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Ground-level ozone's impact on human health in terms of respiratory diseases using Reactive Oxygen Species as an inflammatory marker

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Abstract

Ozone accumulation over time in the human body due to climate change exacerbates existing respiratory diseases and magnifies its negative consequences on human health. Ground-level ozone is artificially produced by catalyzing nitrogen oxides (NO_x) and volatile organic compounds (VOCs). Usually, antioxidants in the human body are sufficient to neutralize the particles, but that ability is reduced when an individual has pre-existing respiratory diseases. Under these circumstances, ozone interacts with various proteins and lipids in the lower respiratory tract, damaging epithelial cells, producing an excess of Reactive Oxygen Species (ROS) and causing symptoms such as inflammation and airway constriction. This study explored the impact of ozone on human health through a representative simulation model that captured the cumulative impact of ground-level ozone on the human lung, including considerations of existing respiratory diseases with ROS as an inflammatory marker. Within the simulation, agents were used to represent oxygen and carbon dioxide, ozone, and physiological saline, with a controlled spread of disease between the agents suggestive of the creation of ROS. Used in conjunction with stoichiometric equations, the model provided a quantitative prediction of the theoretical lifespan of a person under varying ozone concentrations. The simulation found a negative correlation between ozone concentration and average lifespan, of 114 and 52 years at ozone concentrations of 0 and 100 ppb respectively, representing a linear decrease of 0.6 years for every 1 ppb increase in ground-level ozone concentration. More accurately, the simulation results fit an exponential regression with the equation $y=112.08\,e^{-0.008x}$ with an R^2 value of > 0.99. This study provided quantitative evidence from simulation, consistent with empirical studies, of the detrimental effects of ozone on exacerbating pre-existing respiratory diseases by causing an increase in ROS.

Keywords

Ground-level ozone, COBWEB simulation, Reactive Oxygen Species, Environmental science, Health science, Inflammatory marker, Respiratory diseases, Mortality rates, Air pollution, Complex and Organized Behavior Within Environmental Bounds

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1. Introduction

Since the start of the industrial revolution in the mid-eighteenth century, ozone pollution has been steadily rising across the globe, courtesy of the increased number of major chemical plants and gasoline refinaries (1). Currently, global ozone exposures in various countries range from a low of 12 ppb in Papua New Guinea to a high of 67 ppb in India (2). There has also been a rise from 47 ppb in 2010 to ~ 50 ppb in 2019 in the overall average of ozone pollution (2). Independently, death rates attributed to ozone exposure are low at only 0.003%, 22,000 premature deaths in the European Union, translating to 3 premature deaths per 100,000 people (3). However, death rates resulting from ozone exacerbating the harm of respiratory diseases are significant, at a relative risk of death of 1.04 for every 10 ppb increase of ozone concentration (4). Hence, ground-level ozone pollution is not an insignificant factor in exacerbating respiratory diseases, acting as a marker of climate change and declining overall human health.

There are two types of ozone: stratospheric and ground-level. Stratospheric ozone is usually naturally produced through the reaction of an atmospheric oxygen molecule (O_2) with a singular oxygen atom (O); which itself is produced from the decomposition of nitrogen dioxide (NO_2), catalyzed by ultraviolet (UV) radiation in the ozone layer. Stratospheric ozone is beneficial to human health by blocking strong UV radiation from the sun and regulating the Earth's surface temperature (5). If current trends in ozone degradation continue, there will be a dramatic increase in the frequency and severity of skin cancer, followed by the projected extinction of many species as the increase in temperature makes conditions unlivable. In contrast, ground-level ozone is usually artificially produced through the reaction of nitrogen oxides (NO_x) and volatile organic compounds (VOCs), catalyzed by elevated temperatures in manufacturing plant waste emissions and automobile exhausts. Ground-level ozone is detrimental to human health as it reacts in the respiratory tract with various proteins and lipids, damaging the epithelial cells and leaking intracellular enzymes such as lactate dehydrogenase into the airway lumen (5). Detecting the damage, inflammatory mediators that attract polymorphonuclear leukocytes are released, and inflammation occurs. The resulting airway constriction, decreases breathing ability and causes coughing, throat irritation, chest pain, and shortness of breath (5).

Ozone dissolved in physiological saline, generates Reactive Oxygen Species (ROS). ROS are highly reactive chemical molecules containing oxygen that are essential for cell signaling and homeostasis at physiological levels but are also likely to cause extreme oxidative stress (OS) damage when produced in excess (6). Under normal physiological conditions, ROS is produced as a natural by-product of cellular aerobic metabolism; as oxygen molecules (O_2) contain two unpaired electrons in different orbitals with a parallel spin, they are weakly reactive. However, the reduction of oxygen molecules to produce water (H_2O) in the inner mitochondrial membrane by the Electron Transport Chain (ETC) is only univalent, thus producing superoxide anions (O_2^-), a charged ionic ROS species with a single unpaired electron and a net negative charge of -1 (6). Though ground-level ozone produces ROS in plasma, serum, and other bodily fluids, the focus of this study

is on the reaction of ozone with physiological saline (7). The presence of ground-level ozone in the human body is anticipated to increase the frequency of this reaction, thus producing overwhelming amounts of ROS in cells, thus causing oxidative stress.

Despite these negative consequences of ozone exposure, its effects on human health are generally minimal in a healthy individual. Alveolar epithelial lining fluid contains sufficient concentrations of antioxidants, such as ~ 100 μM of glutathione (GSH) among amounts of catalase (CAT) and superoxide dismutase (SOD), to neutralize even 100 ppb of ozone over 8 hours, which is the Occupational Safety and Health Administration (OSHA) Permissible Exposure Limits (PEL) standard (8, 9). Equation set 1 shows that 100 μM of GSH can neutralize 1598 ppb, or 33.3 μM, of ozone within 8 hours.

Equation set 1. Stoichiometric calculation of the amount of ozone (ppb) that 100 μM of GSH can neutralize

$$H_2O_2 + 2GSH \rightarrow 2H_2O + GSSG$$

$$2O_3 + 3H_2O_2 \rightarrow 3{\cdot}OH + 3O_2 + 3OH^-$$

$$100\,\mu M \frac{GSH * 1}{2} = 50\,\mu M\, H_2O_2$$

$$50\,\mu M \frac{H_2O_2 * 2}{3} = 33.3\,\mu M\, O_3$$

Glutathione disulfide (GSSG) is the oxidized form of GSH that is formed when GSH reacts with ROS, such as hydrogen peroxide (H_2O_2) or the hydroxyl radical (·OH), to protect the human body from oxidative stress (OS). Hence, 100 μM of GSH can neutralize 1598 ppb of ozone within 8 hours, which is ~ 16 times more than the OSHA PEL standard (9).

For individuals with respiratory diseases, ozone significantly worsens these medical conditions, potentially causing death. Diseases such as idiopathic pulmonary fibrosis (IPF) and acute respiratory distress syndrome (ARDS) both cause an 80% decrease in GSH production, meaning patients would be left with only 20 μM of GSH in their alveolar epithelial lining fluid (8). However, this is still under the assumption that the patient is in their prime, meaning young and without any respiratory illnesses, which is unrealistic. As individuals age, there is another 50% decline in their GSH concentration, leaving older patients (who are more likely to develop respiratory diseases in the first place) with only 10 μM out of the initial 100 μM of GHG in their epithelial lining fluid (8). 10 μM of GSH can neutralize 158 ppb, or 3.3 μM, of ozone within 8 hours (see equation set 1).

