Self-Adaptive Plasma Chemistry and Intelligent Plasma Medicine

Li Lin, Dayun Yan, Taeyoung Lee, and Michael Keidar*

Plasma-based biomedical applications rely on the reactive oxygen and nitrogen species generated in cold atmospheric plasmas, where complex chemical kinetic schemes occur. The optimization of plasma medicine is thus required for each specific biomedical purpose. In the view of pharmacology, it is to optimize the active pharmaceutical ingredients. This work is thus the first attempt of such a complex task utilizing the recent development of machine learning technologies. Herein, a general method of passive plasma chemical diagnostics and optimization in real time is proposed. Based on spontaneous emission spectroscopy, an artificial neural network provides the gas chemical compositions along with other information such as temperatures. The information further passes through the second neural network which outputs the adjustments of external control inputs including energy, gas injections, and extractions to optimize the plasma chemistry.

1. Introduction

Translational research is needed to address global challenges facing humanity, ranging from environmental stewardship to public health, from hunger to life-threatening diseases. This is particularly true in the time of the global COVID-19 pandemic we are witnessing this year. Controlling biological processes in complex living ecosystems is a grand challenge that requires innovative approaches to resolve. To this end, low-temperature plasmas offer an unmatched, unique platform to affect and control biological processes. Plasma-based engineering of biological processes is a new multidisciplinary field that converges engineering, physics, chemistry, materials science, and biology. It focuses on the interaction of the reactivity produced by atmospheric pressure plasma with soft biological matter and systems (e.g., liquids, cells, tissues, water, food, plants, agricultural products).

Cold atmospheric plasma (CAP) is a type of thermal nonequilibrium plasma at atmospheric pressure. Its ionization degree is usually about $10^{-8}$ to $10^{-5}$. The plasma is thermal nonequilibrium in that only the mean temperature of electrons is elevated to 5–10 eV, whereas those for other heavy particles are near room temperature.$^{[1,2]}$ Therefore, cold plasma naturally becomes a source of complex chemistry and electromagnetic radiation for biomedical and material processing without any thermal damages.$^{[3]}$ The research of CAP-based medicine began in the mid-1990s, followed by a study of wound treatments by the US Air Force Office of Scientific Research (AFOSR), the approval of dermatology applications by US food and drug administration (FDA), and a Class-1Ia medical device certification in Germany in 2013.$^{[4]}$ In recent years, more biomedical applications of CAP have been discovered, including bacteria and biofilm sterilization, wound healing, cancer therapy, and virus sterilization, which include the deactivation of SARS-CoV-2, the very virus causing the global COVID-19 pandemic.$^{[4-9]}$ A simple CAP treatment can cause drastic inactivation on Gram-positive and Gram-negative bacteria not only in colonies but also in biofilm.$^{[10]}$ As a promising anticancer modality, CAP selectively kills many cancer cell lines but just causing limited side effects on normal cell lines in vitro.$^{[11]}$ More importantly, CAP also shows strong growth inhibition on tumors in vivo by a simple treatment even in a transdermal way.$^{[12,13]}$ Reactive species are the key players in CAP to trigger the observable biological effects.$^{[14]}$ Many of them particularly hydrogen peroxide ($\text{H}_2\text{O}_2$), hydroxyl radical ($\cdot\text{OH}$), superoxide anion ($\text{O}_2^-$), and singlet oxygen ($\text{O}_2^\cdot$) are toxic to microorganisms and cancer cells by causing strong damage to DNA, RNA, proteins, and phospholipids.$^{[15]}$

