

Rapid Detection and Prognosis of Lung Cancer

by Yujiao Wu

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the degree of

Doctor of Philosophy

under the supervision of Steven Su

University of Technology Sydney
Faculty of Engineering and Information Technology

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Certificate of Original Authorship

Required wording for the certificate of original authorship

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List of Publications

I have published one journal paper, one conference paper, attended and delivered an oral presentation in 1 international forum. Besides, two journal papers are under review.

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3. **Yujiao Wu**, Ling S H, SW Su, et al. 3DResSA: A Novel Multimodal Deep Learning Framework for Lung Cancer Survival Analysis. (Under review)

Conference Proceedings

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Abbreviation

2D	Two dimensions or two-dimensional
3D	Three dimensions or three-dimensional
4D	Four dimensions or four-dimensional
AI	Artificial Intelligence
ML	Machine Learning
DL	Deep Learning
CNN	Convolutional Neural Network
NN	Neural network
C-index	Concordance
MAE	Mean absolute error
MSE	Mean square error
BS	Brier score
IBS	Integrated Brier score
LC	Lung cancer
NSCLC	Non-small cell lung cancer
SCLC	Small cell lung cancer
ROC	The receiver operating characteristic curve
AUC	The area under ROC curve

kNN	K-nearest neighbors
SVM	Support vector machines
CT	Computed tomography
CAT	Computed axial tomography
LDCT	Low-dose CAT scan or CT scan
ECG	Electrocardiogram
EEG	Electroencephalogram
MRI	Magnetic resonance imaging
PET	Positron emission tomography
WHO	World Health Organization
CA	Classical adenocarcinoma
SRCC	Signet-ring cell carcinoma
MAC	Mucinous adenocarcinoma
SCC	Squamous cell carcinoma, or known as epidermoid carcinoma
QOL	Quality of life
MHGD	Multiple hazard gas detector
RDDS	Rapid disease detection system
DeepMMSA	Multimodal deep learning framework for survival analysis
TCIA	The Cancer Imaging Archive
DC	Direct current
BRI	Building-related illnesses
SBS	Sick building syndromes
IAQ	Indoor air quality

SIDS	Sudden infant death syndrome
PGA	Programmable gain amplifier
S/N	Signal-to-noise ratio
PUFA	Polyunsaturated fatty acids
ROS	Reactive oxygen species
VOC	Volatile organic compound
MOX	Metal oxide
MOS	Metal-oxide-semiconductor
QCM	Quartz crystal microbalance
BAW	Bulk acoustic wave
SAW	Surface acoustic wave
CB	Catalytic bead
TBC	Total bacterial count
MCU	Micro control unit
USB	Universal serial bus
UART	Universal asynchronous receiver transmitter
TBARS	Thiobarbituric acid reactive substances assay
TVBN	Total volatile basic nitrogen
MM	Malignant mesothelioma
ARD	Asbestos-related disease
COPD	Chronic obstructive pulmonary disease
ECOPD	An exacerbation of Chronic obstructive pulmonary disease
BN	Batch normalization

COVID-19 Coronavirus disease 2019

Notations

r_i	i -th 3D radiology image
c_i	i -th clinical information
X_i	i -th data sample, usually a vector
T_i	Time i -th event of interest or censoring occurred
$\hat{T}_i$	predicted or estimated T_i
e_i	i -th event, 1 for uncensored, 0 for censored
$I(x)$	1 if $x = True$ else 0
$S(t)$	Survival function
$\hat{S}(t)$	Estimated survival function
$h(t)$	Hazard function
$H(t)$	Cumulative hazard function
$\hat{G}(t)$	Kaplan-Meier estimator of the censoring distribution
t_{max}	Maximal time for the estimated survival time
$\sigma(x)$	Sigmoid function, $\frac{1}{1+exp(-x)}$
R_L	Load resistance
R_s	Sensor resistance
V_c	Circuit voltage
V_{out}	Output voltage

τ	Time constant
k	DC gain
θ	Time delay
$u(t)$	Input in the time domain
$y(t)$	Output in the time domain
$\dot{y}(t)$	The first-order form of output in the time domain
$G(s)$	Transfer function, ratio of output and input in the Laplace domain

Abstract

Lung Cancer (LC) or lung carcinoma is the uncontrolled growth of epithelial cells that line up in the respiratory tract. LC is a leading cause of cancer death in both males and females and it has contributed the deaths of millions of people around the world. Smoking tobacco products is the major cause of LC.

Tremendous progress has been made in terms of better diagnosis and treatment of LC. However, the majority of LC deaths are caused by the slow spread and development of the disease. Indeed, most LC patients are diagnosed at an advanced stage only after they have presented with obvious symptoms. Owing to this, curative treatment is no longer an option. Thus, developing effective screening methods and accurate prognosis of LC is of paramount importance, not simply for early detection but also to improve patients' quality of life (QOL) and reduce the mortality of LC. Regular chest x-rays have been studied for LC screening, but they have been of limited assistance in prolonging the lives of most patients. In recent years, low-dose CAT scan (formerly known as computed axial tomography or CAT scan) or CT scan (LDCT) has been applied to patients with a higher risk of getting LC. Nevertheless, this kind of screening needs to be conducted by appropriate CT scanners. Besides, these facilities also need to work together with the staff with rich experience in CT scans for LC screening. What's more important, to guarantee a timely treatment, a

team of specialists need to cooperate with the facilities to give patients proper health care and follow-up if there are abnormalities found. To sum up, the existing system have different kinds of deficiencies and hinders the patients of LC from getting timely treatment. Moreover, research shows that 2/3 of the world population, which equals 4.7 billion people, lacks adequate radiology specialists and the right kind of medical facilities.

