How chemical engineers can contribute to fight the COVID-19

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ABSTRACT

The SARS-CoV-2 virus, promoter of COVID-19, already infected millions of people around the world, resulting in thousands of fatal victims. Facing this unprecedented crisis in human history, several research groups, industrial companies and governments have been spending efforts to develop vaccines and medications. People from distinct knowledge fields are doing their part in order to overcome this crisis. Chemical Engineers are also contributing in the development of actions to control the SARS-CoV-2 virus. However, many chemical engineers still do not know how to use the knowledge acquired from Chemical Engineering school to collaborate in the fight against the COVID-19. In this context, the present paper aims to discuss several knowledge fields within the Chemical Engineering and correlated areas successfully applied to create innovative and effective solutions in the fight against the COVID-19.

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1. Introduction

The new coronavirus was identified for the first time by November, 2019, at Wuhan city in China. Since then, the virus has been spread around the world, leading the coronavirus disease 19 (COVID-19) to the pandemic status according to World Health Organization (WHO) already in February, 2020. The SARS-CoV-2 virus, promoter of COVID-19, already infected millions of people around the world and resulted in thousands of fatal victims. By august, 2020, there were 18,614,177 confirmed registered cases of COVID-19 and 702,642 related deaths, as reported to WHO. These numbers keep increasing due to the easy transmission by airways via spittle droplets from cough, sneeze and speak. Thus, a mere proximal contact with an infected person would be enough to promote the transmission between human beings. The easy transmission characteristics lead billions of people, around the world, to stay home under a rigid social distancing quarantine [1−4]. According to the reported data, about 80% of COVID-19 infected patients developed light to mild symptoms, while about 20% can suffer severe symptoms, such as pneumonia, severe acute respiratory syndrome (SARS), pulmonary sepsis, including death as outcome. The COVID-19 also could affect other organs, including heart, brain and kidneys [5,6]. The SARS-CoV-2 belongs to coronavidae family. From electronic microscopy analysis of the coronavirus surface morphology, spikes formed by S protein trimmers, the "spike protein", given a crown-shape appearance, and then the name "corona virus". Therefore, the new virus is from the SARS-CoV family, that infected 8,000 people and killed 800 in 2002 and the MERS-CoV, that infect 2294 people, leading 35% to death. Up to now, 14 different mutations were identified, including structural alteration in the crown making the vaccine development a hard task due to the transition of target points. However, its similarities with other virus from coronaviridae family aids the strategic and fast development achieved in the researches about the SARS-CoV-2 [2,4,7,8].

Facing this unprecedented crisis in human history, several research groups, industries and governments have been spending efforts to develop vaccines and medications. Professional from distinct areas including virologists, immunologists, epidemiologists, oncologists, biotechnologists, chemists, biochemists, bioinformatics, among several others, have been working hard against the COVID-19. People from distinct knowledge fields are doing their part in order to

overcome this crisis. Chemical Engineers are also contributing in the development of actions to control the SARS-CoV-2 virus.

The review was organized starting from the vaccines development, since it is one of most common effective strategy to obtain population immunization. The medical protocols, including the active pharmaceuticals tested in the fight against the COVID-19 were also explained. Then, the most important fluid dynamics aspects were elucidated, since they are directly linked to the disease spread from the transmission routes by air and droplet dynamics. Following, the hard task to fulfill the material demand generated form the pandemic, e.g. individual protection equipment, including the innovative strategies, as the use of reverse engineering and additive manufacturing to overcome such issue was detailed. Finally, some state-of-art technologies in the disease diagnostics and the pandemic monitoring were explored, including Microfluidic-based chips and the use of Artificial Intelligence. Accordingly, this review was divided in the following sections: vaccines and medication, fluid dynamics, 3D printing, microfluidics and artificial intelligence.

The main goal of each one of these sections was to familiarize the reader with the most important researches on COVID-19 and the topic in question, also to provide the reader a direction guide by providing current research in these areas. Our main goal is that the present review serves as a source of information for researchers, professors, professionals and students of Chemical Engineering and related areas.

2. Vacinnes and medication

Currently, the main concern of worldwide community is probably the development of an effective vaccine against the COVID-19. Up to now, there is no drug proven to be capable to combat the virus *in vivo*, however, as the days go by, researchers around the world are looking for more effective treatments of SARS-CoV-2. Researches are advancing and the scientific community is moving towards a resolution at a speed never seen before. The vaccine development is fundamentally important, as it allows the patient to develop an acquired immunity, enabling their immune system to fight a specific pathogen [9]. While researchers around the world are working incessantly to achieve the first vaccines already later this year, the fact is that we still do not have a vaccine for COVID-19 or a specific drug, although there are several vaccine candidates in clinical trial phases, such as mRNA1273, BNT162, AZD1222 and AD5-nCov.

Since the COVID-19 is a disease without historic, protocols with medication already available in market have been tested, reducing the time spent in research and development of active components and increasing the positive response to the disease treatment. Accordingly, some tested medications include: Chloroquine and Hydroxychloroquine (used to treat malaria); Lopinavir and Ritonavir (used to treat HIV); Heparin (an anticoagulant); Remdesivir (antiviral used to treat Ebola virus). The latter one exhibited effective results for recovery time of COVID-19 patient, according to preliminary tests. The Gilead Science, the biopharmaceutical company responsible for Remdesivir development announced its production increment after the FDA authorization in hospitalized patients under severe conditions.

Despite some researchers are against the use of antimicrobials in the treatment of viral infections, drugs such as Azithromycin, Teicoplanin, Oritavancin and Dalbavancin, were also used in tests in vitro, exhibiting positive results in the SARS-CoV-2 inhibition in human cells. The results of medications on COVID-19 treatment are still inconclusive and some of these could lead to major problems to the patient, as reported for the use of Chloroquine and Hydroxychloroquine [10−12].

The discussion about the use of Chloroquine and Hydroxychloroquine is controversial. It is known that both medications could present toxicity, in addition to collateral effects and even could lead to death. However, in vitro tests indicate that the use of these medications could effectively inhibit the infection caused by SARS-CoV-2. Other studies reported that, especially in the case of administration of Hydroxychloroquine combined with Azithromycin, patients presented the viral cure at the sixth day of treatment. Nevertheless, using solely the Hydroxychloroquine, only 57.1% of the patients presented the viral cure. The main worry related to Hydroxychloroquine treatment concerns in its use outside the hospital environment, due to its collateral effects, especially risks related to cardiac rhythm, as alerted by the FDA [13]. In summary, the studies that used Chloroquine, Hydroxychloroquine and Azithromycin have received rough criticism, due its flaw methodology and its inconclusive results [14], up to now, in which its use for research was suspended by the World Health Organization (WHO) [15]. Accordingly, the development of an effective vaccine is mandatory.

Usually, the development of vacines takes some years, since its idealization until pre-clinical and clinical studies. The previous experience in the researches related do SARS-Cov and MERS-CoV, together with the prompt response need in the pandemic, allowed a fast development of candidates to effective vaccines for COVID-19. Furthermore, new production platforms, computational biology, protein engineering and antigen configuration based on structures, spread possibilities to produce vaccines faster and more accurate [16,17].

There is a perspective that one or more vaccines get in market between the end of 2020 and the beginning of 2021. The genetic sequencing of SARS-CoV-2 was first published on January 11, 2020. Since then, more than 40 pharmaceutical companies and academic institutions around the world are searching for an effective vaccine against the COVID-19. By the time, some of these are already in clinical test stage. This is the first time that a new vaccine entered the phase I of clinical test after only three months from the disease discovery [8,13,16,17].