Though the amount of ozone that can be neutralized still surpasses the OSHA PEL standard, it is ~ 2 times more, which may further be rapidly depleted due to other factors such as changes in diet and exercise or existing comorbidities (10).

This study explores the impact of ozone on human health in terms of respiratory diseases through a representative simulation model that captures the cumulative impact of ground-level ozone on the human lung with ROS as an inflammatory marker. Though many studies have explored the negative impacts of ozone on respiratory diseases, a gap remains regarding comparisons between the lifespan lengths of individuals with respiratory diseases in different ozone concentration environments. In this paper, a literature review will first be provided, followed by the methodology of the study that covers the tools used to facilitate the model-building processes, the relevant research that parameters were based upon, as well as the process of the execution of the model. Next, the results will be presented and explained. A discussion of the model follows, including its functioning process and predictions. Lastly, potential limitations will be addressed and concerns recognized, ending with a conclusion.

2. Literature review

2.1 Projection of ozone-related deaths

Concerns surrounding the detrimental health effects of ozone have been the topic of research since the problem of air pollution was first addressed. Poitras presented findings on the impacts of short-term exposure to ground-level ozone and daily mortality by using data from 406 cities and 20 countries and regions, with the use of CMIP6 climate model projections to calculate future ozone-related deaths (11). The study predicted that ozone-related deaths would increase by 45 and 6200 people a year between 2010-2014 and 2050-2054 respectively based on different climate regulatory scenarios and region-specific factors. For instance, when strong climate and air quality controls were implemented, "ozone-related deaths were projected to increase by 0.7%" (11). When weak climate controls but strong air quality controls were implemented, "ozone-related deaths would increase by 56%" (11). When climate and air quality controls were both weak, "the increase was 94%" (11). Finally, the study suggested that countries should implement more rigorous ozone standards to guarantee the safety and well-being of their citizens, specifically suggesting the alignment of their standards with the requests of the Paris Climate Agreement (11).

The dire projections of this study incorporated limitations. The CMIP6 model provided a macro-level analysis of the impacts of ozone in a global scope by considering countries and cities as units of study. However, fluctuations exist in data quality and completeness across cities. For example, urbanized areas in core countries may have superior air monitoring infrastructure and mortality tracking than rural areas in peripheral countries. This could cause bias in global projections, as regions with poor or no data would be severely underrepresented. In addition, the micro-level analysis of the impact of ozone on the individual human body was overlooked, which ignored an essential perspective in making predictions of the complex problem of ground-level ozone pollution. The study limited their analysis to the short-term effects of ozone on death rates, disregarding the impact long-term ozone

exposure has on the individual human body, such as exacerbating asthma and COPD. The CMIP6 model also did not account for the impact of ozone on aging populations or those with pre-existing medical conditions that will appear in the future, especially in cities with baby booms currently in the 35-55 age bracket that will eventually cause an increase in the elderly population. These model discrepancies could cause ozone mortality rates to be higher in the future than the projections provided in the study. Hence, these gaps would cause inaccuracies in the predictions of the model, since many factors affect the number of ozone-related deaths in a community that cannot be fully expressed as parameters.

To address the gaps in the previous study, this paper will develop a comprehensive model that simulates a longitudinal study of the molecular impact of ground-level ozone on the internal composition of the human body over a lifetime. Relevant factors such as respiratory diseases and aging curves will be expressed accordingly through varying concentrations of ozone, GSH, and ROS, and a consistency of no healthcare will be maintained to eliminate assumptions and ensure a fair physiological evaluation.

2.2. The chemistry of Reactive Oxygen Species (ROS)

Many studies have been performed with a focus on the dual physiological and pathological role of Reactive Oxygen Species (ROS) in human health. Juan et al. found that exogenous sources, such as pollution, lead to "irreversible effects on tissue development in animals and plants." Specifically, "mitochondria are particularly susceptible to oxidative damage, as electrons escaping from the ETC in the inner membrane react with oxygen to produce a superoxide anion." Though the anion itself is not permeable across the membrane, it is quickly converted into hydrogen peroxide (H_2O_2), which is permeable. This H_2O_2 then undergo the Fenton reaction, producing the hydroxyl radical – the most powerful ROS oxidant. Three of the main consequences of ROS include damage to DNA, lipid peroxidation of polyunsaturated fatty acids, and the oxidation of proteins. ROS oxidizes the nitrogenous bases of DNA, resulting in breaks in the DNA double helix, (mutagenic) alterations in DNA bases, and hydrogen abstraction. Lipid peroxidation "can give rise to toxic breakdown products" that increase the degree of unsaturation of the polyunsaturated fatty acid (6). Consequences of the unsaturated fatty acids again reacting with oxygen, producing 4-hydroxynonenal, increase the probability for the development of cerebral dysfunction. Lastly, the effects of the oxidation of proteins by ROS include the oxidation of amino acid residues, cleavage of peptide bonds, and aggregation between proteins, which can cause diseases such as Alzheimer's and rheumatoid arthritis (6).

Though Juan et al. provide a comprehensive review of the independent impacts of ROS on the human body, there is limited discussion regarding the interaction of ROS with other physiological factors. For example, a gap exists in the evaluation of antioxidants in terms of their impact on ROS. Since antioxidants contribute to the defense against oxidative stress, concentrations of GSH, CAT, and SOD counter the pathological effects of ROS (8). Due to the omission of antioxidants from the discussion, the magnitude by which ROS exceed the buffering capacity of a cell – a

statistic that is essential in evaluating ROS's true pathologic risk – cannot be quantitated. Furthermore, the study by Juan et al. did not address the effects of ROS on aging and pre-existing respiratory diseases. As antioxidant concentrations can experience a 50% decrease with aging and an 80% decrease in the presence of comorbidities, excess amounts of ROS can start to have lethal consequences as buffering capacity declines (8). Consequently, the impact of ROS is compounded, and its negative effects will likely exceed the predictions of this study. Lastly, the observations made were solely qualitative, limiting its real-world applicability and significance. No discussion of statistical thresholds and dose-response relationships was provided, such as what concentration levels of H_2O_2 or ·OH correlated with pathological outcomes.

This study expresses the effects of aging and respiratory diseases in terms of changes in antioxidant concentration. The comprehensive model will display the effects of ROS on the human body at a molecular level, yielding quantitative results that reflect lifespan trajectories depending on ozone concentration, also considering the interactions between ROS and other physiological factors that may either exacerbate or blunt its damaging effects on the human lung.