The CAP is usually capacitive-coupled atmospheric plasma guided with a noble gas.$^{[16]}$ CAP-based treatment relies on a complex plasma–liquid multiphase chemistry near and on interfaces. Taking CAP jet as an example, during streamer propagation, energetic electrons dissociate bonds such as $\text{O}_2 + e \rightarrow 2\text{O} + e$ and $\text{N}_2 + e \rightarrow 2\text{N} + e$. The atomic N and O thus generate NO and NO$_2$. The atomic O is highly active and is responsible to produce O$_3$ for biomedical sterilization and other reactive oxygen species (ROS) such as H$_2$O$_2$ for oxidic stress. Note that the aqueous solution is the main hydrogen element provider for ROS, along with the humidity in the air. Therefore, these key species of biomedical applications appear at the plasma–liquid interface.$^{[17,18]}$ In view of pharmacology, plasma medicine must show a significant effect with limited side effects during treatment, in other words, to optimize the active pharmaceutical ingredients (APIs). Considering the complex plasma chemistry
at the plasma-target interface, a well-designed control mechanism is required to optimize the CAP chemistry for specific purposes. Recently, the concept of self-adaptive plasma was proposed, which is an idea to make a CAP generator able to optimize its chemical compositions automatically based on real-time feedback signals from the target and the plasma using machine learning (ML) technologies.[19] In other words, such control enables the CAPs to automatically adapt to the environmental disturbances, the dynamic target status, and the variety of treatment goals. Such a new concept of plasma medicine equipped with ML-controlled self-adaptive plasma chemistry is thus named “intelligent plasma medicine.”

The control of plasma chemistry is a two-step process. The first step is a real-time diagnostic of plasma chemistry. The second step is a real-time diagnostic of plasma chemistry. The first step is to optimize the chemical composition by controlling the plasma generator. First, real-time measurement of the species composition is usually based on active measurements such as laser-induced fluorescence (LIF).[20] However, these methods can only provide the densities of certain species, depending on the wavelength of the incoming laser, rather than an entire picture of all the important reactive species, such as molecular beam mass spectroscopy.[21] Also, LIF is an active detection that requires a tunable laser if various species are to be accessed. Similar to other absorption and scattering methods such as laser Thomson scattering (LTS), the active measurement means a trade-off between altering the plasma and a low signal-to-noise ratio.[22] In contrast, passive detections based on the spontaneous emissions of plasma such as optical emission spectroscopy (OES) do not suffer from such a dilemma. However, the main disadvantage of passive methods is the indirect relationship between the spectrum and compositions, considering dozens of species involving hundreds to thousands of collisions (chemical reactions), with dynamic and unique rate coefficients for each collision. As such, it is virtually impossible to conduct a reverse computation by regular analytical and numerical methods due to its complexity. In this work, we develop a reverse computation method using an artificial neural network (ANN) to achieve passive and real-time plasma chemical diagnostics.

Next, based on the chemical information measured, the control of CAP to optimize plasma chemistry ought to be achieved using another ANN. Previously, there were a few ML works published to show control of CAP generator focusing on the power and temperature variation.[21–28] However, as mentioned, the major biomedical effects of CAP treatment are its reactive oxygen and nitrogen species (RONS), although physical effects such as thermal, UV, and microwave emissions are also considered in some recent research works.[26,27] Compared with the physical dose applications mentioned, the chemical dose is a more complicated system to control, due to its higher dimension of the action space, considering each that species density is a dimension. Therefore, applying a ML method might be the only solution to achieve real-time control of plasma chemistry and such an approach is timely while no related publications are found.

2. Methods

Figure 1A shows the flow chart of using the ANN to diagnose the plasma chemistry and adjust the plasma parameters to optimize the composition in real time. The method relies on a real-time OES which produces normalized spectra continuously into the diagnostic ANN. The ANN will produce a plasma chemical composition list and energy distributions for each species. Specifically, for the thermal equilibrium plasmas, it can output the mean gas temperature or the energy distribution function shared by all species. Based on the diagnostic method introduced in this work, we can easily expand the algorithm to control and optimize the chemical composition in plasmas. Receiving the chemical composition and the distribution function from the well-trained diagnostic ANN, the control ANN can thus provide an optimized control including an extra gas species and power inputs into the system to adjust. Note that the control is a set of multipliers to modify the gas input densities, which is defined as the number of molecules per unit volume. Therefore, such a set of multipliers can be applied to the flow rate of each gas input. Such a diagnostic optimization method merely consists of several matrix multiplications, with each matrix at the scale of hundreds by hundreds (details will be discussed in the following sections). Therefore, any modern personal computer can complete such a diagnostic in a millisecond; in other words, this is a real-time diagnostic.

