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Combining computational fluid dynamics, photon fate simulation and machine learning to optimize continuous-flow photocatalytic systems

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Photoredox catalysis is a well-established area with great potential for industrial applications. The need for an optimum process with less waste generation and economic and environmental appeal has led to several advances in this field. Nowadays, continuous flow microreactors are used to improve mass and photon transfer issues with good results compared to batch reactors. The small dimensions minimize the effects of the Beer–Lambert law, and the flow fields can be precisely known. However, when high throughput production is required, the advantages of this technology derived from its small size may be lost due to the increase in its dimensions. As a result, a more careful design is necessary to fully integrate this technology into the industry. On a design-case basis, improvements can be made to minimize some limitations, such as an efficiently illuminated surface-to-volume ratio in numbering up systems. Ray-tracing simulations can be a solution to this issue. It allows the tracking of photon fate and opens the possibility of improving the configuration of the microdevice to increase the reaction rate. A good mixing in the microchannels is also essential for a more homogeneous light distribution in the medium, despite some other flow-dependent issues, such as the formation of dead zones. CFD can clarify the phenomena occurring in a fluid in movement, and it has been applied for this purpose in several studies. Moreover, the CFD model can be linked to the ray-tracing model by using the photon flux simulations in microchannels as the light input for the chemical kinetics. Therefore, all the coupled phenomena taking place in these devices can be successfully simulated. However, the computational cost is one obstacle that cannot be overlooked in simulation-based design, optimization, and scale-out tasks. It is well understood that the more complex the model, the greater the computational effort required. As a result, we propose a framework in this paper that combines CFD, ray-tracing simulation, and machine learning to reduce the computational cost of complex tasks, allowing smart decisions fast and accurately. Data-driven models are used in machine learning, and results from CFD and optics simulations can be fed into the model to generate the predictions.

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1. Introduction

The exceptional capacity of photochemical reactions to induce chemical transformations from light has made this field one of the main areas of chemical research nowadays. This can also be credited to the development of photoredox catalysis, a branch of photochemistry in which activation happens under mild conditions with non-hazardous reagents and visible light. The light-induced concept of such reactions appears appealing, leading to their use in various sectors, such as medicines, fragrances, vitamins, and added-value compounds in general, all in the pursuit of a sustainable technique.[1] In this sense, it is common to see in literature several fine chemicals and high-value compounds synthesized *via* photoredox catalysis[2,3] typically in high demand by the market.

However, to ensure positive results in a photochemical synthesis, a study on the system configuration, the light source, and an understanding of all the phenomena involved in the process is essential. According to the Grotthuss–Draper law, photochemical reactions on a molecule are only activated when light absorption on that molecule is successful. The absorption of light by a molecule greatly depends on the experimental conditions, which include the reaction system

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design, the light source and intensity, and the distance between the light and the reaction medium.[4] Beer–Lambert law also governs the irradiation distribution. This law states that photochemical reactions on a larger scale experience an attenuation in the light intensity along the path.

To minimize those effects, continuous flow microreactors are increasingly being applied to perform photochemical reactions since the narrow microchannels can provide uniform irradiation in the reaction medium.[5] However, the fine chemical and pharmaceutical sectors continue extensively using batch processing for product synthesis. This can be justified by the amount of investment necessary to modify the system since continuous operations may necessitate an investment comparable to, if not more than, that of a batch plant. On the other hand, automating continuous-flow processes can reduce labor and increase yield while reducing costs.[6]

In this sense, computational methods can be applied to design the system and speed the adoption of a continuous process for synthesizing added-value chemicals while lowering costs. A study on the Research & Development (R&D) fluctuation of leading pharmaceutical industries from Europe and the US showed an increase in the approaches of the industries related to computational efforts.[7] This fact can be motivated by the constant evolution of technology toward R&D. The advantages of using computational tools for chemical synthesis optimization are numerous, as it allows the researcher to selectively tune the characteristics of the microreactor, lowering costs and increasing reaction efficiency.[8] Since numbering-up and scale-up techniques can be adopted to increase the throughput of a microreactor, computational tools can be applied to evaluate the best design for the numbering-up microreactor system even before production. A quick screening of the conditions for new operations can be made since the changes in the reactor feed (flow rates/concentrations) or its temperature immediately impact the advancing reaction.[9]

Computational fluid dynamics (CFD) simulations can be performed to examine the behavior of the fluid in motion and aid the scaling up and system optimization.[9] CFD simulations consider all the balance equations (and initial/boundary conditions) of the process in a specific domain, including mass, momentum, and energy conservation.[10] This tool is applied in many engineering domains to model complex phenomena, most of them without a known analytical solution. Therefore, algorithms are applied to approximate the system of equations.[11] One of the numerous advantages of this method is that it enables the optimization and analysis of a system prior to the construction of a prototype or the optimization of an existing system without creating more experimental models. However, in light-mediated reactions the optimization of the light distribution in the reaction medium is of pivotal importance as well since it interferes directly with the reaction rate. In this sense, ray-tracing simulations are encouraged by this work to increase the system's energetic efficiency. Although not widely applied to this end, this technology presents a new chance to address all the unanswered problems concerning optimizing irradiation in the reaction medium.

For instance, photons might follow various courses after light impinges on the microdevice, and unfortunately, a significant proportion of the photons result in energy losses. Corcoran *et al.*[12] stated that many design features can disrupt this distribution of photons in the system, including the thickness of the walls in the reactor, the curvature, and the position of the source of light (such as distance to the reaction medium), among others. Those barriers can reduce the energetic efficiency of the system and consequently decrease the reaction rate.

In ray-tracing simulations, the domain of the microreactor, optical properties, and the source of light can be considered in the simulation. It is possible to analyze the optical behavior and the path of the rays by combing the principles of traditional geometric optics and the Monte Carlo method.[13] The dissipation of light can be determined by the optical properties of surfaces, materials, and emission sources[14] light sources can be modeled, *e.g.*, LED, sunlight, lightbulb, *etc.* However, those simulations can be intensive, and the model's complexity typically results in a high computing cost.

Machine learning (ML) can be applied as a powerful predictive tool to overcome those questions. In this sense, studies devoted to turning microfluidics smarter and automatized have become frequent in literature. A proof of this is intelligent microfluidics, an emergent field of research combining microfluidics and machine learning techniques.[15] However, for photocatalytic systems, the application of these tools combined is still not present literature.

The goal of machine learning (ML), a branch of artificial intelligence (AI), is to automate complex decisions by identifying patterns in data sets. In this instance, simulations can provide this data (CFD and ray tracing). Furthermore, a design of experiments (DOE) can be created to identify the variables that may interfere with the reaction's success. On this basis, the parameters that affect the reaction yield can be utilized to train the model. Thus, ML can be applied to make predictions in difficult tasks that demand extended timescales to be performed.

In this context, this work aims to present current state-of-the-art of computational tools for continuous-flow photoredox catalysis optimization, as well as to propose a new framework that combines CFD, ray-tracing simulations, and machine learning to create a smart and optimized continuous-flow synthesis.