2.3. The role of GSH in immunity and lung inflammation relating to ROS

Oxidative stress was first explored in the 1970s when it was discovered that molecular oxygen (O_2) can be reduced to not only water (H_2O), but also other intermediate species such as superoxide radical (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical (·OH) (10). They are now known collectively as Reactive Oxygen Species (ROS) and are confirmed to have both physiological and pathological effects on the human body (6). Ghezzi found that reactivity in biology is synonymous with toxicity, there are many antioxidant enzymes that are dedicated to ROS detoxification if the species is produced in excess, with one of the most efficient of these agents being glutathione (GSH) (10). As a scavenger of ROS, GSH is a thiol containing enzyme that is an easily oxidizable target for oxygen species to react with to create the harmless products glutathione disulfide (GSSG) and water. Specifically, the -SH group of its cysteine is sensitive to peroxide oxidation, hence making GSH an extremely effective molecular antioxidant. Moreover, though normal antioxidants usually act as a suicidal decoys and are consumed upon oxidation, GSH's oxidized form, GSSG, can be reduced by glutathione reductase to regenerate GSH, thus maintaining its reversible utility (10). A factor contributing to increased GSH concentration is dietary intake of vitamins C, E, and B. In contrast, diseases such as COPD, cystic fibrosis, influenza infection, and alcoholism are associated with decreased GSH levels, making the lung more susceptible to oxidative stress due to decrease in the antioxidant buffering capacity of the cell (10). The aforementioned vitamins are essential to maintain healthy levels of GSH in normal conditions but still may not be adequate enough under oxidative stress caused by disease (10). GSH plays an important role in immunity, with decreased GSH levels suggesting an increased susceptibility to infection and oxidative stress (10).

Ghezzi provides a thorough overview of GSH and its importance in maintaining human health, but does not provide statistical data regarding the amount of GSH needed to prevent oxidative damage, the change in required GSH concentration to neutralize different ROS concentrations, and the efficiency of medical treatment programs to maintain or enhance buffering capacity. In the absence of such quantitative context, the significance of their paper is greatly reduced as it is difficult to apply its research findings in real-world settings. Furthermore, this study fails to address the relationship between reduced GSH and environmental conditions. As many pathological diseases, especially respiratory, are commonly further exacerbated by external factors, the lethality of ROS and the importance of GSH are often only evidenced when reduced GSH concentration is combined with extrinsic factors, such as extreme smog, Particulate Matter < 2.5 μm ($PM_{2.5}$), and ozone. Therefore, the compounding effects of the environment must be considered when determining the true extent of the detrimental effect of decreased GSH.

Aiming to refine and extend prior research, this study proposes a model of the human lung combining the effects of pathological diseases and poor environmental conditions. The simulation calculates the lifespan based on GSH and ROS levels during the lifetime of the individual, with correlations expressed to demonstrate the influence of ozone. In addition, stoichiometric calculations of GSH neutralization reactions to find its required concentration to prevent oxidative damage, as well as other statistical results from empirical studies, are introduced for an additional level of analysis.

3. Methods

3.1. Research focus

Ground-level ozone has long been recognized as a detrimental air pollutant to human health. As early as the 1970s, laws controlling the amount of ground-level ozone in countries have been established around the world, such as the Clean Air Act in the United States (12) and the Ambient Air Quality Directive in Europe (13). However, despite these regulations, the air quality standards have still not been achieved in most countries. For example, in the United States in 2014, 57 million Americans were reported to be living in counties that did not meet national air quality standards (14). Similarly, in Europe, only 19% of all ground-level ozone monitoring stations across Europe achieved compliance (13). With the overarching goal of bringing the seriousness of the issue into consideration, the focus of this study is to explore the impact of ground-level ozone on human health using a representative simulation model that captures the cumulative effects of ozone on the human lung under pre-existing respiratory diseases, with ROS as an inflammatory marker.

3.2. Modeling software

The software used to create the model is termed Complex and Organized Behavior Within Environmental Bounds (COBWEB). It is an agent-based simulation model with a multitude of adjustable parameters that allow for the simulation of relationships within a medical and environmental framework (15).

The base environment of COBWEB is an adjustable 2D grid. As model development commences, placed upon the grid are three main types of objects: agents, resources, and

stones. Agents, represented by triangles with a colored dot depending on their type, have the capability to move, consume food, produce waste, reproduce, and contract diseases. Resources, represented by colored squares, are the food source of agents and have the capability to grow and spawn, and can be defined as those that give certain amounts of energy to certain agents. Last, stones, represented by gray squares, are barriers to the movement of agents and restrict the spawning locations of resources.

The measure of time in COBWEB is ticks. By default, one tick is the amount of time needed for an agent to move one square on the grid. However, this parameter can be adjusted according to the requirements of every model to modify how much movement can be accomplished by an agent in one tick to either speed up or slow down the execution of the model.

The complexity of COBWEB lies within its random genetic and environmental algorithms. With the creation of every new COBWEB project, a random genetic seed is assigned to the model. This seed defines the personality of each individual COBWEB agent type, by extension giving them instructions on how to react, behave, and move. A random environmental seed is also assigned to the model upon its creation. This seed defines the starting position of each agent and resource, hence changing the interactions and paths of movement each agent will have as the model executes. The randomization of these seeds allows trials to be conducted with the same variability of results that would be obtained with multiple physical trials, as well as allow for accurate longitudinal studies to be conducted in a short period of time.

Zones are abiotic factors in COBWEB that can be adjusted to control the movement of agents within a model. When a zone is defined, the survival capabilities of each type of agent can be modified to make some agent types have a better survival probability within a certain zone than in others. The agents of the advantaged agent type will congregate in those zones, thus creating distinct areas where the population of a certain type of agent is much higher than the population of other types of agents. This functionality of COBWEB allows research models to reflect the freedom or restriction of some variables, thus increasing the applicability of their study.

In COBWEB, agents can also become ‘diseased’. Diseases can impact agents in both positive and negative ways, such as changing the amount of energy received from resources, the energy spent to move, or used during reproduction, depending on how the disease is defined. The child transmission rate, which is the probability that the disease is inherited by the children of an agent, and the contact transmission rate, which is the probability that the disease will be contagious upon contact between two agents, can both be defined according to the requirements of the model as well. Vaccinations to immunize also exist, as well as a healing factor that can make diseased agents healthy again. Diseases in COBWEB are often used to simulate the frequency of contact between agents, the literal transfer of diseases in populations, or the accumulation of a certain product from a reaction over time.

In conclusion, COBWEB is a reliable and accurate modeling software with many relevant functionalities that give its simulations real-world applicability. The interconnectedness between agents makes the decisions of each agent have significant impact on both, other agents, and the overall operation of the model.

3.3. Model creation

3.3.1. *Simulation overview*

In this study, the exacerbating effects of ground-level ozone on respiratory diseases in the human lung in terms of ROS are modeled as a visual representation of the process from the intake of ozone from the atmosphere to the accumulation of ROS in the human body, as the ozone reacts with physiological saline, overpowering the buffering effects of weakened antioxidants such as GSH. The model simulates a longitudinal study that follows the lifespan of an individual as they live in a community with a certain level of ozone.