The flow chart of training the diagnostic ANN is shown in Figure 1B. In each training iteration, the diagnostic ANN is fed with a randomly selected normalized OES from a training dataset. After feed-forward computation, the output of the diagnostic ANN is sent to a 0D chemical simulation such that

\[
\frac{\partial n_p}{\partial t} = \sum_q \left( k_q \prod_r n_r \right) \tag{1}
\]

where \( n_p \) is the density of the pth species (product) determined by the summation of several rate equations indexed by \( q \), and the \( q \)th chemical reaction rate equals the rate coefficient \( k_q \) times the products of all the densities of its reactants \( n_{qr} \). Note that the rate coefficient \( k_q \) can be functions of temperatures or energy of reactants, and some of them have to be specified by solving the Boltzmann equation rather than being cited from other experimental publications. Details can be found in the Supporting Information. In the database, the products of chemical reactions include not only chemical species but also photons emitted from the excited atoms and molecules. The photons thus provide a spectrum of theoretical emission. The spectrum will be compared with the original OES input to compute the error

\[
I_{err} = |I_{ex}(\lambda) - I_{com}(\lambda)| \tag{2}
\]

where \( I_{err} \) is the error to minimize, \( I_{ex} \) is the OES intensity input to the ANN, \( I_{com} \) is the ANN-computed OES intensity, and \( \lambda \) is the wavelength. However, only the spectrum dataset as input is known, whereas the actual species composition for each case is unknown. Therefore, we propose a novel gradual-mutation algorithm (GMA), which is a variation of regular evolutionary algorithms (EAs) tailored for the training of diagnostic ANN.[28,29] As shown in Figure 1D, for each spectrum input, ANN computes numerous outputs, and each output is computed with a set of weights that are mutated with random numbers \( \delta \). Then, each output set represents the information of species densities which will be used to run a chemical simulation. Therefore,
each mutated ANN outputs a computational spectrum peak set, which is compared with the actual spectrum input to quantify the error $I_{err}$, as shown in the very right of Figure 1D. The one with the lowest spectrum error is considered the best version. The output difference between the original one and the best-mutated version is thus the error of the ANN. Let $W$ and $W_{opt}$ be the original
weight matrix and the optimal mutation, respectively. The weight is updated according to

$$W ← W + η(W_{opt} - W)$$

(3)

where $0 < η < 0.5$ is a learning rate that enables a gradual movement from the original weight matrix to its best-mutated version. Similar operations can also be applied to the bias. In short, GMA makes ANN compete with its mutated brothers and the best one is considered as a better version of the current generation, which provides the loss function to evolve the weights. GMA thus resolves a difficulty of insufficient information about reasonable composition estimation to prepare the spectra-compositions’ training dataset before training. Also, the range to select the random mutation numbers $δ$ can be a variable through iterations. Note that the elements in $δ$ can be negative and are randomly and independently generated for each mutation. In other words, the range to find the optimum can increase when it successively occurs that the original weight matrix is the best version itself. Overall, due to the random search of a better weight matrix in a vicinity space without relying on the gradient, the GMA can avoid the local optimum and find the global one.

The flow chart of training the control ANN is shown in Figure 1C. Similarly, we will have to use GMA. In each training iteration, the previously trained diagnostic ANN will feed the chemical composition and other information to the control ANN. The control ANN thus computes a set of control multipliers to modify the compositions. The chemical simulation will result in a set of species ratio based on the modified compositions. The training of control ANN is to maximize the gain function.

$$G = γ_2 - γ_1$$

(4)

In the equation, the species ratio $γ$ is defined as $\frac{Σn}{Σn}$, where $n_i$ is the required species density and $n$ is the total density. On the right-hand side of Equation (4), subscript “2” represents the species ratio after the alteration of plasma parameters, whereas subscript “1” represents the initial one. There are two ways to increase the species ratio: increasing the densities of the species wanted or decreasing other species’ densities. Such a definition is more effective than the simple $γ = \sum n_i$, because the absolute concentration can be increased by increasing the treating time.