The potential vaccines against the SARS-CoV-2 present distinct specifications, including vaccines with attenuated or inactive virus, vaccines of viral subunits, conjugated vaccines, vaccines of DNA and mRNA (gene therapy), vaccines with nanoparticles, among others. Each one of these vaccines possess advantages and disadvantages, however, key features as development velocity, manufacture flexibility, safety, stability, immunity period, scale increment and production costs must be considered. Despite the recombinant DNA/mRNA vaccines presents the easy scale-up of production, it is probably that no single vaccine can meet the global need [5,8,18]. The recombinant DNA vaccine is administered to the patient by an electroporation process, or by another device allowing the DNA to enter the cell. The mRNA vaccines use lipid nanoparticles to protect and carry the mRNA to the action site. However, the lack of knowledge and commercial expertise in this technology field could be an issue to develop successfully this type of vaccine [18].

By May 20, 2020 the WHO announced 124 vaccines candidate to COVID-19 immunization. From these, 10 candidates were already at clinical stage, while the other 114 were at pre-clinical evaluation stage. It is possible to access the vaccine candidates list from WHO website at: https://www.who.int/who-documents-detail/draft-landscape-of-covid-19-candidate-vaccines. Some of these vaccines search the neutralization of the protein crown on the virus surface by antibodies action, in the same way that other effective vaccines used in other diseases. Once the SARS-CoV-2 is a pathogen acting mostly in the airways, the vaccines have been developed to induce neutralizing antibodies and to prevent the infection especially in the respiratory tract [19].

Recent publications showed promising results, including Gao et al. [5] and Zhu et al. [20]. The first research group reported a neutralization of SARS-CoV-2 by the candidate vaccine in clinical test in rats, mice and monkeys. Zhu et al. [20] reported results from an effective and safe vaccine, already in phase I clinical stage in humans. The

vaccine was tested in patients of Wuhan (Chine). Immunogenic action was noticed within the 28-day period. No adverse effects were reported in this period. Fast response from T cells/lymphocytes was noticed from the 14th day since the vaccine application. The run for the effective vaccine also is of interest of big pharmaceutical companies, like Pfizer, GSK and INOVIO. The latter one, in a partnership with South Korean National Institute of Health (KNIH), already performed tests in human since March 2020, for a vaccine of recombinant mRNA type [18,20].

Although the optimistic projection of an effective vaccine with accessible cost already in 2021 [21], there is a long procedure to achieve an effective and market available vaccine. Validation of effectiveness and safety, including the clinical studies to ensure the patient to stay immune from new contaminations, the approval of federal and world organs, the production scale-up considering the global demand and logistics, are some of the key factors. Up to now, the only way to restrain the coronavirus spread is to respect the social distancing.

3. How flow physics comprehension can enable mitigation and prevention of COVID-19?

Fluid dynamics analysis tools have been a critical aspect to fight the COVID-19 pandemic [22]. Previous investigations that focused on understanding the behavior of virus-laden particles on air gave to health organizations, as WHO, CDC, and ECDC, sufficient information to prescribe measures to reduce virus spread. Some of these measures include inter-personal distance of 1.5 to 2 m from each other, although there are evidences that show this could not be enough [23]. In this context, we describe here the following topics related to flow physics role regarding to COVID-19, based on a review of recent studies: transmission routes; droplet and aerosol dynamics on air; aerosol infection and ventilation effects; and possible mitigation alternatives on environments to prevent COVID-19 spread.

3.1. Transmission routes

The coronavirus that causes COVID-19, SARS-Cov-2, can be transmitted via droplets and surface contamination. Furthermore, recent studies have brought solid evidence of coronavirus airborne transmission, i.e., it can be carried as an aerosol [24,25]. Indeed, other coronaviruses that caused SARS and MERS also proved to be airborne transmitted, which explains why pandemic spread in just few months, although infection dynamics is more complex [26].

Regarding to infection, droplet transmission is usually referred as the via of virus contamination caused by exhaled droplets containing water and microorganisms, e.g., when a person talks to another, and such droplets have higher diameter than other particles in the air (d > 100 μm) [27]. Since these droplets are heavy, they fall onto horizontal surfaces at distances usually shorter than 1.5 m [28]. On the other hand, airborne cross infection refers to contamination caused by virus-laden particles that remain suspended on air, exhaled already by breathing of an infected person. Such via of transmission involves droplet nuclei, i.e., particles with d < 5~10 μm [27]. Since these particles are aerosols, they not only tends to be suspended on air but also, when expelled, can travel long distances [29,30].

The impact of SARS-CoV-2 airborne transmission is that it turns virus spreading more effective, since cellular entry receptor for such virus, the Angiotensin Converting Enzyme 2 (ACE-2), is abundantly present in humans. ACE-2 is present in the mucosae, i.e., airways, epithelia of the lung, and even in the conjunctiva, in the eyes [31].

3.2. Droplet and aerosol dynamics on air

Researchers have endeavored to comprehend how human cough, sneeze and even speech may spread virus-laden droplets in the air, which explains why COVID-19 is so contagious. During this review, we could identify some important experimental and numerical studies that focused on this aspect, especially airborne transmission. Table 1 summarizes these investigations.

Among these studies, we would like to emphasize on the one carried out by Feng et al. at the School of Chemical Engineering in Oklahoma State University, which elucidates how chemical engineers can contribute to pandemic mitigation with fluid dynamics knowledge [35]. This study was, according to our review, the most complete numerical study on virus-laden droplets dynamics on air, involving effects usually neglected, as wind velocity in an environment. The results obtained showed that interpersonal-distance prescriptions,

Table 1
Summary of recent studies on virus-laden particles on air.

Type of study	Title	Method	Main findings
Experimental	Aerodynamic analysis of SARS-CoV-2 in two Wuhan hospitals	Collection of aerosol samples and quantification of RNA concentration of SARS-Cov-2.	Higher concentrations of SARS-CoV-2 aerosols in areas with low air circulation, as medical staff areas [32].
	Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1	Aerosols containing SARS-CoV-2 or SARS-CoV-1 generation, feeding into a Goldberg drum, and analysis on inoculum.	SARS-CoV-2 remains at least throughout 3 h in aerosols, although there is a reduction in infectious titer; SARS-CoV-2 is more stable on plastic and stainless steel than on copper and cardboard, and remains detectable for days on these surfaces [33].
	Could SARS-CoV-2 be transmitted via speech droplets?	Detection of saliva droplets using a planar beam of laser light in a dust-free enclosure during a human speech.	Droplets of different sizes are exhaled during speech in asymptomatic individuals, and a great part of them becomes aerosolized [34].
Numerical	Influence of wind and relative humidity on the social distancing effectiveness to prevent COVID-19 airborne transmission: a numerical study	Modeling and CFD simulation of transient transport, condensation/evaporation and deposition of SARS-CoV-2 laden droplets emitted by coughs, using two virtual humans and varying distance, wind velocity, relative humidity, and facial covering effect.	Wind effect on the droplet transport and deposition is significant and so, current inter-personal distance policies are not sufficient to protect from SARS-CoV-2 exposure, although wearing facial masks significantly reduces droplets formation; Higher relative humidity causes higher virus-laden particle deposition fractions, which could reduce airborne transmission [35].
	Understanding transmission dynamics of COVID-19-Type infections by direct numerical simulations of cough/sneeze flows.	Modeling and CFD simulation of turbulent flow, similar to expiratory flows, and analysis of temperature distribution in a moist plume.	Temperature distribution in a "dry cough" simulation indicates that liquid content expelled in this situation spreads rapidly (< 1 s) along more than 1 m [36].

even the most severe, with 6 ft distance, just do not fit in real situations, since it is only applicable with static air. Authors also observed that high air relative humidity (99.5%) leads to droplet hygroscopic growths, which intensifies droplet deposition on surfaces. On the other hand, low relative humidity (40%) leads to water evaporation of droplets, intensifying the aerosol formation process. These conclusions may suggest a positive effect of air relative humidity in reducing virus spread since, since if in the one hand, this effect increases surfaces contamination, on the other hand, it reduces airborne transmission, which is far more difficult to control.