3.3.2. *Basic environment development*

The model begins with a 50x50 grid that represents the average maximum vital lung capacity of a human of 450 mL (16), meaning each grid box is 0.18 mL. Globe-style wrap is used, allowing agents to enter and exit the grid anywhere, simulating the free movement of physiological saline. The three main groups of molecules that must be considered are 1] carbon dioxide and oxygen, 2] physiological saline including GSH and ROS, and 3] ozone. The first group of carbon dioxide and oxygen is represented by yellow Agent 1 to mimic the process of ventilation. The second group of physiological saline that reacts with ground-level ozone to produce ROS is represented by blue Agent 2 and red Agent 4, respectively simulating the internal state of individuals who are healthy or suffering from a pre-existing respiratory disease. The third group of ground-level ozone is represented by green Agent 3. As both ventilation (oxygen and carbon dioxide) and flow of physiological saline are dynamic with no set amount, the population size of Agent 1, Agent 2, and Agent 4 is originally set arbitrarily at 100 agents each. The population size of Agent 3 is variable and depends on the concentration of ground-level ozone that is tested. Figure 3 is an example of the starting position of a model of the lungs of an average citizen in Toronto, Ontario. In a study reported by the Government of Canada, the average amount of ground-level ozone in Toronto is 40 ppb (17), which translates to exactly two ozone agents according to the calculation in Equation 2, assuming an average number of 20,000 breaths per day (18).

$$\frac{\left(\left(450\right) * 40 * 20000\right)}{0.18 * 1000000000} = 2 \qquad \text{eq.2}$$

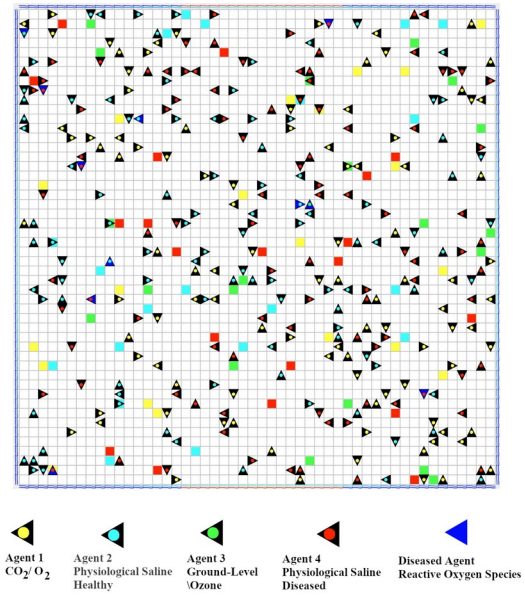


Figure 1. Starting stage of the COBWEB model of the human lung at 0 ticks reflecting the impact of 40 ppb of ozone

Since the model must execute for the entire lifespan of a person, the unit of time a single tick represents must be large to avoid the model running overtime. Hence, each tick is mapped as one day in real life. In the example of Toronto, Ontario, the average lifespan of a resident is 80.9 years (19), which translates to ~ 29529 days or ticks. Therefore, in this situation, a combination of the rates of infection of Agent 2 and Agent 4 should have subjects approaching unmanageable levels of ROS, or death, by 29529 ticks at the ozone concentration of 40 ppb.

3.3.3. *Zones*

In this model, a vertical band zone pattern for Agent 1 and an island zone pattern for Agent 2 and Agent 4 were used. The strict vertical band restricts the movement of Agent 1 to the middle strip of the model to create a respiratory tract for the airflow of the gas agents. As ozone also enters the human body through inhalation, this zone simulates the hindered path of ozone agents to react with physiological saline as it is surrounded by oxygen and carbon dioxide molecules. In Figure 2, the congregation of Agent 1 can be seen, along with the outer dual-colored jagged line on the border of the model displaying the boundaries of the zones.

The gradient island restricts the movement of Agents 2 and 4 to the external edges of the model. This, together with globe-wrap, gives baseline conditions for the constant movement and flow of physiological saline as it fluctuates in and out of the lungs. In Figure 2, the inclination of the physiological saline agents to congregate to the outside of the model space can be clearly seen, along with the inner gradient-colored jagged line on the border of the model displaying the strength of the zone on various parts of the model.

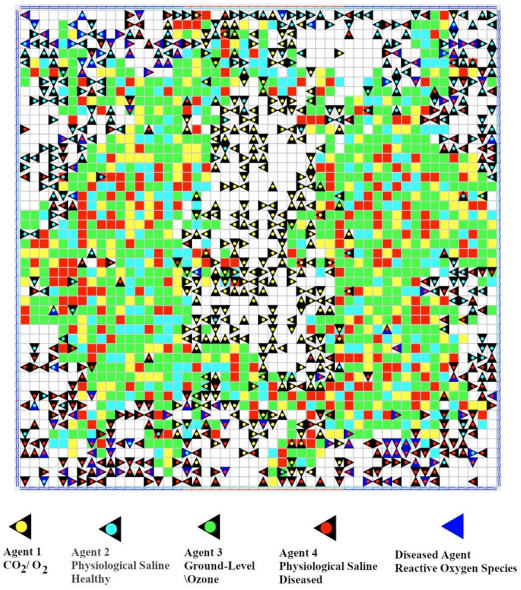


Figure 2. Running stage of the COBWEB model of the human lung at 2480 ticks at an ozone concentration of 40 ppb demonstrating zoning

3.3.4. *Disease*

Diseased agents in the model of this study represent ROS, including cells or molecules impacted by it. Firstly, any Agent 3 in the model is automatically diseased. A variable number of ozone agents are placed into the model based on the air conditions of the location being simulated, with one ozone agent representing an additional 0.18 ppb of ground-level ozone. As ozone is the main reactant creating ROS, all its agents will carry the disease and infect Agent 2 and Agent 4 in the model based on a random probability that they will come into contact with each other from its personality algorithm. As many factors affect the dissolving of ozone into physiological saline, such as solubility, temperature, concentration, and pressure (20) that vary between each test subject, this randomness will yield more accurate results than a constant. Secondly, a constant 2% of the population of Agent 1 is diseased. Other than ozone, ~ 2% of inhaled oxygen also reacts with physiological saline to produce ROS. However, this small amount of ROS will not affect the body, though its effects do become increasingly detrimental as the total amount of ROS increases (21). Hence, except for the beginning, this small amount of Agent 1 ROS is not expressed within the Agent 1 population but is rather lumped into the infected Agent 2 and Agent 4 populations. Thirdly, since two different situations are being simulated with the two different types of physiological saline agents, each of Agent 2 and Agent 4 will have an initial 5% that is diseased. As ROS is a natural by-product of oxygen metabolism, ~ 5% of physiological saline in the body is constantly reacting to create ROS (22). However, more diseased agents are added onto this baseline as Agent 3 enters the body and begins gradually infecting Agent 2 and Agent 4 from contact between the agent types. As Agent 3 establishes a stable diseased population within

the original Agent 2 and Agent 4 population, the visual representation of ozone disappears, and its presence is instead suggested by the growing amount of ROS and oxidative damage, as modeled by the increasing diseased population. This disease transmission rate is managed by the asexual breeding rate, as the disease is assumed to have a 100% chance of being passed onto its offspring, hence having the changing number of offspring affect the number of infected agents.