2. Photoredox catalysis for the synthesis of fine chemicals and added-value compounds

Photochemical reactions occur through a light-induced electronic excitation of molecules. These reactions are

commonly triggered by high-energy ultraviolet (UV) or visible photons,[16,17] and the quantity of photons absorbed determines the success of the process. The higher the number of photons absorbed, the more excited states are produced, which then engage in a chemical reaction.[18] The possibility of producing fine chemicals and advanced materials with chemical reactions mediated by light is of great interest to industries[19] had brought some light to photochemistry again, now with the advent of photoredox catalysis. The fact that the activation mode occurs under mild conditions with non-hazardous chemicals and visible light has made photoredox catalysis a potential application in organic synthesis to produce added-value molecules.

The photoredox catalysis principle is based on a solution for the non-absorption of light in the visible range (390–700 nm) by organic molecules. Organic or transition metal-based photocatalysts gather visible light in photoredox catalysis and, once activated, can conduct single electron transfer (SET) oxidation and/or reduction reactions.[20] When the photoredox catalyst (PC) is excited (PC*), one electron is transferred from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO). As a result of this action, the HOMO loses one electron, and the LUMO obtains an accessible electron. Therefore, the excited photoredox catalyst is a more powerful oxidant and reductant than the ground state.[21]

This process can have two outcomes: the "oxidative quenching cycle" and the "reductive quenching cycle". As the name implies, in the first one, the excited photocatalyst donates an electron to an acceptor before returning to its oxidized ground state. In the reductive quenching cycle, on the other hand, the excited photocatalyst accepts an electron from a donor and then returns to its reduced ground state (Fig. 1). Both quenching cycles can be advantageous concerning the target chemical transformation.[22,23]

In a photoredox process, photocatalyst selection is crucial. According to Arias-Rotondo and McCusker[18] a photocatalyst must meet specific criteria to be used successfully. The excited state must have a long enough lifetime to perform the reaction and a high yield of formation. The photocatalyst must have a large absorption in wavelengths not absorbed by the other species in the reaction mixture. Moreover, the reversibility in photocatalyst photophysics and synthetic modifications of the excited-state properties of the photocatalyst must be possible.

In photoredox catalysis, a variety of photocatalysts are used, including Ru(II) and Ir (III) complexes, as well as organic dyes like rose bengal, eosin Y, and methylene blue, among others.[24] Fig. 2 showcases some applications.

Those successful photoredox reactions can generate highly reactive molecules that can originate profitable synthetically bond structures,[25] which has drawn the attention of industries to produce drugs, fine chemicals, and advanced materials with chemical reactions mediated by light.[19] This review will not focus on the chemical reaction, but excellent papers have been published in this sense and can be accessed.[24,26,27] Nowadays, it is common to observe an increasing number of studies based on the production of added-value compounds by photoredox catalysis,[28–32] with several new methodologies being proposed regularly to improve the reaction rate.

Well-established companies have invested significant efforts in producing novel added-value compounds *via* photoredox catalysis. This is the case for big companies in the field of agrochemicals and pharmaceuticals, which have been investing in academic-industry training in synthetic chemistry applying photoredox catalysis.

In synthetic pharmaceutical transformations, for example, photoredox catalysis can be applied to a variety of methods. Some typical uses of this technique in the literature include selective functionalization of molecules of interest, such as alkylation, amination, perfluoroalkylation, and halogenation.[33] In this regard, publications in the literature can be found using photoredox catalysis to synthesize derivatives that may be used for various purposes in the industry. Some applications are imidazole derivatives that can be applied as antifungal drugs,[34] coumarin derivatives as anticoagulants,[35] fused β-carboline derivatives, disulfides[36]

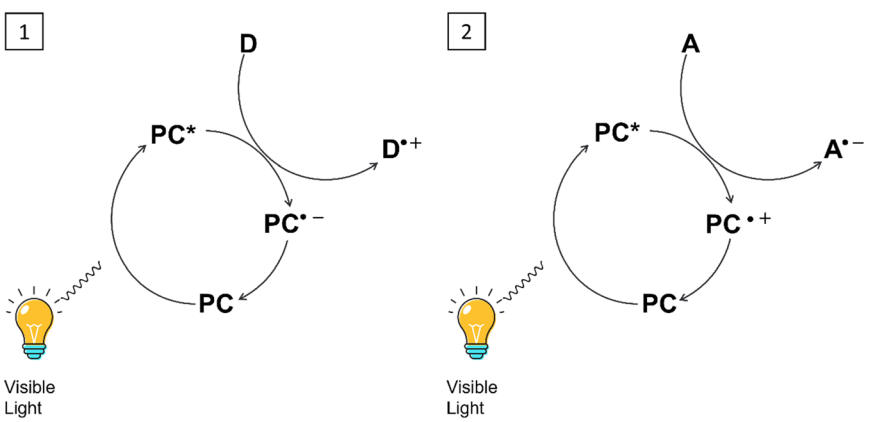

Fig. 1 Quenching cycles of a photocatalyst. Reference: adapted from Ghosh.[22]

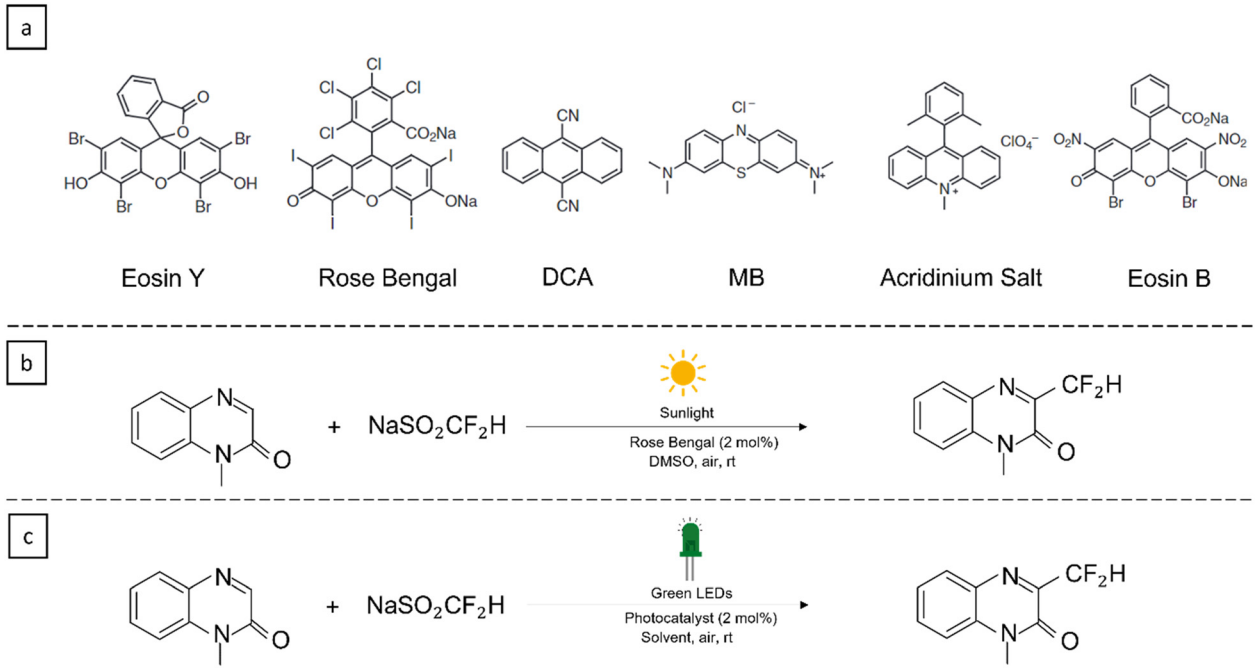

Fig. 2 Direct C–H difluoromethylation of heterocycles *via* organic photoredox catalysis (a) different photocatalyst tested by the author; (b) reaction with sunlight as the light source; (c) reaction with green LEDs as the light source. Reference: reproduced from Zhang *et al.*[113] with permission from *Nature Communications*, copyright 2022.

and carbazoles,[37] that can be applied in cancer treatment, among others.