3.3. Aerosol infection and ventilation effects

A significant investigation on SARS-CoV-2 spread in aerosols was made by Evans et al. [27]. In this investigation, they developed a mathematical model to analyze guidelines for ventilation and occupancy in an indoor environment. From assumptions made for infection probability and infectious dose in droplet nuclei content, solving modelling equations gave results for steady and transient occupancy in some environments where only a contagious individual is. Results showed that in small spaces with low ventilation, e.g., a car or a bathroom, with room ventilation rate of 1 $m^3.min^{-1}$, the infection dose could be crossed in just 10 minutes, only by breathing. In spaces such as an office, this time is after 100 minutes. These times are very much smaller if a contagious individual talks, coughs or sneezes. From that, authors concluded that it is necessary at least 50 $m^3.min^{-1}$ per occupant air change rate for this environment sharing, in order to reduce infection risks.

Evans et al. analyzed how aerosol transmission can occur in a building at steady state. In this case, there is a possibility of transmission through the HVAC system. Since most of the HVAC filters reduces at least 90% of droplet nuclei, on the other hand, the remaining droplets persists even more diluted in the air and spread among all the air space. Results obtained for this condition indicate that it is necessary a 10 $m^3 min^{-1}$ per occupant room ventilation over all rooms, using a well filtered HVAC system to prevent virus spreading.

In this study, they also analyzed how virus spread via aerosol can occur in cases of transient occupancy, i.e., in spaces briefly occupied by many people, in which air patterns do not reach steady state. In such situations, in a 6.5 m^2 bathroom with 1.98 $m^3.min^{-1}$ air fan operation, it is necessary a 16 minutes waiting time between occupants to keep this environment safe. They also concluded that increasing the airflow to 10 m^3min^{-1} could eliminate this waiting time.

3.4. Mitigation alternatives on environments

3.4.1. Air distribution in a room

Nielsen et al. showed that since aerosols are so small that they follow the airflow, air distribution patterns in a room might influence this virus transmission route [28]. Therefore, concentration and distribution of virus in a room are related to aspects as the layout of the room, heat load distribution, positioning between persons and direction and height of their faces, type of air distribution in the room, and location and type of air diffuser, according to previous Nielsen at el. studies [37,38].

Among all cited aspects that influence indoor virus distribution, we can highlight positioning between people and airflow patterns according to type of air diffuser. Considering a vertical temperature gradient, in a room displacement with ventilation, direct exposure occurs between two persons in less than 80 cm distance, although positions of people also influence exposure. Such results showed that exposure is maximum when two persons is positioned face to face, and minimum when they are positioned face to back, considering the infected person is seated. Regarding to air distribution in the room, results pointed that minimum exposure is reached when the diffuser

is located at the roof, just ahead two persons in the room, and air is expelled towards the walls. On the other hand, maximum exposure to virus transmission is observed when the air diffuser is located down the wall and air is expelled horizontally [38].

3.4.2. HVAC system

Evans et al. [27] studies showed that is necessary to increase air exchange rates in an HVAC system to minimize COVID-19 airborne transmission indoors. A stand-alone unit with filtering capacity of 10 $m^3 min^{-1}$ is sufficient to increase safety in bathrooms and small offices, for example. Besides that, they also showed that air recirculation in HVAC systems should be avoided, and local ventilation, as exhauster and bathroom fans help to mitigate infection. Authors also warned about cares to be taken when changing filters in stand-alone units and HVAC units, as they may contain significant viral load.

3.4.3. Wastewater plumbing

In buildings where plumbing systems are fully connected, virus-laden droplets may be transported through empty U-bends in bathrooms, consisting in an airborne transmission route [39]. Authors carefully studied this effect in a Honk Kong super spreading event of SARS in 2003 [40]. Therefore, some recommendations have to be taken to ensure wastewater plumbing transmission of SARS-CoV-2 is minimized as prevent loss of the water trap seal with U-bend, open all water appliances for, at least, 5 s twice a day, monitoring and repairing possible crack or leaks in pipework [39].

3.4.4. Portable air filters and purifiers

Since studies results evidenced there is an airborne transmission route of COVID-19, discussions have been made on the use of special filtering technology in HVAC and indoor ventilation systems. Indeed such measure is not necessary, once most aerosol particles are filtered in commonly used systems [27]. Even so, government authorities also proposed the use of indoor air purifiers to prevent droplet and aerosol infections [41]. However, researchers warned that air purifiers use a dilution ventilation method that may increase virus spreading. Therefore, engineering control measures, i.e., control of room ventilation patterns, is a more effective way of control such biological hazard, instead of mere using of air purifiers itself [41].

3.4.5. Fresh air ventilation rates requirements in confined spaces

Dai and Zhao [42] studied the association of COVID-19 infection probability with ventilation rates in confined spaces employing the Wells-Riley equation. This equation, given as follows, relates the probability of infection, in a room, with the ventilation rate.

$$P = \frac{C}{S} = 1 - e^{\frac{Iqpt}{Q}} \tag{1}$$

Where P is the probability of infection of an individual in the room. C is the number of cases to develop infection. S is the number of susceptible individuals. I is the number of infectors. p is the pulmonary ventilation rate of each susceptible. Q is the room ventilation rate. q is the quantum generation rate produced by one infector, i.e., number of virus RNA copies exhaled, at a time interval. t the is the exposure time [43].

Authors obtained results for different scenarios, considering even the effect of mask wearing. To add this factor in the model, they assumed that this effect is equivalent to increasing the room ventilation rate due to the filtration effect of the mask. The results obtained pointed that, for example, to decrease infection probability in an office to less than 5%, without wearing masks, it is necessary a ventilation rate of 500 $m^3.h^{-1}$ per occupant. To reduce the infection probability in a classroom to less than 1%, without wearing masks, the ventilation rate required is higher than 750 $m^3.h^{-1}$ per occupant [42]. Therefore, such findings suggest that improvements in built

environments are required to mitigate droplets and airborne transmission in confined spaces, especially those asymptomatic.

4. The role of 3D printing in the COVID-19 pandemic

The 3D printing consists in the direct manufacture of physical objects from digital models. This technique, also known as additive manufacturing, allows, in few hours, the fabrication of a device from its initial design using low-cost material, providing also an independence on device design [44]. Zhang et al. [45] presented some advantages of 3D printing: the development of complex geometries; low manufacturing costs; development time reduction; diversity of raw materials; personalized designs. In order to better understand how this technique is present on scientific community and has been playing a fundamental role in the fight against the COVID-19, a brief historic review was provided.