As these interactions continue over many ticks, an accumulation of diseased agents is expected. When the accumulated sum of ROS creation exceeds ten times the normal expected level in the body, the individual is declared dead or in critical condition (22). Thus, this condition is met when total ROS creation over time reaches 50% of the amount of physiological saline in the human body, which is ten times the normal 5%. It is important to understand that the 50% is not the current amount of ROS in an individual. As ROS is extremely reactive, it never truly builds up but instead reacts immediately with elements within the human body, similar to a biological bomb (23). Instead, the 50% of physiological saline is the total amount of excessive ROS ever produced in a person, not the currently existing ROS within that individual, hence simulating non-linear ROS damage, proportional to the amount of excessive ROS, that builds up even if the ROS itself does not (24). Therefore, the threshold that signifies death is at 55% for each Agent 2 and Agent 4, as the 5% infected of the initial population is not excessive and must be disregarded from the consideration of the final amount of ROS ever produced.

The state of the human body does not stay constant throughout an individual's lifetime. The worldwide average life expectancy is 72 years (25). Most people experience at least one respiratory disease by the age of 65 (after 90% of their life has passed) due to a drastic decrease in their antioxidant levels, the reduction also causing ozone to have an accelerating effect on worsening their conditions as they age (for the last 10% of their life) (26). To account for this unequal increase in ROS concentration as time passes, the lifespan of an average person at a certain ozone concentration can be calculated with a combination of the lifespan of a consistently healthy person and the lifespan of a consistently diseased person.

$$Lifespan = (Healthy\ Lifespan * 0.9) + (Diseased\ Lifespan * 0.1) \quad \text{eq.3}$$

Using this knowledge, the disease contact transmission rate parameter was found by mapping the model onto existing data for the city of Toronto, Ontario. As aforementioned, the ground-level ozone condition in Toronto is approximately 40 ppb, with an average lifespan of 80.9 years, or 29529 days (19). The disease contact transmission rate was found by the method of trial-and-error to balance the percentage of infected agents in both the Agent 2 and Agent 4 populations so that the number of infected agents reached 55% in both, then substituting the respective lifespans of each into the Equation 4 formula to get a final lifespan of approximately 29713 ticks, as shown in Equation 5. In Figure 3,

approximately half the Agent 4 population became diseased, suggesting the death of a person with pre-existing respiratory conditions. In Figure 4, 20304 ticks later, ~half the Agent 2 population became diseased, suggesting the death of a healthy person.

$$Lifespan = (31038 * 0.9) + (10734 * 0.1) \cong 29008 \qquad \text{eq.4}$$

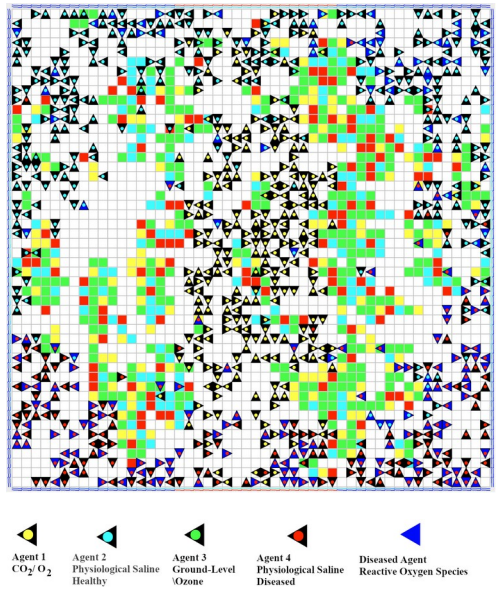


Figure 3. Final stage of the COBWEB model at 10734 ticks displaying the lungs of a person with pre-existing respiratory conditions (red Agent 4) who has deceased at an ozone concentration of 40 ppb

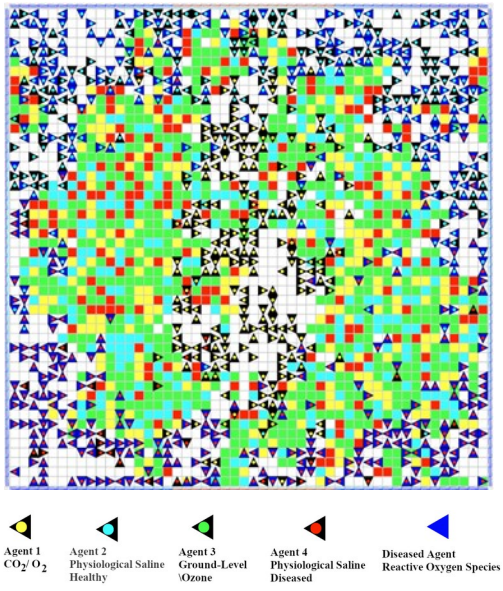


Figure 4. Final stage of the COBWEB model at 31038 ticks displaying the lungs of a healthy person (blue Agent 2) who has deceased at an ozone concentration of 40 ppb

The final disease contact transmission rate derived was 0.17 for Agent 2 and 0.33 for Agent 4.

3.3.5. *Reproduction*

For Agent 1, the asexual breeding parameter was used to maintain a consistent population. As Agent 1 is mostly unaffected by disease, with its initial 2% of infected agents becoming insignificant and eventually blending in as the rest of the ROS concentration increases, asexual breeding manages a realistic representation of ventilation and gas exchange. Mainly, the purpose was to simulate oxygen and carbon dioxide particles partially inhibiting the inter-transmission of disease between the Agent 2 population and the Agent 4 population by providing physical blocks that decreased the rate at which agents came into contact with one another.

For Agent 2 and Agent 4, the asexual breeding parameter was used to manage their reproduction rates. Being closely entwined with the disease factor, asexual breeding controls the diseased population size, as all offspring of Agent 2 and Agent 4 are diseased. Hence, changing the asexual breeding rate would control the disease transmission rate, with the contact transmission rate parameter controlling the activity of the diseased agents. As ozone dissolves almost immediately into physiological saline (27), the pregnancy period was set to zero and the breeding chance to 100% to account for ozone's constant reactions. However, as this would result in the problem of uncontrolled growth of the agent populations, the breed energy was increased arbitrarily via trial-and-error to 60, as it would keep diseased agent proportions steady.

For Agent 3, the split parameter was used to manage the ozone population. The difference between the splitting and breeding parameters is that the former creates an identical agent with the same personality, while the latter creates an agent of a different personality. As the population of Agent 3 should only be present at the beginning of the simulation to establish the initial diseased population according to the ozone concentration, with each agent reacting with saline and producing ROS in the same way, the split parameter was used to maintain a brief ozone agent population that eventually dies out as the number of diseased agents becomes steady. Similar to the aforementioned breed energy, the split energy threshold, which is the amount of energy needed before an agent can split into another one, was increased arbitrarily to 750 via trial-and-error to control the number of Agent 3 active at a time so ROS production induced by ozone could be realistically modeled.