To alleviate the above-mentioned issues, we propose a cheaper, easy-to-use, portable electronic nose (e-nose) system to analyze the biomarkers in human breath to rapidly and non-invasively discriminate LC patients from healthy individuals. The e-nose for volatile organic compounds (VOCs) patterning is cheaper and portable. Using cross-reactive, it can detect and discriminate between complex mixtures. To explore the working principle and discrimination ability of the e-nose system and overcome the limitations of using existing non-intelligent, slow-responding, deficient gas sensors, we proposed a novel artificial-intelligent-based multiple hazard gas detector (MHGD) system that is mounted on a motor vehicle-based robot that can be remotely controlled. First, we optimized the sensor array for the classification of three hazardous gases. After that, the optimal sensor array was mounted on the MHGD to detect and classify the target gases. Finally, MHGD is tested through experiments and the results shows that the designed MHGD system could achieve an acceptable accuracy (70.00%).

Even though the previously mentioned prototype achieved an acceptable performance for hazard mixtures classification, but we needed for medical applications a scalable, stable, and robust device with a sealable gas path and automatic control

system. Thus, to enhance the system’s robustness and overcome the many deficiencies in MHGD, a prototype, namely ‘Rapid Disease Detection System (RDDS),’ was developed. This device is designed for breath analysis in the medical field. In real-world clinical practice, multiple devices based on identical designs will be used in different clinics. Thus, it is essential to perform instrument calibration before the sampling procedure to ensure the data is reproducible and reliable for analysis. In the RDDS system, with time delays, three parameters need to be determined in the calibration process: the time delay, the gain, and the time constant. Based on this, a parameter estimation method for the RDDS system is proposed. We analyzed four different standard gas mixtures(CSGMs) to calibrate the RDDS system. Finally, we obtained the three parameters of the system with the average value for the fit to the estimation data of 92.8%.

Moreover, for a better-individualised prognosis for LC and improved survival predictability, we worked at a deeper level towards survival analysis. To reveal the underlying relation of prognostic information of radiomic images, fully utilise the potential of the prognostic power existing in the radiomic data, and exploit the correlations between radiomic images and survival information, we made the first attempt to develop a deep 3D multimodal deep learning framework for survival analysis (namely DeepMMSA) using the medical image in radiology. Quantitative results on the Non-Small Cell Lung Cancer Radiomics (NSCLC-Radiomics) data show that the proposed method could surpass the traditional methods by 4% on concordance, revealing that our method could provide a more accurate diagnosis method and prognostic decision-making solution in future clinical practice.

Chapter 1

Introduction

In this chapter, I will describe the problems that exist in current LC screening and prognosis methods. Further, I will outline the motivations for the dissertation and put forward a structure for the dissertation along with conveying the main contributions to the related field.

1.1 Problem Statement

Lung cancer(Figure 1.1) or lung carcinoma is the uncontrolled division of epithelial cells that line up in the respiratory tract [4]. Lung Cancer is a leading cause of cancer death worldwide in both males and females [5]. It can be broadly classified into non-small counting for 85% of all lung cancers and small cell lung cancer [6] counting for the remaining 15%, and small cell lung cancer is centrally located in the lung [7]. Both can be fatal, especially if the cancerous cells aggressively spread and establish secondary cancer sites in other tissues. The major cause of lung cancer is smoking tobacco products, which has contributed to the deaths of millions of people over years [8].