Despite the growing number of works being performed in the laboratory, there are still relatively few large-scale applications of photoredox catalysis in the pharmaceutical industry.[38] This can be attributed to the poor light penetration in high throughput reactors. In this regard, continuous flow reactors can play a significant role in bringing photocatalysis into the present era of process-scale synthesis, as improved light penetration in the reaction media is a crucial advantage of microreactor technology over batch reactors.[39] Higher conversions, lower temperatures, better light distribution, less use of solvents, and faster processes are just a few reasons microreactors are becoming more popular daily.

According to Roberge, 50% of the reactions in those industries could benefit from a continuous flow technology-based process[6] keeping in mind that batch procedures can result in drug shortages due to long lead times or quality difficulties.[40] The process of research and development (R&D) of a new medicine is complex and expensive. Lombardino and Lowe[41] stated that a new drug could take 12 to 14 years to be developed, and there is a risk of process failure in the production. The manufacturing stage is a resource-intensive process. Testa *et al.*[42] state that the pharmaceutical sector loses approximately $50 billion annually owing to batch processing inefficiency. As a result, large corporations and institutions have recently emphasized continuous flow as a potential technical alternative for facilitating scale-up.[39]

2.1 Continuous-flow photoredox catalysis

The growing interest in microfluidics technology has solidified it as a great research topic in the literature, with several designs being proposed nowadays. The generic design of a photomicroreactor's system nowadays is usually based on a light source and a fluorinated polymer-based capillary or a microchannel in a plate, with an inlet and outlet manifolds.[43] The process occurs through the transport of the mixture in a capillary or in a microchannel, where the photons are absorbed to generate the photochemical transformations.

The microreactor's small volume allows for more precise control of reaction parameters such as pressure, temperature, flow rate, and residence time. As a result, when compared to large dimensions reactors, known as batch reactors, this configuration has the potential to improve conversion and energy efficiency.[45–46] This statement is supported by a study conducted by Periyasamy *et al.*[47] where the authors compared the production of SnO_2 nanoparticles in a batch reactor and a continuous flow microreactor under identical operating conditions. The nanoparticles produced in the microreactor outperform the batch-produced ones in terms of methylene blue dye degradation, irradiation stability, and agglomeration.

Another factor that drags attention to microflow systems is the possibility of tailoring the configuration of the microreactor to the end application. This factor has resulted in several devices built *in-house* that can also be found in the literature.[48] As a result, nowadays, a study in the design of

the microreactor can be considered pivotal for successful synthesis. A great review of Buglioni *et al.*[49] approaches several innovations of microflow technology in application to photochemistry.

Su *et al.*[50] affirm that several factors must be considered while designing microreactors. Some can be described as follows:

- Selecting the appropriate light source and reactor material.
- Comprehending all the system's phenomena, such as mass transfer and photon transport.
- The distance and location of the light from the reaction medium (since the system's heat dissipation and the light incidence in the reaction medium can significantly reduce the reaction rate).
- The material of the photomicroreactor is also important for high energetic efficiency, as it must have a high light transmission and low scattering in the intended wavelength.[51]
- If the device aims to carry out photochemical reactions, the microreactor must be radiation transparent.[52] Glass, quartz, silicon, and polymers are the most often utilized materials for this end.
- The microreactor's geometry can also significantly impact reaction efficiency since it can influence the light intensity in the reaction medium and the flow distribution.

Despite all the benefits of continuous-flow systems, most reactions in the pharmaceutical industry are still performed in batch systems. This is because the throughput of a single microreactor is often insufficient to cover an industrial company's output rate,[53] making microreactors more useful for analytics than high-throughput manufacturing. A scale-up could be the key to resolving this issue; however, various factors must be considered, as sizing up the system may result in inefficiencies and increased expenses. Several approaches can be considered to apply in this end, numbering-up, sizing up, and a combination of both.[54]

Over the years, numerous experiments have been undertaken in an effort to enhance the throughput of chemical synthesis in microreactors. In line with this, one of the most notable strategies employed is the process of numbering up. This widely utilized approach enables the retention of crucial hydrodynamic and transfer properties associated with the micro-environment.[55] Numbering-up strategies, also known as scale-out strategies, can be implemented either externally or internally. External numbering-up occurs when several devices are arranged in parallel, whereas internal numbering-up occurs only when functional elements are parallelized, not the entire device. This second method can be considered more interesting in engineering terms since the design is more compact and economical than external numbering-up.[56] According to Mason *et al.*,[57] numbering-up in microreactors can avoid large-size reactors while securely increasing system productivity. The authors said that microreactors typically outperform batch spacetime yields in industrial chemical synthesis by producing more products per unit volume and per unit time.

Scaled-out microreactors can deliver high throughput and inherent safety while simultaneously being suitable platforms for the continuous synthesis of materials in small quantities and could greatly supplement traditional batch synthesis procedures in the chemistry laboratory.[58] However, scaling up the size of a reactor for chemical synthesis is already challenging due to mass and heat transfer issues. In photochemical systems, this problem is accentuated due to the distribution of the photons, which is affected by the Beer–Lambert law.[59] Addressing this concern, Zondag, Mazzarella, and Noël provide an effective approach to scaling up photochemical systems in their recent paper.[60] According to Donnelly and Baumann,[61] as the size of a reactor increases, the path length also increases, resulting in a non-homogeneous irradiance. Nevertheless, the implementation of miniaturization techniques can help mitigate this problem by reducing the path length.

Baumann and Baxendale[62] suggest that substantial research on continuous flow applied to commercial synthesis is critical for changing the mindset in the chemical industry. Higher production and, as a result, optimization of continuous-flow systems can lead to greater use of this technology for the synthesis of added-value compounds at the industrial level, as it can provide researchers more confidence in the process while also lowering the cost of implementation.

For a study in the design and optimization of microchannels and microreactors in general, computational fluid dynamics (CFD) simulations are frequently performed in the literature. This tool can be used to investigate phenomena such as mass and heat transport in the system, as well as examine hydrodynamic behavior and mixing in the system. Ray-tracing simulations can optimize the system's optical efficiency to choose the best and most economically viable material and design for the reactor while aiming for optimum energetic efficiency.

However, these simulations can be time demanding and computationally expensive in complex systems. But this issue might be on the verge of being solved. New methods are proposed daily due to the fast-growing technology. In this regard, machine learning can be highlighted as a growing technology these days. This artificial intelligence-based technology has the potential to learn patterns in data and make predictions in much less time than traditional simulations and experimental procedures. This way, it has been used in a wide range of industries such as medical, engineering, games, and biotechnology. According to a study on the impact of A.I. technology on the world, by 2030, almost 70% of industries may have embraced at least one A.I. technology, indicating a significant potential of this method to contribute to global economic activity.[63] Microfluidics is not an exception to this. To optimize photoredox systems, CFD and ray-tracing simulations can be performed and provide a large amount of data, which

can be used to feed those learning models. Machine learning can be used to anticipate the ideal configuration in a continuous flow device while taking into consideration all of the phenomena involved and at a significantly lower computing cost.