3.3.6. *Random genetic and environmental seed generation*

As mentioned before, oxygen, physiological saline, and ozone in the human body are all dynamic factors that experience fluctuations and changes depending on time and other differences between test subjects. Thus, instead of completing trials with the standard method of using static parameters, it is more effective to gain accurate data by generating a new random genetic and environmental seed every trial to shuffle the algorithms used. For both Agent 1, Agent 2, and Agent 4, this method would generate representative variability by changing the personalities of each type of agent, thus having them move along different paths and interact with different objects in the model. More complexly for Agent 3, this

method would both change the personality of the agent type and alter its probability of infecting other agents upon contact, thus giving variability to the rate that ozone dissolves into physiological saline according to specific traits of each test subject. The environmental seed would also be shuffled, further providing a factor of randomness that makes the model more representative. Hence, this functionality produced a wide variety of results that could be averaged to obtain data that more closely reflected the unpredictability of real-life situations.

3.4. Data interpretation methods

3.4.1. *Disease tracker*

The disease tracker allows for the documentation of the overall number of diseased agents compared to healthy agents, providing both numerical data and a visual line graph showing changes in the two populations over time. Using this tool and taking into consideration the level of ground-level ozone exposure, aging, and pre-existing respiratory diseases, the validity of this study can be confirmed by observing an increase in the number of diseased agents with an overall positive correlation as time passes. In addition, an exponential increase should be seen in the number of ozone agents as the number of ticks increases, demonstrating the increased susceptibility of the aging and those with medical conditions to the negative effects of ozone. Lastly, the number of infected agents at the end of the simulation should consist of more than the pass percentage of the total number of agents to ensure that both the diseased Agent 2 and diseased Agent 4 populations consist of at least 55% diseased agents to signify death, as calculated by Equation 5. As a note, the actual percentage of diseased agents should be significantly higher than the pass percentage, as the diseased Agent 4 population should be greatly surpassing 55% of the entire Agent 4 population when the diseased Agent 2 population reaches 55% of the entire Agent 2 population. Hence, the usage of the disease tracker tool further validates the comprehensiveness of the results.

$$Pass\ Percentage = [\frac{(Numbers\ of\ Agent\ 2)}{(Total\ number\ of\ agents)} * 0.55] + [\frac{(Numbers\ of\ Agent\ 4)}{(Total\ number\ of\ agents)} * 0.55] \quad \text{eq.5}$$

In the situation of the model of Toronto, Ontario, with environmental conditions of 40 ppb of ozone, the pass percentage is 41.66%, as calculated in Equation 6. According to Figure 5, at 31189 ticks, the diseased population is approximately 465 agents with a total population of 850, which translates to the diseased population consisting of 55% of the entire model. As 55% is greater than 41.66%, it can be concluded that the results of this trial are valid.

$$Pass\ Percentage = \left(\left(\frac{368}{850}\right) * 0.55\right) + \left(\left(\frac{273}{850}\right) * 0.55\right) \cong 0.4166 \qquad \text{eq.6}$$

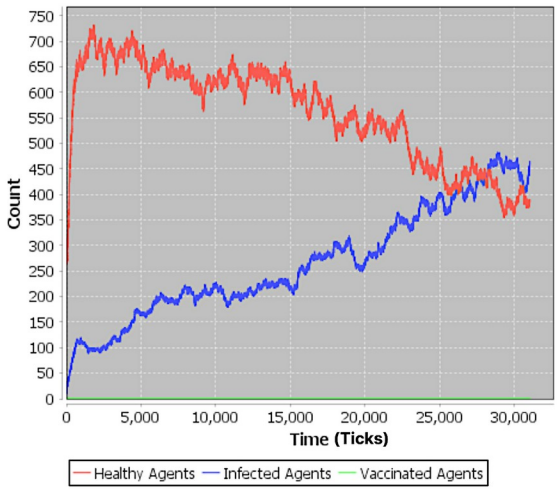
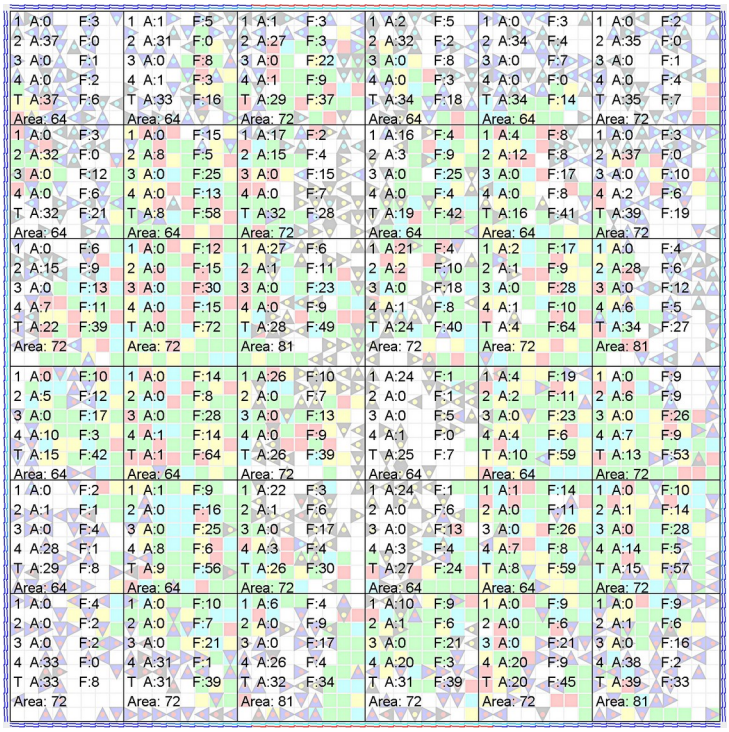


Figure 5. The disease tracker function in the COBWEB software according to ozonic circumstances of 40 ppb, with the healthy agent trendline representing the population change of healthy cells and the infected agent trendline representing the population change of cells affected by oxidative stress from ROS accumulation