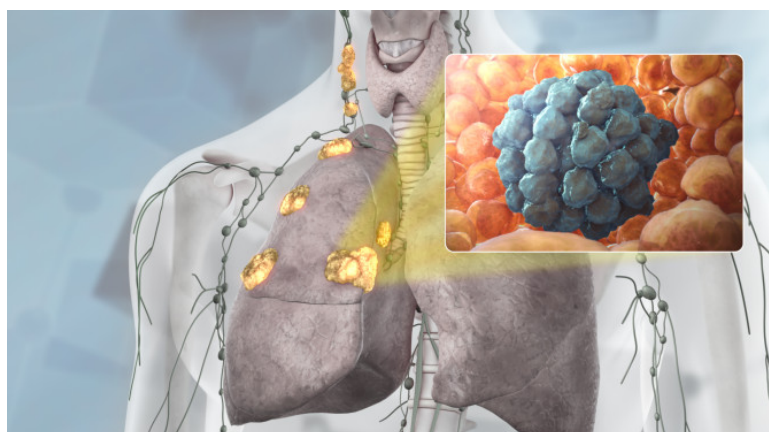


Figure 1.1 : Lung cancer. *Image source: Cancer Walls.*

Lung cancer has the highest mortality rate and the poorest prognosis among cancers. In recent years, the global incidence and mortality of cancer have been growing. Since 2010, lung cancer has become the leading cause of death, and the major public health problem in many countries around the world [9, 10]. The top 10 cancers shown in the 2018 study, as summarised in Figure 1.2, 1.3, 1.4 account for the proportion of incidence and mortality worldwide. Lung cancer is the most common cancer type for the population (accounting for an overall 11.6%) and the leading cause of cancer deaths (18.4% of total cancer deaths). For the onset of cancer, female breast cancer (11.6%), colorectal cancer (10.2%), prostate cancer (7.1%) are the top cancers; for mortality, colorectal cancer (9.2%), gastric cancer (8.2%) and liver cancer (8.2%) are the top cancers. Among them, lung cancer and breast cancer are the two types of cancers with the highest incidence and mortality in men and women in the world. In 2018, the number of male patients with lung cancer accounted for 14.5% of all male cancer cases; for women, the number of patients with breast cancer accounts for a quarter of all female cancer cases. More

than half of the people with lung cancer die within one year of being diagnosed [11]. This is mainly caused by the delayed and complicated diagnosis as well as poor prognosis.

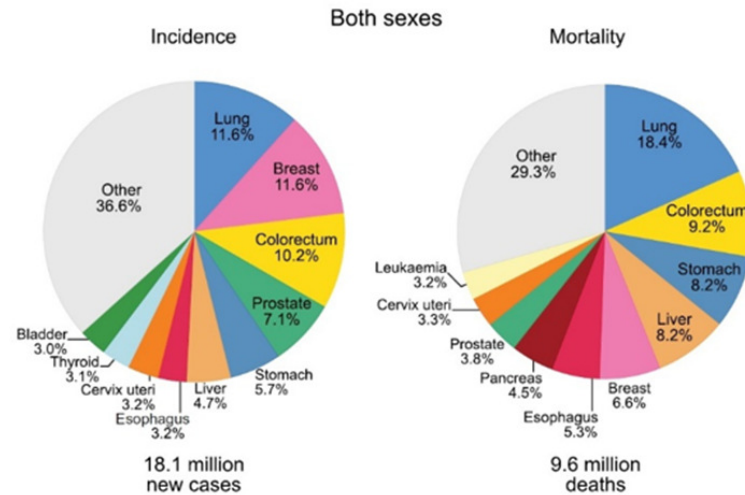


Figure 1.2 : Incidence and mortality of the top 10 cancers worldwide. *Image credit: 2018 American Cancer Society.*

The World Health Organization (WHO) International Agency for Research on Cancer (IARC) recently released a new report saying that they estimate that the number of people who have cancer worldwide is growing rapidly. In 2018 alone, 18.1 million cases were added, and the death toll was 9.6 million. By the end of the century, cancer will become the world's number one killer and the biggest obstacle to the longevity of human life expectancy. A large number of deaths are caused by gradually progressing diseases. In LC, since the lung is an internal organ; therefore, LC can remain asymptomatic and undetected for a long time, and symptoms may only occur once cancer has advanced. In fact, several early symptoms are related to lung cancer (Figure 1.5). A persistent cough is one of the most commonly seen

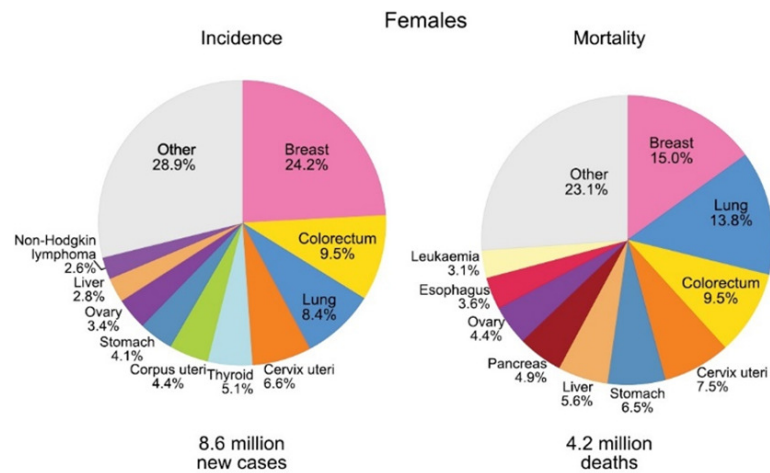


Figure 1.3 : Incidence and mortality of the top 10 cancers worldwide. *Image credit: 2018 American Cancer Society.*