The algorithm is capable of spatially resolving the input OES. As shown in Figure 2, an OES probe, pointing at an atmospheric plasma exposure in open air, collects and integrates all the emissions from an area of detection. In such an area, there are gradients of chemical compositions and temperatures/energies of those species. If such gradients are discretized into consecutive spatial regions, each region should emit a different spectrum. For example, a helium-rich region at the center of the plasma should emit helium peaks, whereas the air-rich region surrounding might produce the famous second positive system (SPS) of $N_2$. The resulting OES signal is the superposition of all the emissions from these regions, as shown in Figure 2. However, such a superposition may either not have a proper chemical species solution or lead to wrong solutions. Therefore, the reverse computation must be achieved with spatial resolution. In the lower part of Figure 2, the discretization of such a chemical composition and energy gradient in the output layer of ANN is shown. When the system is discretized into $N$ regions, the actual neuron number of the output layer equals the neuron number for each region multiplied by $N$. Note that the neurons of each region contain the full information achieved by the ANN for that region, such as the densities of all the species and the temperatures or even distribution functions. Next, each region will pass through its chemical simulation independently to produce a spectrum, and the final spectrum computed for error estimation is the superposition of these spectra acquired from the chemical simulation.

3. Examples and Discussions

3.1. Plasma Chemistry Diagnostics

In the following examples, 900 OES data are collected from the experimental measurements of a helium-guided CAP jet, where 700 of them are used for ANN training and the other 200 spectra are used for testing. These materials are the raw data of the previous publications.[30-32] First, all the peaks in each spectrum data are normalized with respect to the intensity of 337.13 nm $N_2 (C^3Π_u \rightarrow B^3Π_g, υ' = 0, υ'' = 0)$, which is an iconic peak of CAP.[33,34] Next, five normalized peak intensities are collected from each spectrum, 308.9 nm $OH (A^2Σ^+ \rightarrow X^2Σ^+, υ' = 0, υ'' = 0)$, 337.13 nm $N_2 (C^3Π_u \rightarrow B^3Π_g, υ' = 0, υ'' = 0)$, 391.44 nm $N_2^+(B^3Σ^+ \rightarrow X^2Σ^+, υ' = 0, υ'' = 0)$, 706.52 nm $He (3\Sigma^- \rightarrow 2\Sigma^+)$, and 777.4 nm $O (3\Σ^+ \rightarrow 3\Sigma^-)$. The 357.69 nm $N_2 (C^3Π_u \rightarrow B^3Π_g, υ' = 0, υ'' = 1)$ and the 427.81 nm $N_2^+(B^3Σ^+ \rightarrow X^2Σ^+, υ' = 0, υ'' = 1)$ are not considered in error evaluation. This is because the 391.44 nm and 337.13 nm peaks are already sufficient to represent the quantities of $N_2 (C, υ = 0)$ and $N_2^+(B, υ = 0)$, whereas the relative probability of the spontaneous emission rate between $N_2 (C \rightarrow B, υ' = 0, υ'' = 0)$ and $N_2^+(C \rightarrow B, υ' = 0, υ'' = 1)$ is fixed, and it is the same for the $N_2^+(B \rightarrow X)$ series.[33] The ANN for this example includes ten fully connected hidden layers which contain 250 and 100 neurons in the last two and 100 neurons in each layer before them. Note that the extra neuron in the input layer is unity.[36] The mutation range is updated as $W_{opt} ← W + η(W_{opt} - W)$. In other words, the range to find the optimum can increase when it successively occurs that the original weight matrix is the best version itself. Overall, due to the random search of a better weight matrix in a vicinity space without relying on the gradient, the GMA can avoid the local optimum and find the global one.

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the following 0D chemical simulation thus computes the photon numbers of the five emissions mentioned. The errors of the 200 testing results are shown in Figure 3B and their average value is 2.608%.