3.4.2. *Regional Statistics*



1 A:0 F:3 2 A:37 F:0 3 A:0 F:1 4 A:0 F:2 T A:37 F:6 Area: 64	1 A:1 F:5 2 A:31 F:0 3 A:0 F:8 4 A:1 F:3 T A:33 F:16 Area: 64	1 A:1 F:3 2 A:27 F:3 3 A:0 F:22 4 A:1 F:9 T A:29 F:37 Area: 72	1 A:2 F:5 2 A:32 F:2 3 A:0 F:8 4 A:0 F:3 T A:34 F:18 Area: 64	1 A:0 F:3 2 A:34 F:4 3 A:0 F:7 4 A:0 F:0 T A:34 F:14 Area: 64	1 A:0 F:2 2 A:35 F:0 3 A:0 F:1 4 A:0 F:4 T A:35 F:7 Area: 72
1 A:0 F:3 2 A:32 F:0 3 A:0 F:12 4 A:0 F:6 T A:32 F:21 Area: 64	1 A:0 F:15 2 A:8 F:5 3 A:0 F:25 4 A:0 F:13 T A:8 F:58 Area: 64	1 A:17 F:2 2 A:15 F:4 3 A:0 F:15 4 A:0 F:7 T A:32 F:28 Area: 72	1 A:16 F:4 2 A:3 F:9 3 A:0 F:25 4 A:0 F:4 T A:19 F:42 Area: 64	1 A:4 F:8 2 A:12 F:8 3 A:0 F:17 4 A:0 F:8 T A:16 F:41 Area: 64	1 A:0 F:3 2 A:37 F:0 3 A:0 F:10 4 A:2 F:6 T A:39 F:19 Area: 72
1 A:0 F:6 2 A:15 F:9 3 A:0 F:13 4 A:7 F:11 T A:22 F:39 Area: 72	1 A:0 F:12 2 A:0 F:15 3 A:0 F:30 4 A:0 F:15 T A:0 F:72 Area: 72	1 A:27 F:6 2 A:1 F:11 3 A:0 F:23 4 A:0 F:9 T A:28 F:49 Area: 81	1 A:21 F:4 2 A:2 F:10 3 A:0 F:18 4 A:1 F:8 T A:24 F:40 Area: 72	1 A:2 F:17 2 A:1 F:9 3 A:0 F:28 4 A:1 F:10 T A:4 F:64 Area: 72	1 A:0 F:4 2 A:28 F:6 3 A:0 F:12 4 A:6 F:5 T A:34 F:27 Area: 81
1 A:0 F:10 2 A:5 F:12 3 A:0 F:17 4 A:10 F:3 T A:15 F:42 Area: 64	1 A:0 F:14 2 A:0 F:8 3 A:0 F:28 4 A:1 F:14 T A:1 F:64 Area: 64	1 A:26 F:10 2 A:0 F:7 3 A:0 F:13 4 A:0 F:9 T A:26 F:39 Area: 72	1 A:24 F:1 2 A:0 F:1 3 A:0 F:5 4 A:1 F:0 T A:25 F:7 Area: 64	1 A:4 F:19 2 A:2 F:11 3 A:0 F:23 4 A:4 F:6 T A:10 F:59 Area: 64	1 A:0 F:9 2 A:6 F:9 3 A:0 F:26 4 A:7 F:9 T A:13 F:53 Area: 72
1 A:0 F:2 2 A:1 F:1 3 A:0 F:4 4 A:28 F:1 T A:29 F:8 Area: 64	1 A:1 F:9 2 A:0 F:16 3 A:0 F:25 4 A:8 F:6 T A:9 F:56 Area: 64	1 A:22 F:3 2 A:1 F:6 3 A:0 F:17 4 A:3 F:4 T A:26 F:30 Area: 72	1 A:24 F:1 2 A:0 F:6 3 A:0 F:13 4 A:3 F:4 T A:27 F:24 Area: 64	1 A:1 F:14 2 A:0 F:11 3 A:0 F:26 4 A:7 F:8 T A:8 F:59 Area: 64	1 A:0 F:10 2 A:1 F:14 3 A:0 F:28 4 A:14 F:5 T A:15 F:57 Area: 72
1 A:0 F:4 2 A:0 F:2 3 A:0 F:2 4 A:33 F:0 T A:33 F:8 Area: 72	1 A:0 F:10 2 A:0 F:7 3 A:0 F:21 4 A:31 F:1 T A:31 F:39 Area: 72	1 A:6 F:4 2 A:0 F:9 3 A:0 F:17 4 A:26 F:4 T A:32 F:34 Area: 81	1 A:10 F:9 2 A:1 F:6 3 A:0 F:21 4 A:20 F:3 T A:31 F:39 Area: 72	1 A:0 F:9 2 A:0 F:6 3 A:0 F:21 4 A:20 F:9 T A:20 F:45 Area: 72	1 A:0 F:9 2 A:1 F:6 3 A:0 F:16 4 A:38 F:2 T A:39 F:33 Area: 81

Figure 6. The regional statistics function in the COBWEB software according to ozonic circumstances of 40 ppb, with "A" representing the number of each type of agent, "F" representing the number of each type of resource, and "T" representing the total number of agents, demonstrating the impact of ozone on the human lung according to the number of areas infected

Apart from the disease tracker, the regional statistics should also be considered. The function gives a snapshot of the entire model in regions to observe distributions and potential clusters. It splits the environment into sections and shows the number of each type of agent in each section. As seen in Figure 6, the "Area" label at the bottom displays how many squares in total are within the box, occupied and unoccupied. On the left, the numbers represent the agent or resource type (1-4). On the right, the letters "A" and "F" respectively represent "Agent" and "Food". A1 would label the number of Agent 1 within the region, F1 Food 1, A2 Agent 2, F2 Food 2, A3 Agent 3, F3 Food 3, A4 Agent 4, and F4 Food 4. The "T" below the numbers on the left represents "Total" and labels the total number of agents or resources within the box. This tool can show the number of sections of the lung that are impacted by oxidative stress from ROS by counting the number of sections with diseased agents to consider not only the severity of ROS oxidative stress but also the extent of the lung 'area' that is affected.

4. Results

Ten trials were run for each concentration of ground-level ozone. For each trial of a specific ozone concentration, the genetic and environmental seeds are randomized to represent a different test subject with a different cellular composition. Between trials, the "favorite food energy" parameter was adjusted to keep the base population of each agent type stable. After all ten trials were run with the lifespans of each test subject recorded, the average lifespan of a person living in those ozone conditions was calculated. The amount of ground-level ozone was then changed, and trials were run to simulate another set of conditions. In total, 60 trials were run for the six different ozone concentrations tested.

Table 1. Data collected from the COBWEB model demonstrating the relationship between ozone concentration and human lifespan

Ozone Concentration (ppb)	**Average Lifespan ± 2SD (years)**
0	114.33 ± 15.90
20	95.38 ± 5.08
40	81.08 ± 6.38
60	67.12 ± 8.20
80	57.70 ± 8.06
100	52.26 ± 8.88

A strong negative correlation exists between increased ozone exposure and longevity. As ozone concentration increased, lifespan decreased, demonstrating the inverse relationship between the two variables, shown in Figure 7. Starting at 114.33 years of life when ozone concentration is at an ambitious 0 ppb, longevity decreases to 52.26 years of life when ozone concentration reaches a high of 100 ppb, in accordance with the ESHA PEL standards (10). As ROS concentration and ROS damage is non-linear due to ROS-induced ROS release (24), the results, as seen in Figure 7, were represented as an exponential regression

as the line of best fit with an equation of $y=112.08\,e^{-0.008x}$ and an R^2 value of 0.995.