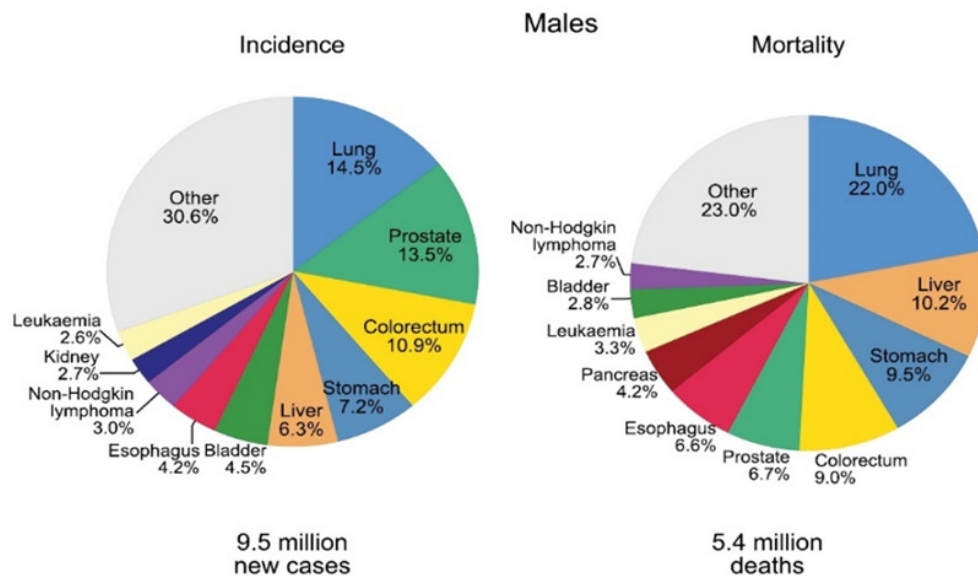


Figure 1.4 : Incidence and mortality of the top 10 cancers worldwide. *Image credit: 2018 American Cancer Society.*

symptoms and found in 50% of people at the time of diagnosis [12]. Another symptom is shortness of breath which is present only with activity [13]. There are also

some other symptoms such as shoulder and arm pain [14], chest pain [15], back pain [16], unintentional weight loss [17] etc. Those are the symptoms that appear at the early stage of lung cancer; while the chance of recovery is very high, while are easily be ignored and overlooked, and even ascribed to weight loss, aging, poor fitness, allergies, or dry air during the winter months.

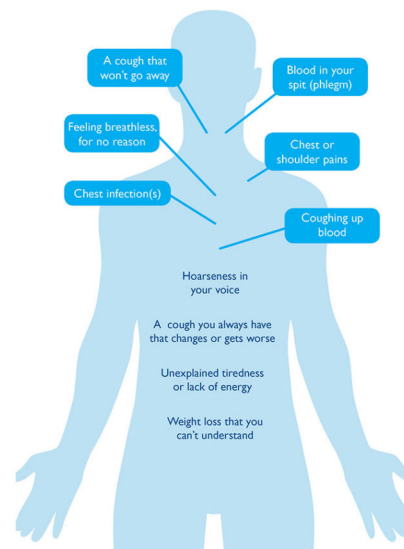


Figure 1.5 : The symptoms of lung cancer. *Image credit: Roy Castle Lung Cancer Foundation.*

Patients who get lung cancer without a screening test while ignoring the early signs will generally suffer from late diagnosis. And the high mortality rate of lung cancer is mainly due to late diagnosis. If LC can be diagnosed and treated at an early stage, the 10-year survival rate can reach 90%. Nowadays, developing new treatments to achieve further advancement in health for lung cancer is far from enough. Even though breast cancer is also one of the most common cancers

worldwide, advances in early detection have meant that the mortality rate for this disease has been substantially reduced, and the chances of survival have been greatly improved. Lung cancer has also benefited from improved treatment. However, only 16% of lung cancers are identified at an early stage [18]. This means that once it has been identified, the cancer cells have already spread. Even with the most advanced treatment methods, the effectiveness of treatment is extremely limited. Hence, it is essential to develop new techniques for detecting the disease early, way before any symptoms occur.

A variety of medical tools can be used to perform screening tests. These range from imaging techniques such as radiography or magnetic resonance imaging to the analysis of blood or tissue. These complex analytical instruments utilised for diagnosing disease are generally highly accurate and give accurate diagnostic results. But these methods are often expensive, time-consuming, and cause stress, anxiety, and pain to patients. Accordingly, many vulnerable people give up on the screening or miss the best treatment times.

Human breath holds tremendous promise for medical analysis and disease diagnosis. It is easily accessible and basically non-depletable, but it has been overlooked for a long time. Human breath has been used to diagnose disease since ancient times, and in different cultures, it has been linked to traditional medicine [19]. The analysis of the smell of breath basically is the detection of VOCs within the breath. VOCs are released from cancer cells and exist in our breath, skin, blood, bodily odor, etc. During the last decade, advances in molecular technologies have shown that the identification of cellular changes at the molecular level can be a promising

approach for the early detection of disease [20]. In 1989, a British journal, *The Lancet*, published the first dog sniffing out cancer report [21]. In a letter to the editor, two dermatologists described how a dog reportedly spent several minutes each day sniffing a colored lesion on its owner's thigh. The doctor performed diagnostic tests and confirmed malignant melanoma. Dogs can also detect lung cancer from a person's breath. A study found that a trained dog had a very high accuracy in distinguishing between the breath of people with and without lung cancer. Some human beings can have this ability too. Joy Milne, a 68-year-old retired nurse from Perth first noticed the "musky" smell on her husband [22–24], who was later diagnosed with Parkinson's disease.