Malet-Sanz and Susanne[64] stated that the first major investment in new technology (continuous-flow) to replace batch equipment is the more significant barrier to this implementation. In this sense, these tools can assist the process to be less expensive while lowering labor time, as well aiding the elucidation of all the phenomena present in the system, resulting in a more profitable and optimized design of microreactor.

3. Computational tools towards a continuous-flow photoreactor design

To achieve high rates in photochemical reactions, the modeling of a continuous-flow system must take several factors into account. The microreactor's configuration and geometry can affect heat and mass transfer, light distribution, light dissipation, and overall reaction rate. As a result, to fully optimize the reaction, all the factors that influence its efficiency must be considered and elucidated.

3.1 Simulation of photoredox catalysis in flow

Computational fluid dynamics (CFD) is a numerical tool that models fluid flow and allows the prediction of mass and heat transfer rates, chemical reactions, and so on. CFD simulations consider all the governing equations (and initial/boundary conditions) of the process in a specific domain, including mass, momentum, and energy conservation.[10] This tool is used in a wide range of engineering domains to model complex phenomena, most of them without a known analytical solution. Therefore, algorithms are applied to approximate the system of equations.[11] In the simulation, the domain of interest is defined as a large number of elements that are much smaller than the domain of interest's macroscopic volume. After creating a discrete representation of the relevant conservation equations for each control volume, an iterative procedure is used to obtain the solution of the nonlinear equations.[65] One of the many advantages of this approach is that it allows for optimization and analysis of a system before building a prototype, or the optimization of an existing system without the need to build testing physical models. This method can both speed up and save resources. Currently, several CFD software are available, with the most popular being COMSOL Multiphysics®, ANSYS Fluent®, and OpenFOAM®, being the last an open-source alternative.

CFD can provide critical insights into the behavior of microreactors, allowing researchers to explore the effect of different geometrical configurations and operating conditions on the device performance, for example, emphasizing flow non-idealities.[66] This tool is essential for fully comprehending how chemical processes work to improve photochemical reactions. Questions about the mass transfer rates, the presence of dead zones, velocity fields, and radiation transport in microreactors can be answered. CFD integration with microfluidic devices has achieved promising results in liquid-phase systems. The behavior of an incompressible liquid, as well as the laminar flow regime (which is a consequence of the microreactor's small dimensions and usually results in good simulation predictions based on first principles), can be attributed to these results.[67]

CFD simulations are not a new trend in chemistry. However, only a few studies have used it for photoredox catalysis, which is why this paper proposes using this technology to speed up the development process. However, at the same time, numerous studies have applied CFD tools to enhance the performance of continuous flow microreactors in general. In this sense, Sen *et al.*[68] demonstrated the synthesis of tributyl phosphate (TBP) in a microreactor for the first time. Two types of micromixers were used in the study: the T-junction micromixer and the split-and-recombine micromixer. To quantify the mixing in the micromixers, CFD simulations were performed. The simulations predicted better mixing in the split-and-recombine process. TBP synthesis, according to the authors, is feasible in microreactor systems.

Santana, Silva Jr., and Taranto[69] also utilized CFD to evaluate the mixing of *Jatropha curcas* oil and ethanol in micromixers for biodiesel synthesis. The simulations were run on ANSYS CFX-14.0 software. Micromixers in three different configurations were studied: T-micromixer, cross-micromixer, and double-T-micromixer. Fluid mixing was evaluated using various Reynolds numbers, and oil conversion was evaluated using various Reynolds numbers as well as residence times. The authors discovered that the conversion in all the micromixers was roughly the same in all configurations tested and that the Reynolds number had no effect on these results. Regarding the mixture efficiency, a low Reynolds number resulted in an excellent mixture in all configurations. In contrast, a high Reynolds number resulted in a better mixture in the T-micromixer and a lower mixture in the Double-T-micromixer. Finally, it was demonstrated that CFD simulations could aid experimental observations and flow-related evaluations.

CFD is also widely used for geometry evaluation, as several authors have demonstrated in the literature that a careful design of microreactors can provide excellent chemical throughput. Yusuf and Palmisano[70] utilized COMSOL Multiphysics® software to investigate the effect of microreactor geometry on 4-nitrophenol photodegradation. The photodegradation simulation was carried out in a recirculating and single-pass photocatalytic microreactor with simulated solar radiation. A dynamic transport model was used in recirculation mode to predict the effect of changing the initial concentration of 4-nitrophenol. According to the

authors, changing the geometry's height and length, combined with lowering the flow rate, can improve conversion.

Oliveira *et al.*[71] investigate the effect of the geometry of a microreactor on reaction rate. The authors developed a CFD model for the [4 + 2] cycloaddition of 9,10-diphenylanthracene, a reaction selected as a benchmark reaction. The reaction's kinetic law takes light intensity into account, and a feedforward control algorithm was implemented in the system to keep the conversion stable regardless of light changes. The effect of two new microreactor geometries on the reaction rate was also investigated. As a result, the CFD model agreed well with the experimental data in different residence times and light power. The responses of the new geometries were very similar, considering conversion and velocity profiles. Finally, the authors concluded that the CFD simulations are a viable option for fluid dynamics analysis and microreactor design.

Therefore, fluid dynamics analysis can elucidate several phenomena present in photocatalytic systems, facilitating process optimization. Optimal results can be reached, particularly when analyzing complex single-phase laminar flow problems, which, according to Kuipers and Van Swaaij,[65] have simulation accuracy so high that validation experiments are frequently considered unnecessary. This is not the case for single-phase or multiphase flow problems, eventually associated with turbulence, in complex geometries, which require significant computational effort. In particular, this is the scenario where machine learning stands out as a current option. Machine learning is now being used to accelerate fluid dynamics simulations while lowering computational costs.

Mohammadpour *et al.*[72] applied four ML regression models (*k*-NN, RF, GPR, and MLP) to save computational costs, where *k*-NN was the model with high accuracy. Ribeiro *et al.*[73] proposed a convolutional neural network (CNN) based model that efficiently approximates solutions for the problem of non-uniform steady laminar flows. The authors achieved a speedup to three orders of magnitude over the typical CFD approach while maintaining low error rates. Kochkov *et al.*[74] achieved computation speedups of 40 to 80 times. Using a data-driven numerical technique with the same accuracy as traditional finite difference/finite volume methods but significantly coarser resolution. The approach learns exact local operators for convective fluxes and residual components, matching the precision of a high-resolution numerical solver while executing the computation 40 to 80 times faster.

Despite these benefits, such computational technologies are still primarily utilized to solve fluid flow. Being unable to explain factors such as light distribution in the reaction medium, photon fate, and energetic losses, among others, which are critical in photoredox catalysis reactions. Fortunately, ray-tracing simulations can be applied to enhance the optical efficiency in those systems.

3.2 Photon transport simulation

Loubière *et al.*[75] states that notwithstanding the photoreactor being in optimum process conditions hydrodynamically, the reaction rate is entirely dependent on light irradiation to be successful. Nonetheless, the authors argue that the "ideal reactor" concept in photochemical engineering should be reconsidered. All these losses present in photochemical systems are undesirable since they cause energetic inefficiency and low reaction rates. For these reasons, it is of paramount importance to understand the photon fate in the system for further optimization. To determine which optical losses are present, ray-tracing software such as LightTools®,[76] Matlab®,[77] Ansys Speos®,[78] and ZEMAX Optics Studio®[79] are available today to determine which optical losses are present in the reaction system. Pvtrace, a Python-based statistical photon path tracer, is also an open-source solution for ray-tracing simulations. One advantage of Pytrace is that it may be customized since it is written in Python.