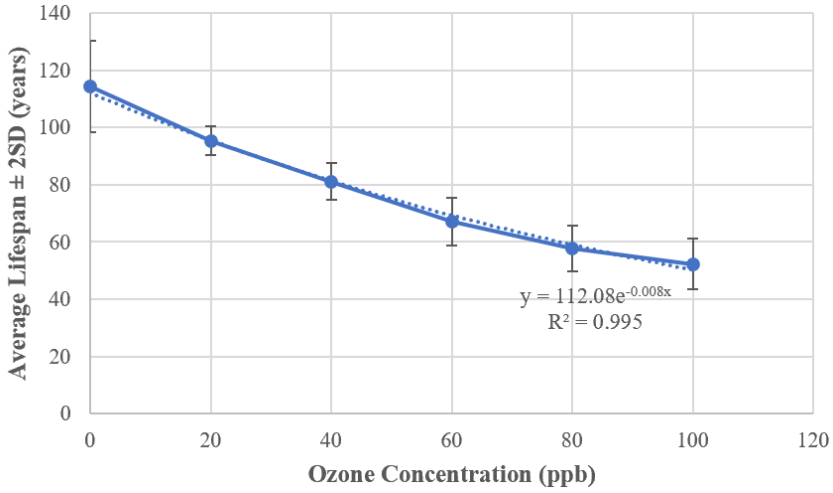


Figure 7. Data collected from the COBWEB model demonstrating the negative correlation between ozone concentration and human lifespan

5. Discussion

A negative correlation exists between ozone concentration and average lifespan, with consideration given in the model to both old age and pre-existing respiratory conditions. As the ozone concentration in the environment increases, the average lifespan decreases. The exponential regressive line of best fit has an equation of $y=112.08\,e^{-0.008x}$, with an R^2 value of 0.995. It can thus be projected for future estimates to yield new, accurate findings according to untested parameters of ozone concentration or average lifespan.

This study first considers the control environmental conditions of 0 ppb of ozone. Under these circumstances, the average human lifespan was calculated to be 114.33 years, which seems reasonable. As comparison, it is less than the lifespan of Jeanne Calment of France, the human with the longest longevity in history, who lived for 122 years and 164 days (28).

The rest of the results from this study can be interpreted within real-life contexts by comparing the theoretical average lifespans at certain ozone conditions as derived by the model with the actual average lifespans at certain ozone conditions in different countries. For instance, Guyana has an ozone concentration of 23 ppb with an average lifespan of 70 years (29, 30). Since this longevity is much lesser than the predicted lifespan of 95.38 years, it can be concluded that ozone exposure is not the only contributor to lifespan in Guyana. Instead, it is likely that there are other health threats that exist in developing countries such as Guyana that also influence longevity. Another consideration is Guyana's lower level of healthcare and infrastructure than Toronto, Ontario. Hence, even though Guyana has a lower ozone concentration, they also have less adequate tools to combat these threats (31). Toronto, Ontario, has an ozone concentration of 40 ppb with an average lifespan of 80 years, making

the model prediction quite accurate, as expected, since the parameters of the model are decided based on Toronto's level of advancement in healthcare and infrastructure. Finally, South Korea has an ozone concentration of 59 ppb with an average lifespan of 80 years (29, 32). As the longevity is much higher than the lifespan of 67.12 years as predicted by this study, it can be inferred that there are other factors at play that act to decrease the detrimental effects of ozone on longevity. South Korea is a developed country with more advanced healthcare and technology than Toronto, Ontario. Hence, even though it has a higher ozone concentration, South Korea also has more adequate tools to combat these threats. There are currently little to no areas in the world with ozone concentrations of 80 ppb, 100 ppb, or more. The average lifespans of 57.70 years and 52.26 years in environments with ozone concentrations of 80 ppb and 100 ppb, respectively, calculated by this study, are projections that give countries an expectation and a benchmark in the future that allow them to evaluate whether ozone exposure is the biggest contributor to their death rate.

The results of this study align with the results of Poitras (11) addressing the past effects of ozone and providing predictions for the future. Specifically, results from both studies agree that as climate and air quality controls weaken, ozone-related deaths will increase. However, while Poitras does not specifically mention the quantitative extent to which "strong" and "weak" climate controls and air quality controls affect ozone-related death rates, this paper presents that the average rate of change is a decrease of 0.621 years of life for every 1 ppb increase in ground-level ozone concentration. In addition, the results of this research also align with the findings from conventional Cox proportional hazard models in other studies. A positive correlation was observed for an exponentially regressive exposure-response curve between exposure to ozone and the risk of death from respiratory causes, graphed from the results of a random-effects survival Cox proportional hazard model (33). As the daily 1-hour maximum ozone level increased, the residual risk also increased exponentially, suggesting a higher mortality rate as ozone became more concentrated within an environment (33). Similarly, the results from this study show that as ozone concentration increases, lifespan decreases, hence demonstrating a higher mortality rate as well (33). The difference between the two studies exists in the dependent variable that is being observed in each, one researching the residual risk and the other researching average lifespan, preventing a quantitative comparison from being made (33). Nevertheless, the overall trend and correlation in the figures of the two studies support each other (33). Another study that utilizes single pollutant Cox proportional hazard models investigated the relationship between exposure to each pollutant and dementia incidence (34). A hazard ratio of marginally greater than 1 was observed for every 10 $\mu g/m^3$ increase in ozone concentration, therefore suggesting an increased risk despite the small change (33). Hence, these study supports the evidence from this paper that increases in ozone concentration harm human health, even though differences do exist between the studies in research focus (dementia incidence versus lifespan) and dependent variables (hazard ratio versus average lifespan) (34).

Though this study calculated reasonable lifespan projections consistent with other empirical studies, there still exist limitations to its applicability. One such limitation is its sole focus on the role of ground-level ozone on the effects on the human body. Needless to say, the well-being of a person is extremely complex and is determined by a multitude of factors other than the concentration of ground-level ozone. Hence, the theoretical lifespans predicted by this model could be inaccurate by not accounting for these other factors contributing to human health. In addition, the simulation described in this study also only targets the effects of ozone in terms of ROS and inflammation, when in fact, there are also other health implications as well, such as effects on metabolism, reproduction, and the nervous and cardiovascular systems that could impact an individual's longevity as well and contribute to the number of ozone-related deaths (35). Lastly, the presented model is heuristic. The values of the split energy threshold, breed energy, agent food energy, and agent eating efficiency, among other parameters, were found using the method of trial-and-error to prevent algorithm breakdown as the inconsistent agent personalities and behaviors with every shuffle of the seed would result in unwanted and inaccurate fluctuations in population.

Overall, this study accounted for both aging and pre-existing respiratory diseases and demonstrated a negative correlation between ozone concentration and average lifespan through a comprehensive COBWEB model mapped to the conditions of Toronto, Ontario. In the future, additional steps could be taken to incorporate the reversing impacts of healthcare on ROS damage into the model to provide a more accurate prediction on the average lifespan of an individual under certain ozone conditions and according to the availability of healthcare.

6. Conclusion

This research demonstrated the negative correlation between ground-level ozone concentration in the environment and average lifespan. In this study, a model of the human lung was created using the COBWEB modeling software incorporating the agents of physiological saline and antioxidants, oxygen and carbon dioxide and ozone to explore the effect of ground-level ozone on human health, capturing the cumulative impact of ground-level ozone with ROS as an inflammatory marker. In the future, health studies are advised to leverage this research to provide a more comprehensive view of ozone exposure by also considering the benefits of healthcare and future advanced technologies on human well-being. Though research can guide the setting of laws and regulations to protect the health of citizens, significant actions still must be taken on a global scale to regulate the growth of the problem of air pollution as a whole.

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Data availability

The dataset used in this study is publicly available on GitHub at: https://GitHub.com/Dyannejiang/ozone-lifespan-dataset/raw/main/Dataset.xlsx
The model used in this study is publicly available on GitHub at: https://GitHub.com/Dyannejiang/ozone-lifespan-dataset/raw/main/model.xml

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