However, the evaluation of VOCs by an animal or the human sense of smell is subjective. Analytical instruments, for example, gas chromatography/mass spectrometry (GC/MS), nuclear magnetic resonance (NMR) spectroscopy, can effectively separate VOCs, but they are extremely expensive to purchase, operate and maintain. These instruments require labor-intensive operations by highly trained and skilled operating personnel. Therefore they have not been applied to clinical practice.

By contrast, e-nose for VOCs patterning is cheaper and portable, using cross-reactive, detecting and discriminating between complex gas mixtures. Although e-nose cannot provide information of individual component of VOCs, it can differentiate the VOCs' composition, provide information about the origin of gas, chemical characteristics regarding mixtures, and the type and classification of odor [3, 25]. Using e-nose for disease diagnosis has been proposed for many years. Various research has developed the e-nose and tested its efficacy in medical diagnosis. Current

commercialised e-nose products include: Cyranose 320, Aromascan A32S, Artinose, ChemPro 100i, DiagNose, NIOX, Fox 2000, 3000, and 4000, artinose, etc. The Cyranose 320, as one of the most successfully commercialised e-nose, has been tested in hundreds of publications for disease detection, including: airway bacterial infection (ABI) [26, 27], amyotrophic lateral sclerosis (ALS) [28], acute respiratory distress syndrome (ARDS) [29], asthma [30], cystic fibrosis (CF) [31], chronic obstructive pulmonary disease (COPD) [26], pulmonary sarcoidosis (PS) [32], upper respiratory tract infection (URTI) [33], ventilator-associated pneumonia (VAP) [34, 35], active tuberculosis (TB) [36], and inflammatory lung disease (ILD) [37]. These types of e-noses can provide acceptable test results, but their price is very high. In addition, these types of e-noses are designed as general analytical devices. Thus redundant sensors are added to the system to ensure that they can be used in various scenarios. For example, Artinose has 38 MOS sensors, Aromascan A32S has 32 conducting polymers sensors, Cyranose 320 contains 32 sensors in their sensor array, DiagNose contains 12 MOS sensors, while Fox 2000, 3000, and 4000 have 6, 12, and 18 MOS sensors respectively. Excessive sensors can pose difficulties for pattern recognition algorithms. Therefore, a flexible, portable, and low-cost e-nose for personalised lung cancer detection is worth developing.

Apart from diagnosis and treatment, the prognosis is one of the fundamental components of general medicine. However, LC has a poor prognosis: its five-year survival rate (18.6%) is lower than many other leading forms of cancer, such as colorectal (64.5%), breast (89.6%), and prostate cancer (98.2%) [11]. Prognosis is used for the predicted course of the disease: it shows the probability of recovery, and

refers to an individual's life expectancy, including how long the person is likely to live, whether the signs and symptoms will improve or worsen (and how quickly) or remain stable over time, expectations of quality of life, etc [38–41]. Although diagnosis plays an important role in treatment decision-making, there is much evidence to show that the patients do not always benefit from it. By contrast, prognosis has displayed its great potential to provide more effective healthcare and treatment decision-making solutions. Moreover, the concept of prognosis is largely neglected, the prognostic process made by medical experts is vague, and it lacks clear consensus on its systematisation in practice, teaching, and evaluation [42]. Reportedly in clinical trials, the prediction of life expectancy is achieved by statistically assessing all the information regarding diseases such as stage and types, symptoms, and the results from relevant tests. But for each patient, the illness is unique even with similar diagnoses; thus, prognoses can be highly variable. Besides, a clinical history may span the lifetime of an individual; therefore, there is uncertainty for family medicine consultation, which makes it even more difficult to make a prognosis [43]. When facing such degrees of uncertainty, doctors normally require more tests, directly leading to increased financial costs for patients. In addition, diagnostic errors will inevitably appear when medical experts perform the interpretation of medical information. Around 20 million radiology reports contain clinically significant errors each year [44], which is due to the subjectivity and/or fatigue of medical experts as well as the huge workload in terms of reading large volumes of complex medical information.

Thus, it is worth developing a fully automated system for a personalized lung

cancer diagnosis and prognosis that can improve survival prediction accuracy and assist doctors in accurate prognostic decision-making.

1.2 Motivation and Aims

Motivated by the importance of early detection of lung cancer and the limitations existing in lung cancer prognosis procedures, this dissertation focuses on developing a non-invasive, portable, low-cost, and easy-to-use system for personalised lung cancer detection and improved prognosis procedures. In terms of lung cancer detection, a novel e-nose for rapid disease detection is proposed. It addresses many deficiencies existing in the currently available e-nose systems and is capable of analysing the biomarkers in human breath to monitor the abnormalities and track the variations found in the VOCs of human breath. Accordingly, it serves to provide useful information for lung cancer detection. In addition, to improve the current non-small cell lung cancer (NSCLC) prognosis procedure, increase prediction accuracy, and provide better personalised treatment, a deep learning-based framework is proposed.

The research in this dissertation has the following aims:

1. Undertake a pilot study by designing an e-nose system to evaluate the feasibility of using the e-nose for aroma identification. Specifically, a robot (namely MHGD) using e-nose technology to discriminate against harmful gases is designed.
2. Conduct experiments to validate the potential of the designed e-nose sys-

tem(MHGD) to perform tasks of discriminate between mixtures.