By combining the principles of traditional geometric optics and the Monte Carlo method, optical ray-tracing simulation can analyze the optical behavior and path of the rays.[13] The dissipation of light is determined by the optical properties of surfaces, materials, and emission sources.[14] Different light sources, such as LED, sunlight, lightbulb, and so on, can be modeled. Since these simulations work through the stochastic Monte Carlo probability method, random numbers are considered to determine the direction, position, and energy of the photons, among other parameters.[80] The fate of the rays can be elucidated since these algorithms can evaluate the rays that are absorbed, reflected, refracted, diffracted, and scattered in the domain. However, despite the great importance of this subject to a successful reaction, few studies evaluating photon transport in continuous flow photoredox catalysis can be found in the literature today, making this subject a gap in the literature.

To optimize a photoredox reaction, Cambié *et al.*[81] applied a ray-tracing simulation to determine the optimum aspect ratio, channel height, and the number of channels of a microreactor based on the luminescent solar concentrator technology. The author was able to successfully optimize all the parameters using the ray tracing simulation, demonstrating that ray-tracing algorithms can be a powerful tool for photochemical system optimization.

Similarly, to determine the most appropriate light source for a photochemical reactor, Meir *et al.*[82] also applied ray-tracing simulations. LEDs were used as the light source in the investigation. The authors were able to observe the reactor's energetic efficiency using the simulations and concluded that the optimal optical performance could be achieved using the most collimated LED possible. Furthermore, the authors could conclude about the most suitable material for the reactor, the thickness of the glass wall, the reactants concentration, and the length of the reactor for optimal optical performance.

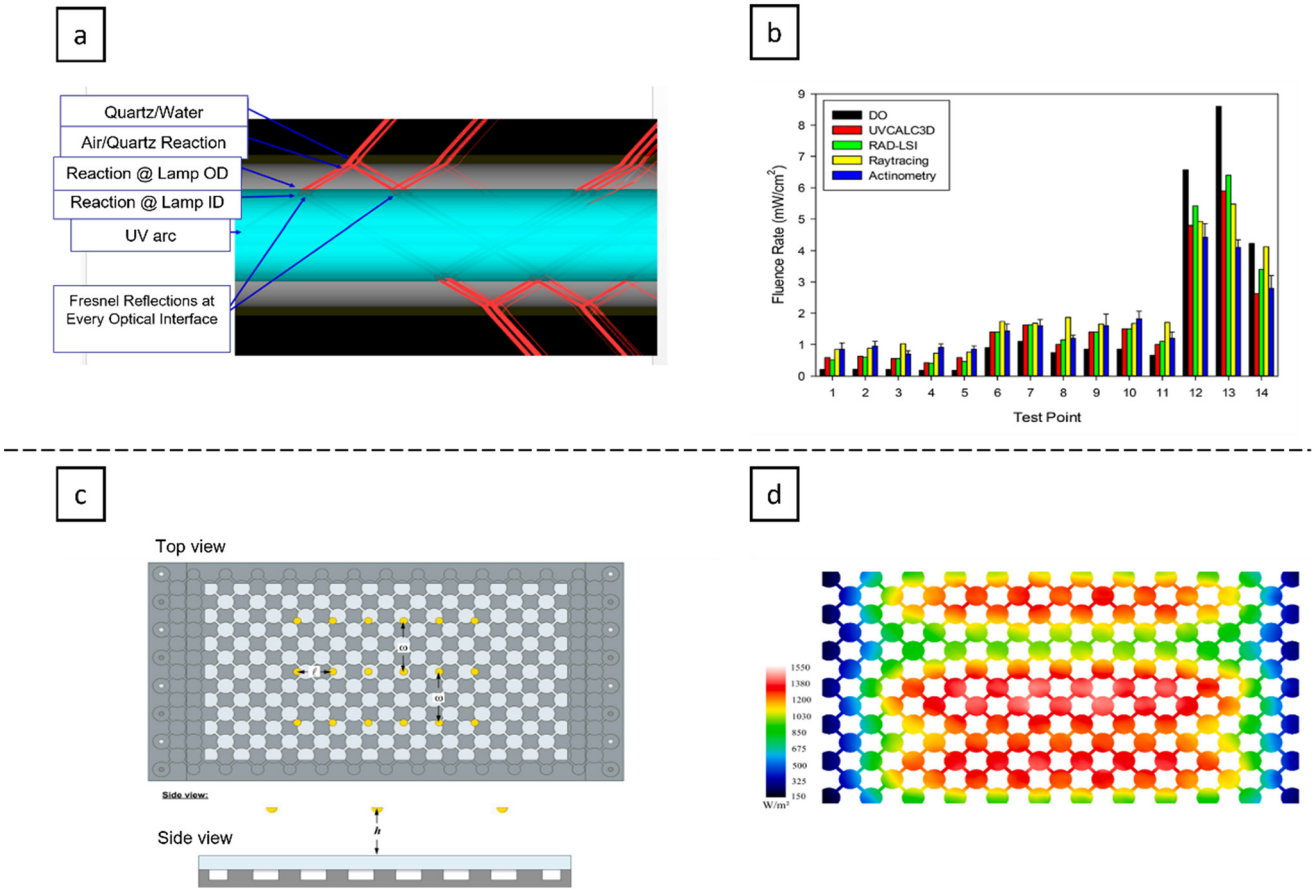

Fig. 3 (a and b) Ray-tracing simulations in ultraviolet photoreactors. (a) Fate of a single ray after coming out from the Hg lamp; (b) performance of the ray-tracing simulation from fluence rate prediction over other methods. (c and d) Ray-tracing simulation on the NETmix milli-photocatalytic reactor. (c) Position of the LEDs in the reactor; (d) irradiance map of the reactor. Source: (a and b) reproduced from Ahmed, Jongewaard and Blatchley[83] with permission from American Chemical Society, copyright 2022. (c and d) Reproduced from Matiazzo *et al.*[78] with permission from *Chemical Engineering Journal*, copyright 2022.

Ahmed *et al.*[83] used commercial ray-tracing software to examine fluence rate fields in an ultraviolet (UV) photoreactor. Three UV reactors were simulated, with a low-pressure Hg lamp as the light source. According to the author, the fluence rate was calculated in ray-tracing software using the formal definition of fluence rate, which is calculated as the incident power from all directions on a small spherical receiver divided by the sphere's cross-sectional area. Fig. 3(a) depicts a fate of a single ray after being emitted by the UV Hg lamp surrounded by a quartz jacket. Fig. 3(b) presents the fluence rate predictions obtained for the ray-tracing simulations and comparison among other numerical models, as well as an experimental measurement from an actinometer. The ray-tracing simulation produced a result more closely related to the experimental value than the other numerical tools, demonstrating its usefulness in predicting fluence rate fields in ultraviolet (UV) photoreactors. The authors concluded that ray-tracing simulations might be used to correctly estimate the fluence rate in UV photoreactors, resulting in values near experimental measurements.