Figure 2. The chemical composition and energy gradient during measurements. The optical emission spectra are integrations along the aiming line of the probe. In an ANN, such spatial resolution can be discretized in the output layer.
Two of these testing samples are selected arbitrarily to show the error visually in Figure 3C,D, where the input OES is in black and the five computed peaks are shown in red. All the computed peaks agree well with the experimental OES, whereas a significant difference between sample 24 and sample 100 exists. This means that the ANN is well trained to flexibly predict the plasma chemical composition with a variety of chemical conditions.

Figure 4 shows the detailed results of the predicted chemical compositions of these two cases. Combining with Figure 5A which indicates the helium–air ratio distribution (see Figure 2), one can double check the ML results with other publications of CAP chemistry using Figure 5. For example, in Figure 5A, both sample 24 and sample 100 show a higher oxygen mixture in region 1 (red) and region 3 (blue). Therefore, Region 2 is the helium-rich region located in the center of the helium-guided plasma jet in open air, whereas Region 1 and Region 3 are located between Region 2 and surrounding air with a lower helium–air ratio. According to Lietz et al., the densities of H, N, NO, NO₂, HO₂, and H₂O₂ are reversely proportional to the oxygen admixture, whereas the values of OH and O₃ are nonmonotonic. In Figure 4, the densities of H, N, NO, NO₂, HO₂, and H₂O₂ are higher in the oxygen-low Region 2, and no such monotonic relations exist for OH and O₃, which agrees well with the simulations in other studies. However, it is interesting that H₂ density is the highest in Region 3 but the lowest in Region 1 with the same oxygen level of Region 3. Considering the mean electron temperature shown in Figure 5B, where the peak of Region 1 is wider than the one of Region 3, the H₂ density depends on not only the oxygen admixture but also electron energy. Note that the OH density is higher in high-energy...
Figure 4. The resulting species compositions with a spatial resolution. Two examples are compared in this figure, whereas the features of O$_2$ and H$_2$O admixtures agree with other publications.
Region 1 compared with Region 3. This also agrees with the LIF measurement results published in the study by Pei et al.\textsuperscript{[40]} Similarly, the reverse proportional relationship between NO\textsubscript{2} and air indicated in Figure 4 can also be found in the study by Van Gaens et al.\textsuperscript{[39]} along with the nonmonotonic relationship between electron density and air admixture. Many other chemical

Figure 5. The prediction of spatial resolution. A) The spatially resolved helium–air ratio. B) The spatially resolved mean electron temperature. C) Reactive species versus H\textsubscript{2}O admixture.
features can be checked such as the monotonic relationships between O and O₂ admixtures that are measured\(^{[41]}\) whereas in our ML examples, we found its reverse proportional part. Moreover, as shown in Figure 5A, the helium densities are much lower than the air species densities. This means that the OES probe points at the tip of CAP jet where the helium–air ratio is low. In contrast, in Figure 4, the electron density is more concentrated in Region 2. This agrees with the well-known deformation of the streamer from a donut-like pattern to a bullet-like appearance during its propagation in CAP jet.\(^{[42–47]}\) Moreover, as environmental humidity can also vary plasma chemistry, it is important to check the ML-predicted RONS with respect to the H₂O admixtures. As shown in Figure 5C, these species densities are proportional to the H₂O admixture, which agrees with the monotonic relationships revealed by previous publications.\(^{[38,48]}\) Note that multiple publications have shown the effects and the importance of environmental and target-vicinity humidity on CAP,\(^{[48–50]}\) whereas a shielding-gas technology can be applied to avoid the environmental chemical disturbance.\(^{[51–53]}\)