3. Enhance the stability and robustness of the e-nose system by optimising system structure and control logic. Develop a rapid disease detection system (RDDS) to distinguish the breath biomarkers of lung cancer patients.
4. Propose a calibration method regarding gas sensors in the e-nose system.
5. Proposed a MultiModal Deep learning model for non-small cell lung cancer (NSCLC) Survival Analysis (DeepMMSA).
6. Validate the effectiveness of DeepMMSA on The Cancer Imaging Archive NSCLC patient datasets.

1.3 Project Scope

1. Design and construct a rapid, non-invasive robust, e-nose system that is highly sensitive to exhaled VOCs and can discriminate the VOCs exhaled from LC patients from those of healthy individuals.
2. Propose a multimodal deep learning framework using multiple modalities for rapid and accurate NSCLC prognosis.
3. Use clinical data collected from real LC patients to calibrate the device and test its efficacy. Unfortunately, the breakout of coronavirus disease 2019 (COVID-19) directly led to the cessation of the clinical trial using the RDDS system, which resulted in a lack of experimental results for LC's VOCs data, and the

e-nose based diagnosis time series modality for the multimodal deep learning framework for LC prognosis.

1.4 Dissertation Contribution

This dissertation presents the development of novel systems for lung cancer detection and individualised prognosis. First, regarding lung cancer detection, two e-nose systems are proposed to solve the existing problems. Then, a calibration method for sensors in the e-nose is proposed. After that, a deep learning-based framework for lung cancer prognosis was presented. These systems show great potential in terms of non-invasive and rapid lung cancer detection. They also show potential concerning individualised and accurate prognosis, resulting in earlier, more effective treatments and more rapid patient recovery from various afflictions.

The primary contributions of this dissertation are listed below:

1. A pilot study regarding the development of an e-nose system is undertaken.

A novel artificial-intelligent-based multiple hazard gas detector (MHGD) system mounted on a motor vehicle-based robot that can be remotely controlled is proposed. It overcomes the many limitations of the current e-nose using existing non-intelligent, slow-responding, deficient gas sensors. Further, we have optimised the sensor array for the classification of three hazardous gases. Using the optimal sensor array on the MHGD, we tested the MHGD in a controlled environment to detect and classify the target gases. The experimental results show that the proposed odor classification algorithm achieved the de-

sired classification sensitivity and specificity. By integrating mobile devices, wireless communication, data acquisition, and analysis systems, MHGD as a multi-functional gases detection helped us explore the principle of an e-nose system and accumulates valuable experience for the second e-nose prototype development.

2. Then, based on MHGD, by deploying functional mechanical parts, designing an optimal control logic, and adding additional features, a more robust e-nose named Rapid Disease Detection System (RDDS) is proposed. RDDS aims to perform more sophisticated sensing tasks and provide reproducible results in lung cancer detection. The proposed system has the potential for early and non-invasive lung cancer detection that can discriminate lung cancer patients from healthy individuals and can be used either in clinical practice or in-home application. In addition, since multiple devices based on identical designs will be used in different clinics, it is essential to perform device calibration before testing. Therefore a method for sensor calibration is proposed.
3. To improve the current prognosis procedure and increase the prognosis prediction accuracy, we provide a novel individualised survival analysis framework named DeepMMSA for lung cancer patients. To our knowledge, this novel multimodal framework represents the first attempt to explore the prognostic information within CT images and successfully extract the 3D features for survival analysis. This framework overcomes the weakness of traditional non-parametric methods, which cannot incorporate multiple variables. Moreover, it can provide a more accurate survival analysis with sufficient granularity. Ex-

perimental results show its superiority. Indeed, the DeepMMSA can surpass the state-of-the-art methods by 4% on concordance.

Overall, this dissertation is proposed to present novel systems to assist doctors in LC detection and prognosis. The system can improve the current delayed LC diagnosis status and inaccurate prognosis, aims to detect LC at an early stage, provides precise survival analysis, assists doctors in making the optimal treatment for LC patients, and works to reduce the overall LC mortality rate.

1.5 Outline of This Dissertation

This dissertation is structured as follows: Chapter 1 discusses the topic, focus, and importance of this work. Chapter 2 discusses the preliminary background information and existing works related to the topic of this dissertation. Chapter 3, 4, and 5 are the main chapters. Chapter 3 details the development of MHGD which is a pilot study to evaluate the feasibility and discriminability of the e-nose system. Chapter 4 outlines further improvements and undertakes large-scale research regarding LC detection through biomarkers and the proposed RDDS system. Chapter 5 works towards the prognosis of LC, and a novel method for NSCLC survival analysis is discussed. Finally, the dissertation conclusion is given in chapter 6.

A detailed summation of the thesis and its research contribution appears below:

Chapter 1

This chapter gives an introduction to the problem and provides the motivation and aims of the dissertation. An introduction to the contribution and outline of the

dissertation is also provided.