Using Monte-Carlo ray-tracing software, Matiazzo *et al.*[78] evaluate the optical efficiency of the mesoscale NETmix photoreactor with LEDs as a light source. The authors discovered that light absorption is directly proportional to the distance between the LEDs, as well as the distance between the LEDs and the reactor window. Fig. 3(c) depicts the geometry of the microreactor and the distance from the light source. From Fig. 3(d), it is possible to notice that the irradiation is higher right above where the LEDs are placed, indicating that there is room for optimization in the LEDs position to increase the homogeneity of irradiation in the microreactor. As a result, the authors concluded that ray-tracing simulations can be used to determine the optimal point of illumination in the reaction medium.

Ray-tracing simulations in continuous flow photoredox catalysis can assist in the fabrication of energetically efficient designs considering the light source, the location of the source, the power of the source, the overall geometry of the domain, and the optical characteristics of the raw material of the microreactor. Furthermore, the software can consider the reactive species mean free path, the absorption spectra, the emission spectra, and the quantum yield. The importance of

this analysis is pivotal. Cambié *et al.*[84] reported that photon losses occur in light-driven systems, which are directly dependent on the fate of the photons. In the case of the LSC-PM, photons can travel by the following paths: top reflection, transmission, emission in the escape cone, edge emission, adsorption by the reaction media (ideal), and, finally, photons can be lost by matrix absorption or non-unity fluorescence quantum yield.

As a result, ray-trace modeling can now be regarded as a promising tool for the design, performance evaluation, and optimization of optical systems, which, when combined with CFD simulations, can produce excellent results in terms of both fluid dynamics and optical efficiency. One crucial aspect especially relevant for simulations based on LED light sources is that its emission is usually modeled using the far-field intensity distribution (mostly provided by the manufacturer). However, many LED light sources are placed close to the illuminated reactor surface and potentially in the near-field region. Consequently, to properly represent the light source in ray-tracing simulations, their spatial emission of irradiation subject to the LED-reactor distance can be quantified using a goniophotometer.[85] This is exemplified in Roibu *et al.*,[86] where it is shown that irradiance profiles calculated based on the manufacturer datasheet underestimate the width of the LED emission at short distances between the LED and the illuminated reactor surface, which could be corrected using near-field goniophotometer measurements.

In general, ray-tracing necessitates significant computational effort, which can be costly in more complex cases. In today's computational era, several options for overcoming this issue are available and highly recommended by this work. One of these options is machine learning. Machine learning methods can be trained using CFD and ray-tracing simulation results to predict behaviors. The advantage is that this method can be used for high-level decision-making, indicating optimal scenarios faster and at a lower cost.

3.3 Machine learning strategies applied to continuous-flow design optimization

Machine learning (ML) is a subgroup of artificial intelligence that aims to emulate human intelligence by learning from sample data. The goal is to provide predictions or decisions without explicitly programming the machine to perform these actions.[87,88] Tom Mitchell[89] in 1997 provided an accurate definition for ML: "A computer program is said to learn from experience *E* with respect to some class of tasks *T* and performance measure *P*, if its performance at tasks in *T*, as measured by *P*, improves experience *E*".

There are three important subsets of machine learning algorithms: supervised, unsupervised, and reinforcement learning. Fig. 4 depicts the three learning methods and their associated techniques and algorithms most utilized. Supervised learning can be applied when the user already has

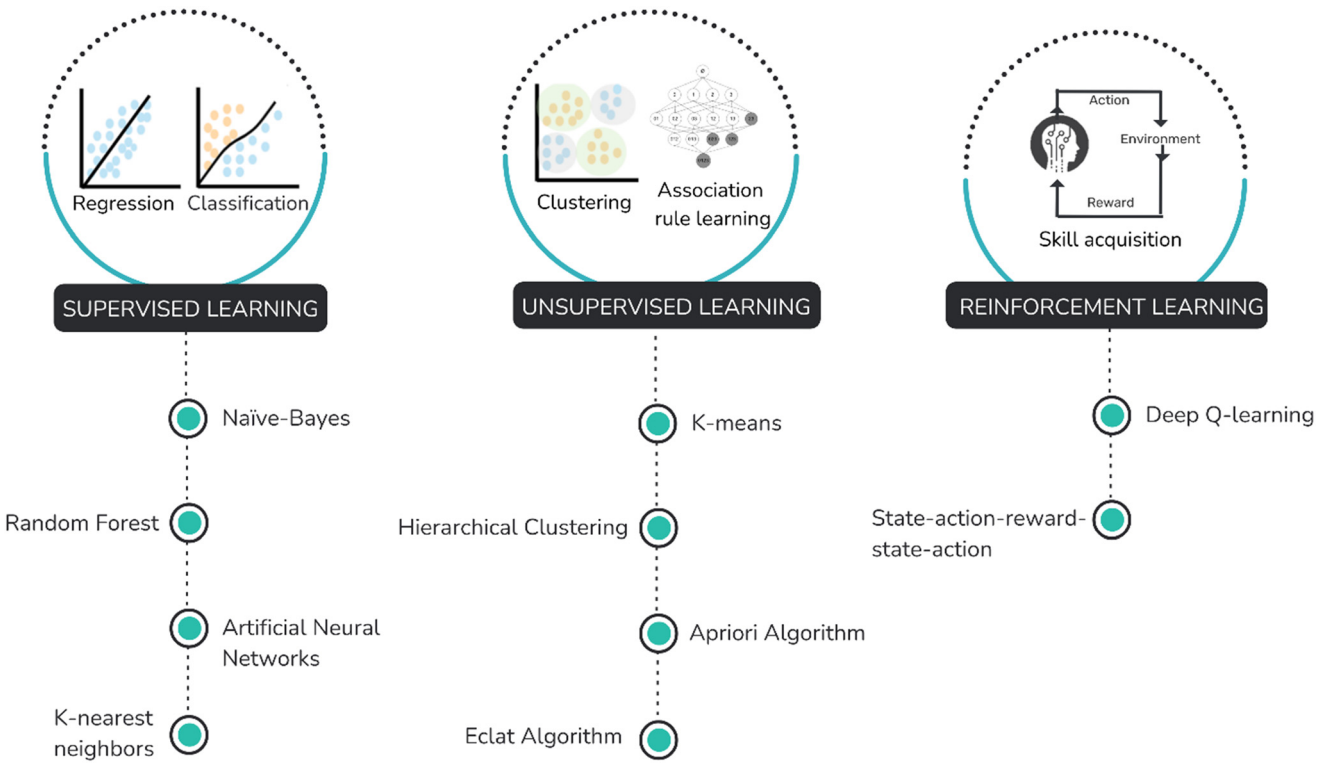

Fig. 4 Learning methods of ML and their associated techniques and algorithms most utilized.

a set of data or labeled data. The algorithm, in this case, receives a set of input variables that are used to predict a response, and a comparison of the model output with the correct one is responsible for correcting the parameter.[90]

Unsupervised learning by itself does not receive labeled data. This procedure is convenient to discover a way to group, or cluster, a set of elements by its similarity.[91] Finally, reinforcement learning is accomplished through trial and error, as well as reward and penalty feedback from the environment. The goal of reinforcement is to learn how and what to do in a specific situation to maximize the reward.[92]

The success of a learning model is strictly dependent on some assumptions. First, an evaluation of the data is necessary to initiate the data analysis. Structured data or unstructured data require different approaches. At this point, it needs to be elucidated. Afterward, a problem definition must be created, and the description of the problem must be very clear, with the targets well defined. The following step is reserved for data analysis in the data set. This process is necessary to determine which features of the data set are crucial to the insights of the model. After that, data cleaning can begin.