### 3.2. Plasma Chemistry Control

Three examples of CAP applications on plasma medicine are demonstrated. In the first example, we would like to maximize the summation of densities of OH, HO₂, H₂O₂, and OH ions as the API for cancer treatments, as these species play a key role in leading cancer cells to their apoptosis\(^{[41–43]}\) In the second example, we trained the ANN to maximize the summation of the densities of NO and its ions as the API for wound treatment due to its effect of inflammation reduction and support of tissue regeneration.\(^{[44]}\) In the third example, we would like to maximize the summation of the densities of O₃ and its ions as the API for sterilizations. Please note that the UV emissions are not considered as an API for sterilization in this general example, due to the potential of damaging the carbon bonds of short-wavelength peaks, which may damage the certain plastic surface and human tissue. In these specific examples, the control ANN includes five hidden layers with 200 and 300 neurons for the last two and 100 each for the others. The output layer includes 106 neurons which are defined as the parameter multipliers normalized. The first 100 outputs are the multipliers of the temporally resolved mean electron temperature. To ensure that the multipliers lie between 0 and 2, we utilize the next output corresponding to the overall scale, and the first 101 outputs are divided by half of the maximum. The next four outputs from 102 to 105 are the multipliers for the densities of N₂, O₂, H₂O, and He. Similarly, the additional 106th output is also utilized for normalization. After the multipliers are applied on the four gas densities, these values will be recomputed to ensure that their summation agrees with the total particle number under atmospheric and room-temperature conditions, but the newly acquired ratio of N₂:O₂:H₂O:He is unchanged. Next, such a modified chemical composition and temperatures are sent to chemical simulation. The simulation thus computes a chemical composition variation in a period to evaluate the error. The evolutions of function G for the three cases are shown in Figure 6A,C,E. The gain values of the desired species for these three cases after training are at about 10⁻⁴. Next, 200 samples are tested. As shown in Figure 6B,D,F, the average increments of γ are about 15, 7.5, and 27 times for the case of OH, NO, and O₃, respectively.

In Figure 6G, the combination of N₂, O₂, H₂O, and He is shown for the three examples suggested by the ANN to achieve the optimizations. These values are the averages over the 200 testing samples. To maximize the G of OH species for cancer therapy, the ANN suggests approximately a combination of 39.61% of N₂, 21.15% of O₂, 4.44% of H₂O, and 35.35% of He. Note that the chemical composition of H₂O is extremely high compared with regular humid air. For example, a 4% molar fraction of H₂O in 300 K and 1 atm air shows almost 100% relative humidity, which means the saturation of vapor and the fact that it is about to rain.\(^{[54]}\) However, it is still practical to achieve such H₂O composition, as the gas input can be a mixture including H₂O-droplet aerosols rather than containing H₂O vapor in the air. To maximize the G of NO species and the one of O₃ for wound treatments and sterilizations, a high composition of O₂ is required. The values are 93.05% and 91.38%, respectively. Note that in the example of OH optimization the O₂ composition is low as H₂O is the main oxygen element provider. The gas composition between NO and O₃ examples is close. However, NO requires more N₂ and H₂O inputs but less He than the O₃ example. In contrast, the peak of mean electron temperature denoted as <\(T_e\)> for these three cases is shown in Figure 6G. It agrees with common sense that the values of NO and O₃ cases are much higher than the ones for OH optimization. Considering the high O₂ compositions for the NO and O₃ cases and the high negativity of the oxygen element, a lower electron temperature causes a higher loss of electron due to the attachments. Therefore, higher electron temperatures are required when extra O₂ is added. Note that these examples are controls of CAP jet, and the peak mean electron temperatures shown in Figure 6G are the mean electron temperature values of streamers passing through the area of OES probe detection. For a mean electron temperature spatially averaged over an entire CAP jet, the value will be around 3–5 eV as measured in a previous publication.\(^{[22]}\)

### 3.3. A Challenge to Adaptive Chemistry

In addition to the tests shown earlier, we can challenge the self-adaptive plasma chemistry system in external disturbances. In the following test, we manually and arbitrarily add several external disturbances of the gas composition and the mean electron temperature to evaluate the performance of the control of plasma chemistry, as shown in Figure 7A. The controlled results will be compared with the uncontrolled one. The uncontrolled one is a result of the chemical simulation receiving outputs from the diagnostics ANN directly such that the modification of these outputs by the control ANN is bypassed (Figure 7B). As shown in Figure 8A, first, the O₂ density was multiplied by 10⁻³ from 600 to 1000 μs. From 1400 to 1800 μs, the mean electron temperature was multiplied by 0.75 (Figure 8B). From 2200 to 2600 μs, the H₂O density was multiplied by 10⁻¹ (Figure 8C). At the end of the test, from 3000 to 3400 μs, all four parameters were modified together to challenge the control system such that the O₂, N₂, and H₂O densities were multiplied by 10⁻², 1.2, and 10⁻² respectively, whereas the mean electron temperature was multiplied by
Please note that the disturbances shown in Figure 8A–D are applied simultaneously.