Chapter 2

This chapter mainly introduces the background information and some basic concepts within the scope of the dissertation, including the e-nose, LC, ML classification algorithms, multimodal learning, deep learning (DL) in medical imaging as well as survival analysis. In each part, a literature review of related research topics is presented. These reviews aim to give a clear understanding of the challenges which exist in relation to developing an e-nose for environmental and lung cancer applications. Furthermore, some reviews concerning the use of DL in medical images and NSCLC survival analysis are introduced.

Chapter 3

This chapter details the development of the Multiple Hazard Gas Detector (MHGD). First, we present the architecture of the whole system, hardware, and software. Then, the ML and data analysis methods used in the system are introduced. After this, we present the data processing and gas classification with the associated experimental results. The experimental results show that MHGD can automatically track tracing and avoid obstacles based on ultrasonic sensors. When the equipped e-nose system is used, it can perform automatic tracing indoors so as to find out where the potential danger source is, especially for the gases generated at hazardous events. Finally, an exhaustive strategy is used to balance the cost of the whole system with the classification accuracy. Importantly, this work is a preliminary preparation for the design and development of the e-nose (Chapter 4). Moreover,

as a pilot study, it aims to solve several existing practical and technical challenges before the development of the e-nose for disease detection is outlined in Chapter 4.

The work in this chapter has been published in:

1. **Yujiao Wu**, Liu T, Ling S H, SW Su, et al. Air Quality Monitoring for Vulnerable Groups in Residential Environments Using a Multiple Hazard Gas Detector[J]. *Sensors*, 2019, 19(2): 362.
2. **Yujiao Wu**, Liu T, Ling S H, SW Su, et al. A Smart “E-Nose” System for Indoor Hazardous Air Monitoring. *Australian Biomedical Engineering Conference(ABEC)* 2018.

Chapter 4

Even though the first prototype achieved an acceptable performance for hazard mixtures, we realised that we needed a more stable gas path and a more robust device for the purposes of medical applications. We, therefore, made further improvements based on the MHGD system in Chapter 3. The details about the development procedure and calibration of the Rapid Disease Detection System (RDDS) are introduced in this chapter. RDDS consists of three parts: the whole system, hardware, and software. In terms of the whole system, we introduce the six modules in detail. For hardware design, the hardware components and mechanical parts are presented. The software is designed to allow for the adjustment of setting parameters for sample gas introduction, data acquisition, and data analysis. After the whole system is built, a calibration procedure is designed. Then extensive experiments following the procedure are performed and three parameters are calculated for the sensors which

are used in the system. The work in this chapter has been presented and published in:

1. **Yujiao Wu**, SW Su, et al. A rapid disease diagnosis system based on electronic nose. China-New Zealand Investment Forum on Innovative Technologies (IFIT) 2018.
2. **Yujiao Wu**, SW Su, et al. Estimation of Parameters in Electronic nose. (Under review)

Chapter 5

This chapter mainly discusses a novel framework named DeepMMSA for NSCLC survival analysis. Unlike existing survival analysis methods, a novel multimodal deep learning framework using 3D features extracted from CT images (in combination with clinical data for survival analysis) is put forward. In this chapter, we introduce the technical details about how this framework is designed, the structure of DeepMMSA, the features that are extracted from modalities including clinical data and CT images, and the feature fusion method. Finally, we test this framework on the data of 422 NSCLC patients. The experimental results not only verify our hypothesis but also reveal that this framework can effectively improve LC prediction accuracy.

The work in this chapter has been finished and under review in:

1. **Yujiao Wu**, Ling S H, SW Su, et al. 3DResSA: A Novel Multimodal Deep Learning Framework for Lung Cancer Survival Analysis. (Under review)

Chapter 6

This chapter summarises the work of this dissertation and presents avenues for future research.

Chapter 2

Background and Literature Review

2.1 Introduction

In this chapter, some basic concepts related to this dissertation are provided, including a brief introduction to the electronic nose (e-nose) system, the background information about lung cancer types, how LC is staged and graded, and information about details of LC prognosis. Then, followed by a literature review of related research topics. The literature review focus on an in-depth investigation of the LC detection methods is provided, including traditional methods and the novel non-invasive method using bio-marker from human breath for LC early detection. Then, the development and current status of the e-nose system and its applications in environmental monitoring and using biomarkers for disease detection is introduced. After build-up the e-nose system, a calibration method is proposed. The main idea of this calibration experiment is to use a system identification method. Thus, the concepts for the system identification method are introduced accordingly. Finally, I move deeper to improve the current lung cancer prognosis methods. A multimodal deep learning framework for survival analysis is introduced; therefore, a literature

review of related topics about multimodal, deep learning, and the current survival analysis method is provided to help understand this research work.

2.2 Electronic nose

In this section, basic development history, the working principle, and the application fields regarding e-nose are introduced. Besides, gas sensors as the core component in e-nose, background information about the type selection and calibration methods are present.