4.1. 3D printing historic

The 3D printer with FDM (Fused Deposition Modeling) or FFF (Fused Filament Fabrication) technology was invented by Scott Crump, founder of Stratsys corporation, being patented in 1989 [46]. The 3D printing was popularized only after the fall of patent right in 2009 and the RepRap project (Replicator for Rapid Prototyping). The RepRap project was born in England in 2004, aiming the fabrication of 3D printer capable to rapid prototype and to manufacture their own components in plastic [46]. Furthermore, the RepRap project accounted with Arduino (open code for microcontrollers) project collaboration and the Marlin developer community, a free program that currently operates the mostly of 3D printers [46,47]. The main project goal was to become the 3D printing accessible to all scientific community.

Accordingly, with the popularization of 3D printers, a growing number of scientific researches using this technique were observed. Fig. 1 presents the number of publications with topics "3D printing" and "Chemical Engineering" from 1989 to 2020, taken from Scopus base data [48]. A rapid grown of documents from 2010 was observed from Fig. 1. In 2020 (up to June, 06), the number of published

documents was superior to the one produced in half of 2019. This confirms the importance of RepRap project on the popularization and low cost of 3D printing technique and its grown application in chemical engineering. The major advantages of 3D printing on chemical engineering are related to design independence and fast testing of manufactured components. In the following section the main characteristics of 3D printing are detailed.

4.2. 3D printing: operation and characteristics

Before the 3D printing procedure, it is necessary to provide the digital model of the part. The drawing can be generated from CAD software, such as *Autodesk Inventor* and *Sketch-up*. The direct use of the digital modeling from CAD allows superior design independence, relative to other manufacturing techniques. The drawing parts do not have to be in accord with the machine standards (except to the printing area limit from the 3D printer) or pre-molded shapes. The 3D drawing is exported to STL extension, providing a 3D object from the drawing. The STL file is sent to the slicer program that generates a multilayered object (according to the required object resolution) in a G-code file, being the 3D printer input. The 3D printing based on FDM or FFF technology occurs from the heating of a polymer wire up to its melting point. The polymer is then deposited, layer by layer by a nozzle in the printing desk, producing the physical object.

4.3. 3D printing applied to chemical engineering

The Chemical Engineering is composed of several fields, including chemical synthesis, separation, nuclear, environmental and bioprocess engineering, among others. Due to the inherent multidisciplinary field encompassed in Chemical Engineering, the chemical engineers are complete professional with high analytical capacity and an excellent processes overview, capable to quickly solve problems and propose innovative improvements to existing processes. Accordingly, the 3D printing is a support tool for such professionals in the research and development of new technologies and processes. Some examples of 3D printing in Chemical Engineering are presented below.
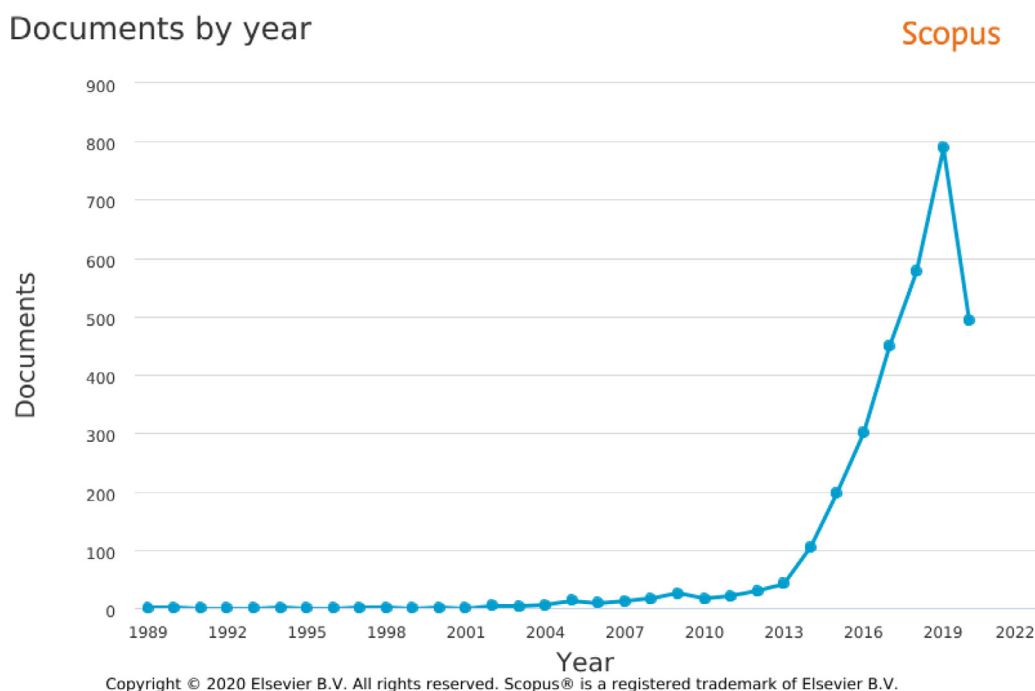
Fig. 1. Number of published documents per year considering the topics: 3D printing and Chemical Engineering. Source: Scopus [48].

The 3D printing can be employed to fabricate a chemical micro-plant for biodiesel synthesis, including microreactors, flow distributors and mechanical supports [49,50,51]. In the separation engineering, 3D printers were used to manufacture distillation and absorption columns, including the development of trays and packs aiming higher specific area internals to enhance the separation [52,53]. In the nuclear engineering, 3D printing was employed to manufacture parts of nuclear fusion reactor, substituting the traditional configuration to improve the packing and minimize issues from tension concentration [54]. In the environmental area, the 3D printing provides alternatives for water treatment including new membranes for filtration and desalinization, adsorption, among others [55].

Wolf [56] stated the growing use of 3D printing in laboratory facilities aiding researches to fabricate equipment in their own laboratory with a reduced cost. In this context, the 3D printing presents a great potential related to process improvement in Chemical Engineering.

4.4. 3D printing applications in the fight against the COVID-19

The chemical engineer is a complete professional and, together with 3D printing, is capable to create innovative solutions for chemical engineering processes. This professional also can aid the fight against the COVID-19 pandemic by applying its critical sense and analytical capacity to develop solutions and to solve problems. The COVID-19 pandemic is promoting a world scale high demand of masks, face shields, medical ventilator valves, clinical test kits and other individual protection equipment (IPE) [57]. However, the industries have not been capable to produce and to supply materials in the demanding rate. The 3D printing is an innovative technology and a practical tool that has been applied to create solutions in the current scenario. The pandemic enforced scientist and researchers to an urgent situation requiring fast and effective solutions to save life. In the next section some of developed 3D printing solutions for COVID-19 will be discussed.

4.4.1. Medical equipment

Shortness of breath is one of the most serious symptoms of COVID-19 [58]. This symptom is responsible for the most part of hospitalization, once the infected patient is not capable to supply oxygen to the body tissues, requiring mechanical ventilators [59]. In Italy, at beginning of the COVID-19 pandemic, the Chiari Hospital experienced a lack of ventilator valves, specifically the Venturi valve (Fig. 2), a device used in Venturi oxygen masks, i.e., low-flow masks

Fig. 2. Original (left) and 3D printed Venturi valves. Source: Italian hospital saves COVID-19 patients' lives by 3D printing valves for reanimation devices [61].

that use the Bernoulli principle to drag ambient air when pure oxygen is supplied through a small orifice [60]. Such valves are used in patients' masks to aid the oxygenation, thus requiring a new valve for each patient. Nevertheless, the manufacturer did not have enough valves to supply to the hospital due to the demanding urgency. In this context, an Italian engineering startup received an order from the hospital. The startup founder, Christian Fracassi, employed reverse engineering to develop the digital model and used 3D printing to fabricate the Venturi valves (Fig. 2). In two days, Fracassi and his team designed, tested and manufactured 100 valves for the hospital and saved many people's lives. The 3D printed valves were donated to the hospital [61].