The test thus was run for 4000 μs, and the resulting ML optimization of the OH family species ratio is shown from Figure 8E, H. As shown in Figure 8E, the increment of γ due to the control was about $10^{-8}$ when there was no disturbance. This agrees with the previous test results, as shown in Figure 6. When O₂ was removed at 600 μs, there was a slight decrement of the OH family density for both the controlled and uncontrolled cases. Such a drop of OH maximization was due to the loss of oxygen element. As shown in Figure 8G, the ANN noticed such a loss of O₂ and added a multiplier to compensate for it. Under the ML control, γ was first decreased to lower than $6 \times 10^{-8}$, then, the ML made its return to $6.5 \times 10^{-8}$ after a small oscillation. In Figure 8F, the γ ratio of controlled over uncontrolled dropped from 10 to 9 for the O₂-decrement disturbance. After 1000 μs, both the controlled and uncontrolled cases recovered to their regular γ values in a few microseconds. Next, from 1400 μs, the uncontrolled γ slightly decreased due to the mean electron temperature loss. However, the ANN noticed such a loss of electron temperature and boosted up the temperature over 2.4 times as a response (Figure 8H). Then, the maximization of OH was kept at around 8.5 times higher than the uncontrolled one, as shown in Figure 8F, due to the effort of the ML control. After fast recovery, both cases suffered γ decrement due to the loss of H₂O from 2200 to 2600 μs. Again, the ANN noticed the loss of H₂O and increased the H₂O input almost 100 times, as shown in Figure 8G. As a result, the ML-controlled case was still maintained at γ ten times higher compared with the uncontrolled case. The last challenge was a combined disturbance that started at 3000 μs, and it finally significantly damaged the ML maximization of the OH family, such that the γ value decreased lower than seven times but higher than the uncontrolled value, as shown in Figure 8F. However, the efforts of ANN included the increase in O₂, H₂O, and the mean electron temperature. Also, as shown in Figure 8G, the ANN tried to decrease N₂ in the last challenge from 3000 to 3400 μs. Interestingly, N₂ and the nitrogen element are never the reactants to synthesize the OH family. Therefore, adding N₂ in the last challenge was also an obstacle to increasing the OH species densities. Obviously, the ANN discovered such a feature and used it. Note that the ANN also decreases N₂ slightly to help to increase the OH family during the challenge from 1400 to 1800 μs. Therefore, the ANN correctly identified the parameters to adjust immediately based on the OES input after the disturbances were added. Overall, the ML algorithm can boost up the OH family and keep it near one logarithm with multiple extra disturbances added.

Figure 6. The training and testing of control ANN. A) The convergence of gain function of OH species including OH, HO₂, H₂O₂, and their ions. B) The testing results of 200 samples using the ANN trained for OH species. C) The convergence of gain function of NO and its ions. D) The testing results of 200 samples using the ANN trained for NO species. E) The convergence of gain function of O₃ and its ions. F) The testing results of 200 samples using the ANN trained for O₃ species. G) The ML-suggested gas composition and peak mean electron temperature to maximize the composition of APIs of the three training cases.
4. Conclusion