By this time, it is already possible to see what learning method fits better to the task. Therefore, this step is reserved for this decision. Lastly, the experimentation process is performed. This step can be considered pivotal to achieving great performance in the model. Evaluations of the response will be performed during the experimentation to determine the best model for the target. At this point, the machine learning engineer must be aware of the techniques that have already been used as well as the new possibilities for improving the model response.

There are many techniques available for each learning algorithm. In supervised learning, classification and regression are two possibilities of algorithms. The regression models are based on a quantitative response, where a numerical value can be predicted continuously.[93] In this method, the independent and dependent variable relation is represented by a linear function, that must have a reasonable accuracy.[94] On the other hand, classification is a binary process, where only two options of response are available (except in multi-class classification). In unsupervised learning, clustering and association rule learning algorithms are commonly applied. Data clustering is used to group unlabeled data based on pattern similarity, whereas association rule learning is responsible for discovering relationships between items in the data set. Finally, reinforcement learning can occur through the skill acquisition method, in which the model acquires skills through a reward and penalty approach.

Learning methods are not usually applied in continuous flow photoredox catalysis. However, studies involving microreactor optimization are easily found. Dressler *et al.*[95] suggested the combination of microfluidics and ML techniques to solve the problem of lack of performance in microfluidic systems after a long timescale. Reinforcement algorithms were proposed by the authors. Model-free episodic controllers and Deep Q-networks. The authors stated that the algorithms outperformed human-level performance, being able to control factors such as droplet size and laminar flow, as well as process all the experiments. On the other hand, Lavín, Kanizawa, and Ribatski[96] utilized the *k*-means clustering method to detect patterns in a microchannel's flow. From that, they discovered different types of patterns with different characteristics in the flow.

In terms of reaction efficiency in microreactors, ML can support by predicting an optimal reaction condition, clarifying the importance of operational parameters in the processes, and identifying retrosynthetic routes.[97] In this regard, Watanabe *et al.*[98] investigated the effects of reaction parameters on the synthesis of nanoparticles in a microreactor. Artificial neural networks (ANNs) were one of the techniques used to achieve this goal. The ANNs' predicted values had a good linear relationship with the measured ones. The method proved to be effective for visualizing a manifold parameter.

Motivated by the challenge of controlling nanomaterial synthesis, Orimoto *et al.*[99] proposed the use of ANNs to predict the properties of the nanomaterial and the conditions. The algorithm produced good results, accurately predicting the properties of the nanomaterials in new experimental conditions. Furthermore, patterns in properties conditions were discovered through this method. The data set was derived from the experimentation in a microreactor.

Moon *et al.*[100] also utilized learning techniques to identify the parameters that have a direct influence on the reaction. A random forest (RF) model was developed in this case to predict the stereoselectivity outcome of glycosylations. The model was successfully applied, and it was able to provide predictions and define a method for controlling stereoselectivity in this scenario. The experimental procedure to validate the predicted results was performed in a microreactor platform.

Xing *et al.*[101] constructed a model with RF, ANNs, and empirical correlations (EC) to predict the kinetic parameters of biomass devolatilization for application in CFD simulations. The validation results presented an R^2 of 0.92 for the RF model, and the ANNs presented the second-best result. The two ML algorithms were superior to EC predictions, proving that ANNs and RF can provide accurate estimates.

ML presents an important role in the field of reaction control and optimization. Furthermore, data post-processing and the ability to solve complex fluid dynamics problems such as design optimization, modeling, and analysis are some of the contributions that ML can make to improve chemical processes. In this context, Granados-Ortiz and Ortega-Casanova[102] exploited a framework composed of an RF classifier algorithm and a kriging method to predict the optimal geometry configuration for the formation of a vortex shedding in a microdevice. The framework presented an efficient response for the microreactor's design with good

results from the RF algorithm, with no need to be substituted by a more complex algorithm. The author also concluded that by utilizing the framework proposed, it is possible to reduce the computational resources necessary to locate vortex shedding.

From this perspective, it is possible to assert that studies using microreactors and ML are becoming more common. However, the combination of ML and continuous-flow photoredox catalysis remains a gap in the literature.

4. CFD, ray-tracing and ML: a framework

The prospect of combining predictive approaches and flow reactors is exciting in the synthetic chemistry community and has been seen as a great opportunity of improvement in the field.[103] The ability to automate the process while minimizing waste and increasing safety is necessary for all sectors.[104] In this sense, intelligent microfluidics is gaining space in the scientific community. This approach refers to the use of machine learning and computational fluid dynamics (CFD) to improve microfluidics systems and is already applied in a variety of industries, including biotechnology and chemistry. In the chemical field, for example, ML and CFD can provide insights into difficult challenges involving optimum conditions in chemical reactions and even reverse design of microfluidics devices. ML and CFD can be used to assess, develop, and control continuous or discrete fluids in microchannels. Even if the yield is only enhanced by 1%, for example, the ability to optimize reaction conditions can create profit and save resources in industrial chemical processes.[15]

When CFD simulations are computationally demanding, a surrogate model can be built. Surrogate models are statistical models capable approximate the simulation outcome accurately. Following that, this trained statistical model can be used to replace the original computer simulation in sensitivity analysis, optimization, or risk analysis. It is critical for the evolution of microfluidic technology to have an economically effective and rapid solution for optimizing microfluidics technology on an industrial scale. By applying a framework comprised of CFD, ray-tracing, and ML, this total system optimization might be achieved. CFD and ray-tracing simulation can shed light on all aspects of optics and fluid flow. Simultaneously, ML can help as a smarter and faster optimization tool that is completely effective. Despite ray-tracing being a new technology when it comes to its application in photomicroreactors, a growing number of studies implementing CFD and ML in fluid dynamics systems can already be found in the literature. In this sense, Hanna *et al.*[105] coupled ANNs and RF to CFD simulations to decrease the simulation computational cost. Afterward, the author proposed a coarse grid in the simulation coupled with ML techniques to predict the local errors in the grid in the function of flow features. The method generated good results by correcting the coarse grid locally. Furthermore, the model could predict results for new cases, such as those with different geometrical dimensions and distinct Reynolds numbers. Bao *et al.*[106] employed ML techniques to estimate the error in a coarse-mesh CFD. The author used deep feedforward neural networks in this case (NFNN). AI's grid optimization can result in a significant reduction in computational time. As a result, this type of application is becoming increasingly common in the literature.

Regarding design, Liang and Yuan[107] studied mixing optimization in a microreactor. The authors proposed a supervised learning method, a support vector machine (SVM), which was trained using CFD data simulations to achieve this goal. The authors' proposed framework managed to yield the main product approximately 4.3 times more than the original microreactor.

To perform data post-processing, Yu *et al.*[108] combined CFD simulation with a non-supervised learning algorithm called *K*-means. The goal was to find the most advantageous partition in various zones of an engine combustion chamber. The combustion chamber was successfully partitioned into different zones based on the *K*-means results. Marcato *et al.*,[109] using CFD to produce a data set, predicted the permeability and the deposition rate in porous media with ANNs. This model's execution produced highly accurate predictions.