The Leitat technological center and its partners designed an in-field respirator by 3D printing, the Leitat 1. The respirator had its design and parts reduced and simplified, aiding the achievement of a robust device, with low complexity and easy assembling and production. From such technology, a daily production throughput of 50-100 units was achieved [62]. This project contributed to the fast production of high demand equipment, aiding hospitals in the combat against the pandemic. In the University of Campinas, Brazil, professors, researchers and volunteers used 3D printers to print parts required for mechanical ventilator maintenance. Thereby, such equipment could be used again in the hospital intensive care units (ICU) to treat severe cases of COVID-19 [63].

Inside this urgent scenario inherent from the pandemic state, the demand for hospital supplies and equipment, such as ventilators and respirators were overcharged at world scale. However, the manufacturers were not capable to quickly achieve the production to the required demand. Accordingly, 3D printing appeared as an interesting alternative in such scenario, allowing a fast and low-cost fabrication of the required the parts [64].

4.4.2. Individual protection equipment (IPE)

The coronavirus transmission occurs from droplets produced by cough or sneeze of an infected person [59]. Therefore, the use of individual protection equipment (IPE), including masks and face shields, that provides a protection barrier, became indispensable in the pandemic. This protection is even more fundamental for the medical team and essential service professionals that deal directly with infected patients. The N95 mask is capable to retain particles up to 0.3 mm in the air with an efficiency of 95%. The use of N95 masks by health professionals treating COVID-19 patients was recommended by the Centers for Disease Control and Prevention [57]. Another important feature of a mask is its sealing on the person face. The 3D printer, associated with facial scanners, can be used to manufacture personalized sealing cast according to the health professional face, even taking into account facial expressions [65]. These features could ensure higher safety levels to the use of mask by health professionals.

N95 masks are disposable and due to the growing demand at COVID-19 pandemic, a serious scarcity in the market was experienced. Some N95 masks were passed through a disinfection/sanitation procedure aiming at its reutilization. The disinfection procedure must ensure the virus inactivation, without deprecating the filtration efficiency and the mask sealing, ensuring the required safety level for personal use [66]. In order to increase the number of masks in market, some alternatives have been proposed, including 3D printed masks. Swennen, Pottel and Haers [67] developed a reusable personalized face mask from facial scanning application (mobile app) and 3D printing. The mask is composed of two parts: the reusable one, including the facial barrier and the filter support, both 3D printed; and the disposable one, including rubbers and membrane filters (barrier used for air filtration), as illustrated in Fig. 3. A cleaning protocol and disinfection for reusable parts was proposed. However, validation tests evidencing the absence of viral activity after one or several cleaning cycles are still missing. The authors made available the STL file of the mask assemble. Aiding the enhancement of protection for

Fig. 3. Individualized protection mask made by 3D printing: (a) 3D printed mask, (b) filter membrane support, (c) filter membrane made by polypropylene, (d) digital file of the 3D prototype. Source: Swennen, Pottel and Haers [67].

health professionals, the use of face shields together with masks was recommended. Face shields (Fig. 4) were composed by a fixed rod that must be positioned at forehead and by a transparent polymer visor, resulting in a physical barrier for droplets.

Face shields also experienced a market scarcity due to the COVID-19 pandemic. 3D printing also provided a fast and cheap alternative applied to manufacture this item. Different protectors were developed, printed and tested according to the medical application necessity. Some examples include interventional radiology [68], otorhinolaryngology professionals [69], general protection [70] and personalized protectors with air flow barriers [71]. The 3D printing

companies made available for free the STL files of the developed face shields. Accordingly, people around the world with 3D printers are capable to fabricate this face shields and also donate it to health units along the COVID-19 pandemic. Typically, polylactic acid (PLA) filaments are applied in the construction of face shields by 3D printers due to their biodegradable characteristics [70]. An example was the biofabrication research facility (Biofabris) of the Chemical Engineering School of University of Campinas. The Biofabris received a donation of polymers to be used for 3D printing of face shields, that were destined to public units of healthcare involved in the fight against the COVID-19 [63]. When it comes to manufacturing costs for the face
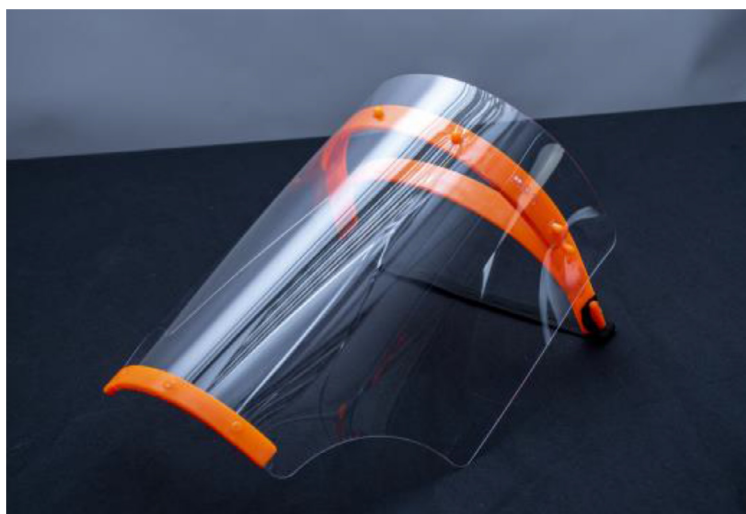
Fig. 4. Face shield made by 3D printing (orange part). Source: PRUSA PRO Face Shield [72]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 5. Nasopharyngeal swab collector made by 3D printing. Source: 3D Printed Test Swabs for COVID-19 Testing [74].

shields, only Amin et al. [70] had a cost of $ 7.30 per piece. In other cases, the material and the product were donated.

4.4.3. Sampling collector for COVID-19 test

The COVID-19 diagnosis test is a fundamental parameter to regulate the public policy for pandemic control, for example, the definition of social distancing rules. The COVID-19 diagnosis tests and its reactants also suffered from scarcity due to the fast growth of cases. Specifically, the molecular RT-PCR test (Reverse-Transcriptase Polymerase Chain Reaction) that analyses samples from nasopharyngeal material of the infected person, detecting the COVID-19 by the presence of RNA from the virus [73]. This test employs nasal swabs, a kind of flexible plastic rod with cotton in one of the tips. Due to the lack of these biological material collectors, 3D printers were used to supply the demand (Fig. 5)

The USF Health, the Northwell Health and the Formlabs worked jointly to develop a nasal swab prototype to be manufactured by 3D SLA (stereolithography). In the validation tests, the 3D printed nasal swabs exhibited good performance and received the FDA certification (U.S. Food and Drug Administration). The Formlabs Company is capable to fabricate up to 100,000 swabs per day and the kit is being sold at cost price [74].

The 3D printing could be used in a near future to manufacture fast tests for COVID-19 detection by antibodies from blood samples. The 3D printing is currently used to manufacture several components of biosensors, including electrodes, substrates, parts for liquid handling and devices' packing [75]. The additive manufacturing appears as an important platform for biosensors development when applied jointly with Microfluidics in the detection of pathogens [75]. These characteristics could make feasible a faster production of materials for a massive population testing.