In this work, we developed a real-time diagnostic of chemical composition and a control method for CAPs. Taking the real-time and passive measurement of the spontaneous emissions from plasma as a continuous input, the diagnostic ANN can reversely compute the chemical compositions and temperatures behind such spectra. To verify the reliability of such a method, we predict the helium-guided CAP chemistry with a variety of O2 and H2O admixtures. The trends of species variations agree well with previously measured data. However, those works are either simulations or active methods which may alter the plasma during the measurements. Therefore, this method is at the other end of diagnostics: using simple hardware but relying more on the computation, rather than using a complex hardware system with simple computation. Thanks to the power of ML, the acquisition of chemical compositions from spontaneous emission spectroscopy is achieved. Next, three examples are included in this work to show the training of such a control ANN aiming at certain species families. First, CAP-based cancer therapy relies on the API of the OH family including OH, HO2, H2O2, and their ions. The ANN is authorized to control the gas and power inputs to maximize the total density of the OH family species as a ratio over other species in the plasma. The second and third examples focus on the NO family for wound treatments and the O3 family for sterilizations. After the training, the ANN finally can keep the ratio at about one logarithm higher for these examples. Applying this method to plasma medicine, we can achieve the following two features. First, the plasma treatment can be immune to external disturbance, such as the sudden change of the target position, leading to extra gas flow, and a different electromagnetic boundary condition for the electron temperature. During in vivo treatment such as surgery, such a disturbance can be common. Also, the conditions of patients are different from one another. This means that the treatment goal, the chemical environment, and the boundary condition can be different and dynamic. Therefore, the real-time control system we developed in this work is a necessity to make plasma therapy automatically adaptive to dynamic situations. In other words, self-adaptive plasma chemistry is the core of intelligent plasma medicine. Second, a single CAP generator can be used for several different plasma treatments. Each type of plasma therapy requires unique plasma chemistry and must be trained independently. These weight matrices can be stored in a single microcontroller chip controlling the same plasma generator where the working mode can be switched among the types of plasma therapy. For example, the CAP generator can be switched to optimize the OH family aiming at a certain cancer cell line, whereas the
Figure 8. The external disturbance manually added. A) The sudden removal of O₂. B) The sudden decrement of mean electron temperature. C) The sudden removal of H₂O. D) The sudden increment of N₂. E) The test of ML control of OH species composition in CAP chemistry. The species ratio γ for the controlled case and the uncontrolled case. F) The increment of γ due to the ML control represented as a ratio of the controlled case over the uncontrolled one. G) The ML-controlled parameter multiplier to compensate for the disturbance of species densities. H) The ML-controlled parameter multiplier to compensate for the disturbance of mean electron temperature.
same hardware can also be switched to maximize O3 for solid surface sterilization.

It is interesting to point out that making intelligent plasma therapy can bypass the diagnostics of plasma chemistry but map the space of target condition and the space of the plasma control inputs. However, such mapping is established in specific situations. For example, due to the different responses from different cancer cell lines, each type of cancer requires standalone training. Alternately, focusing on the self-adaptive plasma chemistry (composition optimization) can lead to broad-spectrum therapy. Also, sometimes, the target feedback signals may not be available, such as the real-time measurement and prediction of in vivo situations of cell/bacteria/virus. Note that the in vitro biomedical diagnostics has been introduced in some publications, such as using electric impedance spectroscopy.[55] Also, the temperature of the target is easy to be measured in real time and passively,[25] but chemistry is usually the key to plasma therapy. Overall, without a real-time diagnostic of target situations, especially in vivo, the optimization focusing on the self-adaptive plasma chemistry might be the only choice to achieve intelligent plasma therapy.

Finally, this method should not be limited to the biomedical community, which depends on the spontaneous emissions. Theoretically, any plasma with certain species temperatures should contain excited species due to the collisions. Therefore, one can expect that the diagnostics and control algorithms introduced in this work are general for all types of plasmas, from a fusion reactor to plasma-enhanced chemical vapor depositions (PECVD) and etching. Taking PECVD as an example, issues like deposition rates, the growth mechanisms, and the deposition accuracy on complex geometries are being solved using ML.[56–58] Meanwhile, OES is a commonly used diagnostics in the community of PECVD and nanomaterials.[57–59] Therefore, it is easy to apply this general method to other plasma communities, especially the plasma-based material synthesis.

**Supporting Information**

Supporting Information is available from the Wiley Online Library or from the author.

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**Conflict of Interest**

The authors declare no conflict of interest.

**Data Availability Statement**

The data that support the findings of this study are openly available in "Open Codes" at https://mnpj.seas.gwu.edu/open-codes/, reference number "Adaptive Plasma Diagnostics and Controls".

**Keywords**

active pharmaceutical ingredients, cold atmospheric plasma, machine learning, plasma chemistry, plasma medicine

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