Ren *et al.*[110] demonstrated how machine learning, CFD, and ray-tracing simulation can be used to optimize a photocatalytic hydrogen production system. The author obtained the flux of sunlight on the reactor's surface using a ray-tracing simulation. To investigate fluid dynamics, radiation transfer, and chemical reaction kinetics, a CFD model was developed. A Gaussian process regression was used to reduce the computational effort. According to the author, the results demonstrate the applicability of those tools in the optimization of hydrogen production systems, as they successfully found the optimum operational conditions that lead to a high yield of hydrogen productivity.

Therefore, it is possible to conclude that ML and CFD can be great allies for an accelerated synthesis. However, as previously stated, the optics events in the system must also be considered for optimization. Thus, we propose combining ray-tracing simulations with CFD simulations and ML techniques to develop a new optimization method. With this combination, ML can enter the framework with the task of predicting the best configuration possible, considering physical and optical phenomena, reactions, and microreactor design. Fig. 5 illustrates the framework principles.

The ray-tracing simulation is capable to evaluate the irradiation in the microdevice while accounting for all-optical properties. This enables a tuning up in the microreactors configuration considering the optical efficiency. Furthermore, the photon path in the domain can be observed, and the optical losses can be determined. From the ray-tracing simulation, the photon flux in the microchannels (or another domain) can be set as the light input for the chemical kinetics in the CFD software. As a result, the entire

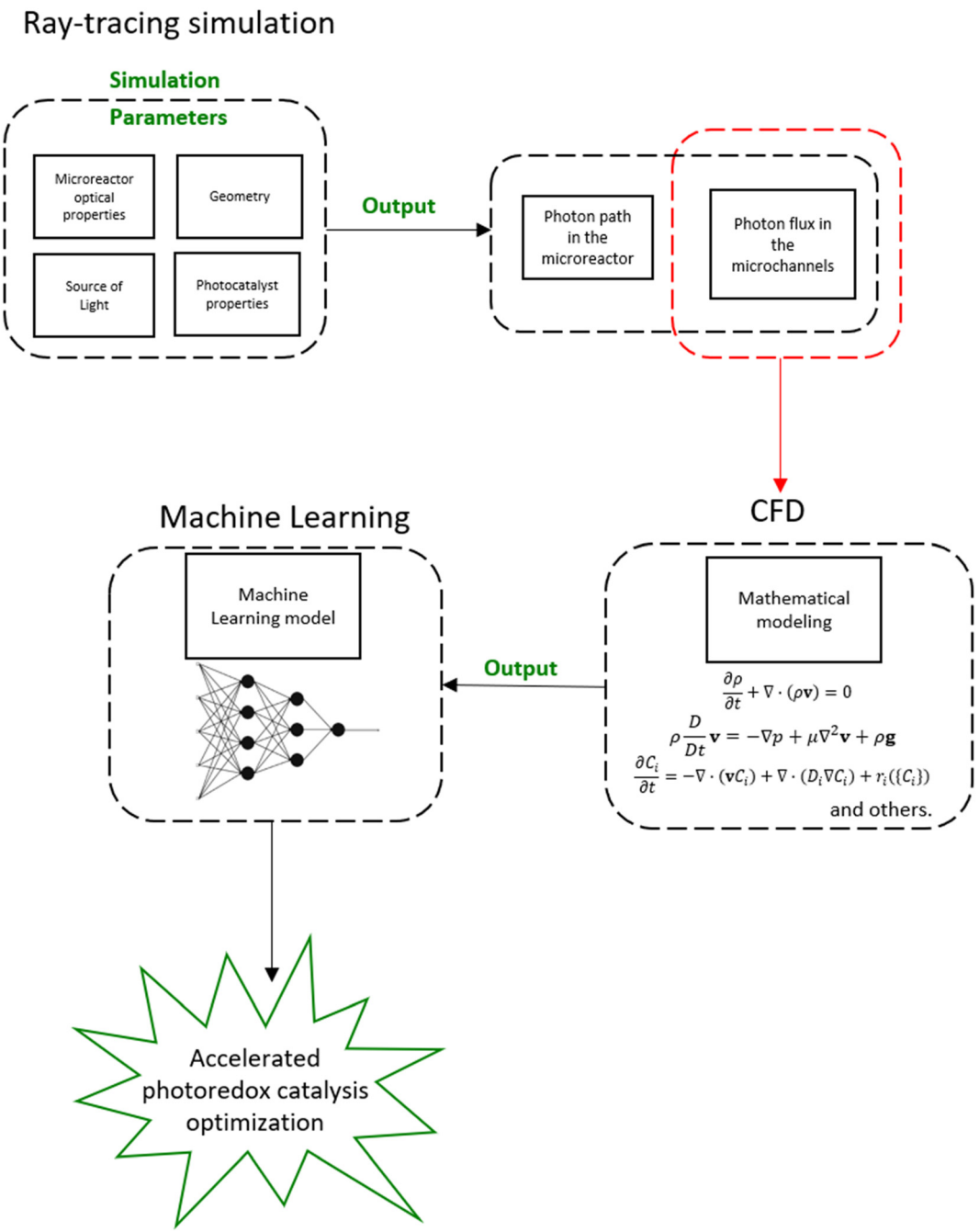

Fig. 5 The framework's basic flowchart for continuous-flow photoredox optimization.

computational procedure will consider the precise irradiation that reaches the reaction medium, and the simulation result can be performed while taking into account all of the phenomena involved in the reaction.

However, as previously stated, complex models necessitate a high computational cost, which may result in simulations that are no longer worthwhile. In this case, machine learning models can be fed with the simulation results, being able to perform the predictions faster and at a lower computational cost. There are only a few studies applying those techniques together that can be found in literature nowadays. Thus, this work aims to propose the use of this method to accelerate optimization in photoredox catalysis systems, thereby speeding up the evolution of synthetic chemistry.

The adoption of this technique can aid not only single-phase flow reactions, as also the complexes multiphasic reactions conditions. Heggo and Ookawara[111] in a comprehensive review about multiphasic reactions in microdevices, stated that the design and the size of multiphase photocatalytic micro- or mini-reactors still need to be optimized in order to attain greater efficiency in terms of quality and quantity in different area of applications, as

well as from a perspective of capital and operating costs. Laudadio *et al.*[112] showed how a multiphasic reaction can be improved if performed in a microflow reactor which enable the safe use of oxygen and enhance the irradiation in the mixture. Therefore, we believe that this framework can aid the innovations in the microfluidic field while also directly assisting scale-out strategies for microreactors.

5. Discussions on future directions and concluding remarks

The growing industrial interest in photoredox catalysis to produce added-value compounds has firmly established this field in the literature. Most of the research is devoted to determining methods to improve the reaction rate and reduce costs. In this review, we summarized powerful computational tools that can meet this need in synthetic chemistry. Despite the current robustness of photoredox catalysis, there is still plenty of room for improvement, and computational simulations may be a valuable tool in this regard. The ability to optimize a photochemical system without using reagents, raw materials, or overall resources is the main attraction of these technologies. The applicability of those tools for optimized photoredox catalysis is important for a new perspective in the field of photochemistry improvements. There is still much to be discovered in this field, but the ability to investigate a reaction while taking optics and fluid properties into account and in a faster way can be game-changing.

Conflicts of interest

The authors declare no conflict of interest.

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