients owing to the individualized genetic makeup and biological characteristics of their tumors. This necessitates tailored treatment approaches to optimize the chances of successful outcomes [102,103]. To achieve personalized treatment, with CAP is emerging as a promising approach as the parameters of the plasma device can be fine-tuned during the treatment to suit the patient's specific dosage. CAP has shown to reprogram the tumor microenvironment [104] inhibiting tumor growth with high selectivity and even enhancing the effectiveness of other treatment modalities like chemotherapy, radiotherapy, immunotherapy, and nanomedicine with improved treatment outcomes and minimized side-effects [17,105–108]. The self-adaptive nature of the adaptive plasma system complements the power of AI. As CAP devices can dynamically adjust treatment parameters during the therapy session, they can respond to real-time changes in tumor characteristics or patient physiology. AI-driven feedback loops can enhance this self-adaptation, ensuring that CAP treatment remains optimized and effective throughout the course of therapy, making it a promising avenue for achieving optimal treatment outcomes in personalized cancer care.

Better cross-disciplinary collaboration with plasma physicists, mathematicians, AI engineers, data scientist, oncologists, and clinicians can make these effective proposals achieve in the future that can be tailored towards personalized cancer treatment strategy. Advancing diagnostic tools, exploring new combination treatment strategies with CAP treatment, and modeling with AI will pave the way for more precise and personalized plasma-based therapies. AI is transforming plasma medicine, improving treatments with precise models, data analysis, real-time diagnostics, and protocols, despite ethical and transparency concerns [108]. The ongoing advancements at the frontiers of plasma technology in oncology are poised to revolutionize cancer treatment paradigms, providing new hope and improved outcomes for cancer patients worldwide. With continued efforts and interdisciplinary cooperation, plasma technology holds the potential to become an indispensable asset in the fight against cancer.

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