5. Microfluidics and the virus detection

The emergence of COVID-19 brought a new global reality about the control and measures needed for a pandemic status. The scientific community consensus lies on a closer monitoring of zoonotic viruses and their rapid identification, assisting in a potential upcoming pandemic. However, the vigilance and the discovery of new viruses are still a great challenge related to procedures and technological maturity [76]. The researches related that the virus monitoring requires several stages, including virus concentration growth in the culture media. These stages require adjustment times to achieve the desired efficiency, and it can be an issue when samples have to be disposed or modified with time [77]. The virus detection requires previous studies about structure and sequencing. Immunological and molecular methods, as the ELISA (Enzyme-Linked ImmunoSorbent Assay) and PCR (Polymerase Chain Reaction) are capable to identity the virus without the knowledge of the virus chains, which sometimes can be at low and undetectable concentrations. In order to correct this, an increase in virus concentration (enrichment) in the media should be performed, by specific equipment and reactants [77,78]. In this context, the Microfluidics appears as a potential technology to provide solution about these issues.

Defined as the science and technology applied in structures of dimensions ranging from tens to hundreds of micrometers, Microfluidics represents a great potential for chemical processes design, development and optimization [79]. Microfluidics is an interesting proposal to cost reduction in research and production, also allowing an increase on the vigilance efficiency. Microdevices can be associated with different virus capture, enrichment and detection procedures, using much reduced reactant and sampling volumes [78]. In a worldwide range, researches related to virus detection and infection monitoring are using microfluidic methods, with distinct techniques of detection. The following section reports some of these researches approaching virus detection and improvement of data processing for virus detection.

Wu et al. [80] evaluated the efficiency of four rapid tests (ALLTEST 2019-nCoV IgG/IgM Rapid Test, Dynamiker 2019-nCoV IgG/IgM Rapid Test, ASK COVID-19 IgG/IgM Rapid Test, and Wondfo SARS-CoV-2 Antibody Test) based on the antibodies detection by lateral flow immunoassays. The results suggested that all four tests presented

good sensibility and specificity to detect antiboides after a 3-week period of contamination. Insignificant differences among the four tests were reported for detection time and efficiency. These devices have been widely used for COVID-19 detection tests around the world.

The detection strategy knowing the physical structure of the virus, e.g. the dimensions, could be an interesting alternative to the conventional approaches. Yeh et al. [76] developed a microdevice capable to capture, to enrich and to detect the virus by spectroscopy from database and Machine Learning techniques. The device, named VIRRION, possess a microchannel with carbon nanotubes spaced by a gap capable to capture different virus by its characteristic length scale. After the enrichment, the virus is detected by Raman spectroscopy, since each virus presents a different signaling. The study was validated in the identification of rhinovirus, influenza and parainfluenza.

The fluorescence methods using nanoparticles and Quantum Dots (QD) appear as an efficient alternative for detection and differentiation of viruses. Zhang et al. [81] used a controllable magnetic field and a heating zone associated with magnetic nanoparticles and quantum dots to detect and to classify influenza viruses (H1N1, H3N2 and H9N2). The QD entered the complex formed by nanoparticles and the complementary DNA, so that the component had specific fluorescence for later identification. The goal of the study was to use the magnetic field and the heating area (45 °C) to create a specific magnetic zone of reaction for each type of virus by the emitted fluorescence.

Wang et al. [82] observed the necessity to perform simultaneous and automatic detection of subtypes of hemagglutinin (HA) of influenza virus in microfluidic chips. The device presented the advantage of possessing microvalve components integrated with software, avoiding the human contact with the samples, minimizing the contamination risks. Another important feature was the separation of magnetic beads linked to the protein chain by magnetophoresis and the distinction by size. Also, the device accounted for Quantum Dots to accomplish the luminescence of the HA linked to magnetic beads for later analysis. The authors report that the device presented good specificity and detection of concentration of 3.4 ng/mL and 4.5 ng/mL, for H7N9 and H9N2, respectively.

One fundamental key to develop new products for virus analysis is to ensure process efficiency and human operator safety along the sampling collection and processing. Wang et al. [83] designed a microdevice with 8 chambers capable to detect nucleic acids from Influenza viruses. The device was developed to correct issues of the LAMP (loop-mediated isothermal amplification) device that handles the samples in an exposed manner, allowing possible aerosol contamination and false-positive results. The microdevice generates a colorimetric response from violet to sky-blue, when the nucleic acid signal is amplified. The system works from the patient airway sampling with a swab. The sample passes through lysis and magnetic beads were used to extract the nucleic acids. The latter one flowed throughout the 8 chambers that are capable to distinguish the virus. Fig. 6 presents the procedure used to obtain the virus characterization.

Lin et al. [84] evaluated the method LAMP to diagnose four types of Ebola viruses. The methods consisted in four LAMP standards, a microfluidic disk and a portable real time fluorescent detector. The results showed that the device was capable to distinguish the four types of viruses without cross contamination. The method lasted about 50 minutes from sample addition to reactant mixing. The authors suggested that such method is low cost and simple, with a sensibility level useful for application to remote locations that fight against the Ebola.

These innovative Microfluidic-based detection methods must be always fast and sensible than traditional methods, ensuring an immediate and safe response to the patient. Another desirable feature is to transform the product into a personalized detection method, as for example, to an application installed in the own patient smartphone. Jin et al. [85] developed a microfluidic system to accomplish diagnosis and differentiation of human adenovirus in one hour, considering the sampling time. The microdevice performs the DNA extraction and employs a bio-optical sensor to conclude the reading. The extraction is carried out in 30 minutes inside the chamber containing dimethyl suberimidate. The identification of 10 adenovirus copies by the biosensor occurred in another 30 minutes. The authors compared the designed device to the traditional PCR, considering the device 100 times more sensible and with superior velocity. These features
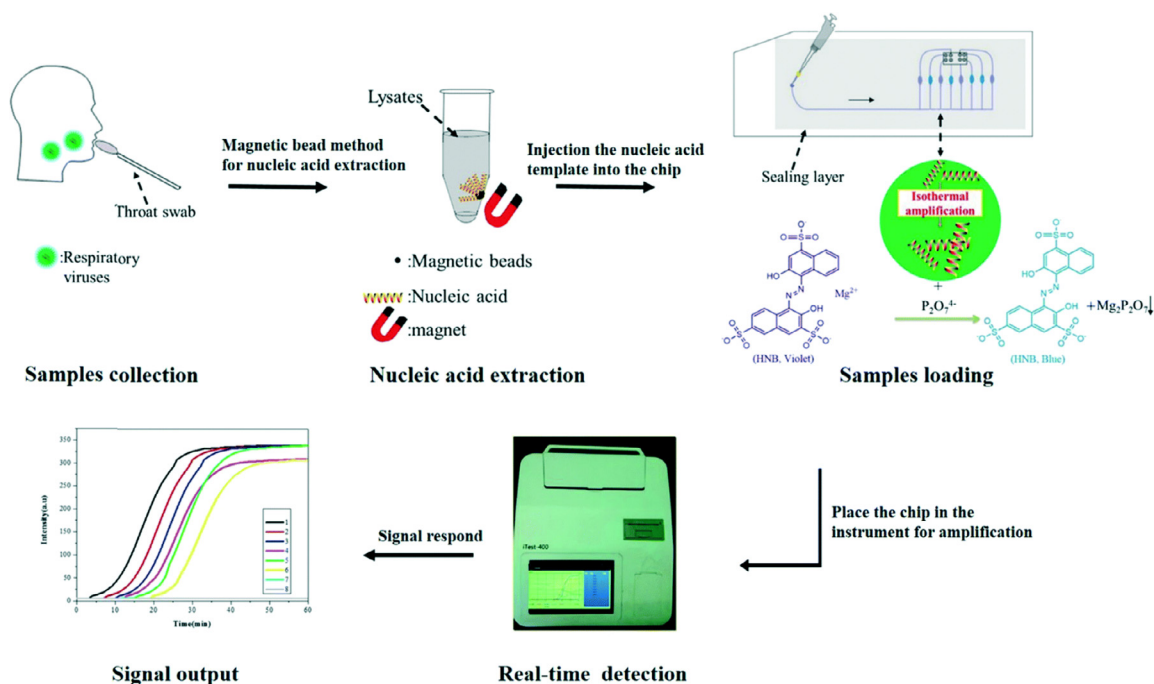

Fig. 6. Procedure scheme for the microdevice developed by Wang et al. [83]. Reproduced from Ref. [83] with permission from the Royal Society of Chemistry.

make the proposed device competitive for the respiratory virus detection.

Recently, Nishiyama [86] performed the detection of anti-H5 antibodies, a subtype of Influenza A virus using an 8 channel microdevice coupled with a device of polarized fluorescence. The coupling is advantageous since it provides an increment of signal per area unit, since the channel present the dimensions of 200 × 900 μm. The authors suggested that the method could be amplified to detect the SARS-CoV-2 virus and also can identify infection with several samples at same time.

Xia et al. [87] developed a low-cost microdevice coupled to a smartphone to detect the Influenza virus. The colorimetric method was used, presenting more sensible responses than the ELISA method. The microdevice consisted in a fishbone cast, made by PDMS, to conjugate the antibodies and to capture the virus. Gold nanoparticles were employed allowing the colorimetric reaction to detect the virus. The capture and detection of the virus lasted about 1.5 h. Despite the good response, the microdevice still requires improvement concerning clogging and camera sensibility, once smartphones possess distinct hardware qualities, and consequently, could lead to different responses. The authors suggested a microdevice equipped with its own camera, capable to be integrated in the smartphone by Bluetooth or USB.

Although the current situation requires faster and safer ways to identify the presence of virus, scientific researches points out for detection methods capable to ensure results reliability and low contamination risks. Despite several methods still requires the sample preparation procedures that can be considered expensive and time consuming, devices as the proposed by Xia et al. [87] pointed out the direction of future healthcare, which the microfluidic devices must be personalized according to the individual necessity.

6. Artificial intelligence

The SARS-CoV-2 virus is a variation from the coronavirus (COVs) family, infecting distinct mammal species, including camels, cattle, cat and bats as receivers and affected species. In human, other variation of virus are known, as the MERS-CoV (Middle East Respiratory Syndrome) and SARS-CoV (Severe Acute Respiratory Syndrome) [88]. The infection is caused by human contact, i.e. from person to person, through the airways. A great number of contagion cases are related to an asymptomatic or pre-symptomatic state [89,90]. Fig. 7 shows the infection distribution considering the cases in China [91,92], in which most part of cases did not develop any clinical aspect. Upon being infected, the angiotensin 2 (ACE2) converting enzymes - present in the cells of lungs, intestines, heart and kidneys - act as

receivers for the intracellular entrance of SARS-CoV-2 [93]. The first infectious symptoms are noticed in pulmonary tissues, being detectable by computed tomography (CT) [94]. The confirmation of infectious condition is performed by molecular tests, as the reverse transcription polymerase chain reaction (RT-PCR) [95], or even by the reverse transcription loop-mediated isothermal amplification (RT-LAMP) [96].

The COVID-19 pandemic has been confronted in distinct scopes: database formulation to monitor the cases [97–102], development of effective vaccines and medication against the SARS-CoV-2 and the virus detection from patients. A common point from these distinct scopes is the use of Artificial Intelligence (IA) that is growing fast as its diverse applicability and promising results are obtained by already existing diagnose formulations and treatments from other diseases [103–105]. By the means of AI application, the medical practice has been changing, so that restricted areas of experienced professionals can be optimized or complemented by machine learning (ML) and the growing formulation of database [106]. Supporting this scenario, the US government, on March 16, 2020, collaborating with research institutes and technology companies, called for global action to assist AI researchers to develop data mining guidelines and techniques to support research related to SARS-CoV-2 [107].

The main AI application within the SARS-CoV-2 pandemic scope is listed following: early detection and diagnosis of infection; monitoring of treatments performed; tracking personal contacts made by infected individuals; projection of cases and mortality; development of medicines and vaccines; reduction in health professional demand; preventive actions of the disease, and prediction of survival in severe cases of the disease [103,106,108,109]. For each of these current applications, there is infrastructure and mobilization of the international community to accelerate the development of such tools. However, the early detection and diagnosis have proved to be one of the main weapons of AI against COVID19 and therefore, in the next section it is further detailed.

6.1. Early detection and diagnosis of infection

Among the most effective and most widely used methods for detecting SARS-CoV-2 are the systems using artificial neural networks algorithms to analyze computed tomography (CT) images. The use of CT for diagnosis is a precise technique to identify interstitial pulmonary infections, as in diseases leading to development of opaque areas between the lobes of the lungs [110,111]. From the CT images, radiologists are capable to identify the exposed patterns and made the correct diagnosis. The clinical condition is further confirmed by reports and tests. Considering the high demand and the
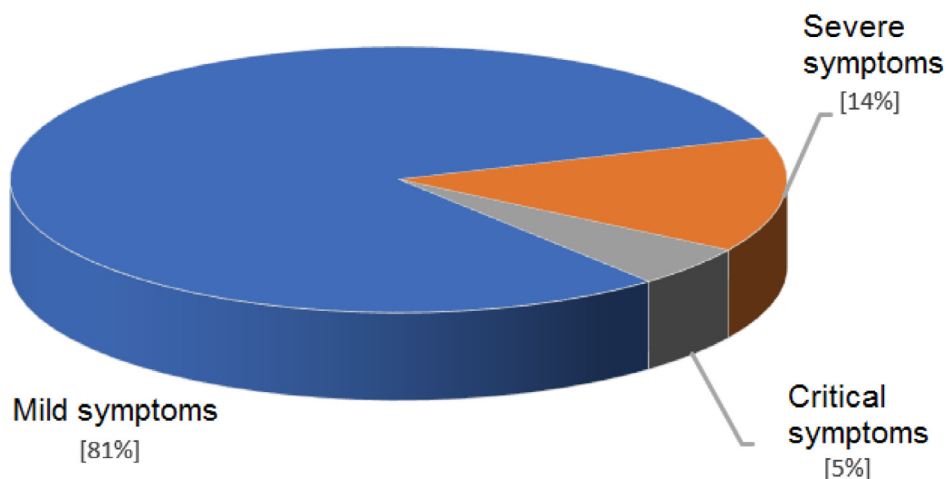

Fig. 7. Percentage distribution of clinical conditions: mild, severe and critical. Data from patients in China [91].

overload experienced by the professionals of CT analysis in the pandemic scenario, the use of AI achieved a great level of relevance in the measurements of clinical report [109]. Using CT images from patients with pulmonary infections as inputs for AI systems, the algorithms transcript the data in layers to identify existing patterns. Within the expected limits of SARS-CoV-2, the system was capable to deduce whether the patterns found in samples presented similar topologies, and consequently, to conclude the clinical conditions.

Ardakani et al. [109] applied 10 different deep learning models to distinguish cases of pneumonia, reporting which of these fitted as infections caused by COVID-19. The authors reported the tested neural networks: AlexNet, VGG-16, VGG-19, Squeeze Net, GoogleNet, MobileNet-V2, ResNet-18, ResNet-50, ResNet-101 and Xception. The CT images used also presented technical reports from specialists, aiming at the system validation and replicability. The authors noticed satisfactory results from all tested models, reporting sensibility levels over 80% and accuracy over 78%. The superior performance was provided by ResNet-101 (99.02% of sensibility and 99.51% of accuracy), regarding the technical reports from radiologists (89.21% of sensibility and 86.27 of accuracy) determined by the authors. These results highlight the potentiality of the adopted system, including the rates of assertiveness and velocity of results inference.

Li et al. [112] used a 4,356 CT scans of 3,332 patients from 6 distinct medical centers to analyze the AI model ResNet-50 (COVNet) performance. From these scans, 1,296 where identified with COVID-19, 1,735 with acute infection of the lung parenchyma and 1,325 with other clinical conditions than pneumonia. The convolutional structure used in the RenNet-50 provided a detection of 96% of SARS-CoV-2 clinical conditions. Ghoshal et al. [113] used 5,941 radiographs distributed among 1,583 normal pneumonia, 2,786 bacterial pneumonia, 1,504 pneumonia conditions not related to SARS-CoV-2and 68 pneumonia cases related to SARS-CoV-2, to evaluate the performance of the Drop-weights based Bayesias, a convolutional model of neural network (CNN). An accuracy of 89.92% was observed.

X-ray thoracic images [114] (Fig. 8) are indicate as an alternative in cases of inability to obtain CT images. Rajaraman and Antani [114] used X-ray thoracic images jointly with Deep Learning to evaluate different neural network structures: Custom WRN model (accuracy of 89.74%), VGG-16 (accuracy of 93.08%), Inception-V3 (accuracy of 91.03%), Xception (accuracy of 92.82%), DenseNet-121 (accuracy of 90.26%) and NASNet-mobile (accuracy of 92.82%). Following the aforementioned logic, the prescribed models presented a favorable replicability for application in real and practical cases.

The advances of Artificial Intelligence in knowledge fields until then restricted to specialists, as the case of CT and X-ray images, represent optimistic projections in the fight against the SARS-CoV-2. The development of AI diagnosis systems, based on Machine Learning and Deep Learning, contributes not only to superior accuracy and speed to identify clinical conditions from SARS-CoV-2, but also, allows an improved safety to health professionals, once a lower level of contact with infected patients are required [107,115].

7. Conclusion and future perspectives

The novel coronavirus dramatically changed the currently world, forcing all knowledge areas to be adapted to the new reality. The role of the engineer has always been to propose creative solutions to society's problems. Since the beginning of the 20th century, chemical engineers have specialized in design and operation of processes related to a wide range of value-added products, ranging from energy, polymers to computer chips.

These engineers work for environmental companies, government agencies, offices and bank companies. The chemical engineer is taught to work on the threshold with other sciences and technologies, using their knowledge bases of Thermodynamics, Transport Phenomena and Engineering of Chemical Reactions, in addition to scientific bases of Mathematics, Physics, Chemistry and Biology [116,117]. In this present review we show how chemical engineers can use their knowledge and collaborate in the fight against COVID19. The review was divided into distinct section approaching vaccines and medication, fluid dynamics, 3D printing, microfluidics and artificial intelligence.

The development of an effective vaccine against COVID-19 is perhaps the main concern on the world today. Up to now, there is no drug proven to be able to combat the virus in vivo, however, as the days go by, researchers around the world are looking for ways to treat effectively the SARS-CoV-2.

Fluid dynamics analysis tools have been a critical aspect to fight the COVID-19 pandemic. Previous investigations that focused on understanding the behavior of virus-laden particles on air gave to health organizations, as WHO, CDC, and ECDC sufficient information to prescribe measures to reduce virus spread.

The pandemic status generated a high demand, in global scale, for masks, face shields, ventilator valves, mechanical ventilators and test kits, among other individual protection equipment (IPE). However, companies are not being able to quickly produce and supply these
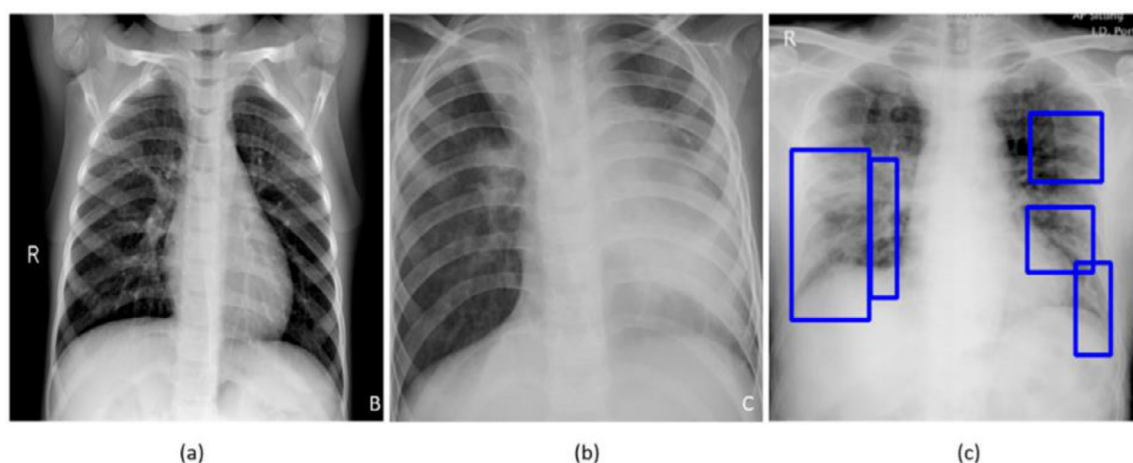
Fig. 8. X-rays of thoracic region showing: (a) lungs without infectious traces; (b) consolidated bacterial pneumonia in the upper right lobe and lower left region of the retro-cardiac lobe; (c) pneumonia resulting from COVID-19 where the blue rectangular markers indicate the infected regions. Reproduced from Ref. [114]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

materials. The 3D printing is an innovative technology and a practical tool, and it have been used to create solution in the current scenario. The pandemic status enforced scientist and researchers to urgent situations in which fast solutions can be the best way to save life. The 3D printing is currently used to manufacture several components of biosensors, including electrodes, substrates, parts for liquid handling and devices packing. This technology could be an important platform in the development of biosensors when applied jointly with Microfluidics in the pathogen detection.

The advances of Artificial Intelligence in knowledge fields until then restricted to specialists represent optimistic projections in the fight against the COVID-19. The use of Machine Learning and Deep Learning contributes to superior accuracy and speed to identify clinical conditions from SARS-CoV-2, and improved safety to health professionals, due to the lower contact to infected patients.

Our main goal is that the present review provides fundamental information for researchers, professor and students and professionals from Chemical Engineering and correlated areas, contributing to the fight against the COVID-19.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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