2.2.1 Development of the E-nose

The first studies involving odor measurements were done in the 1920s by Zwaardemaker and Hogewind [45]. The electricity of a fine spray of water was studied. During the experiment, spray-electricity of the water was increased when volatile substances were added to the water. The electricity of a fine spray of water was studied. During the experiment, the spray-electricity of the water was increased when volatile substances were added to the water. This phenomenon inspired that the presence of small amounts of aromatic compounds cannot only be detected through the sense of smell. The first device for measuring aroma was not developed until 1954. Hartman used microelectrode [46], a simple platinum wire of 0.8 mm in diameter, as the sensing element and measured the current flow of a sensitive millivoltmeter. Hartman also was the first to propose the idea that the apparatus could operate with several different coated sensitive elements and that some different

electrode-coating substances could be capable of giving differential responses with different compounds [47]. Moncrieff first work on using different coatings materials, such as polyvinyl chloride, gelatin, and vegetable fats, opens a new way of offering distinct and complementary information for the discrimination of simple and complex aromas [48]. In 1965, Buck et al. worked on the modulation of conductivity as a solution to differentiating aromas bouquets [49]. Meanwhile, Dravnieks and Trotter used the modulation of contact potential to monitor aromas [50]. Those works were only viewed as aroma evaluation because of a lack of analytical instruments. Twenty years later, in 1982, the sensor technology of artificial olfaction had its beginnings with the invention of the first gas multisensor array. Dodd and Persaud introduced the idea of an e-nose as a device to mimic the discrimination of the mammalian olfactory system for smells [51]. The concept of a smart chemical sensor array was proposed. By that time, the development of computers and electronic sensors made it conceptually possible to obtain an electronic device capable of imitating the mammalian olfactory system. At the 8th Annual European Conference on Chemical Induction Research held at the University of Warwick in the United Kingdom in 1987, the Gas Sensing Research Team from Warwick University, lead by Gardner, focus on the concept of pattern recognition, which has aroused widespread interest in academia.

The term "electronic nose" was coined in 1988 by Gardner and Bartlett, who later defined it as "an instrument which comprises "an array of electronic chemical sensors with partial specificity and appropriate pattern recognition system, capable of recognizing simple or complex odors" [52]. In 1989, the NATO Advanced Re-

search Workshop organized a high-level symposium on chemical sensor information processing, dedicated to the two topics of artificial olfaction and system design. Until 1994, Gardner formally proposed the "electronic nose" concept, marking that the electronic nose technology has entered a steady development stage. Since 1994, after more than ten years of development, the study of the electronic nose has made great progress.

At present, the research on e-nose mainly focuses on developing and designing new gas-sensitive materials, the standardization of sensor arrays and e-nose hardware production, the processing of sensor array signals, the application of e-nose, and the research of gas sensitivity mechanism. The e-nose is a gas/odor analysis instrument that simulates biological olfactory. Gardner defined it in 1994 as an instrument composed of a partially selective electrochemical sensor array and a suitable pattern recognition system. It can recognize a single odor or gas mixture. The e-nose has the advantages of simple operation, rapid analysis, portability, low cost, and is a novel gas/odor analysis instrument that can be widely applied.

2.2.2 Principle of Operation of E-nose Systems

E-nose devices mimic the human olfactory system that can detect and recognize odors using an array of sensors that can simulate mammalian olfactory responses to odors. The structure of a sensor-based e-nose resembles most closely the biological model. Every part of the mammalian nose has its technical equivalent(Figure 2.1) [19]. The typical e-nose consists of a sample delivery system, a detection system, and a computing system. The odor samples are drawn into the e-nose using sampling

techniques. They will transfer across the airflow all the way down to the sensor array, which is the counterparts of biological receptors are gas sensors. The odors will cause an associated change in electrical properties, such as conductivity, which therefore induces a reversible physical or chemical change in the sensing material [53]. Every single sensor in the array behaves like a receptor by responding to different odors to varying degrees [54]. E-nose attempts to mimic the principles of smelling that gives another view on the whole scene of volatiles compared to its biological inspiration [19].

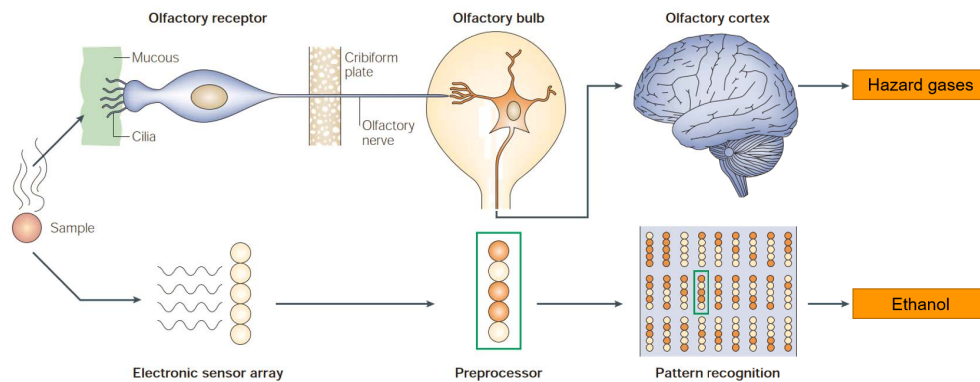


Figure 2.1 : Mammalian olfactory system vs e-nose system. *Image credit: Nature.*

2.2.3 E-nose Sensor Types

The core component for the e-nose detection system is the sensor array. The functions of the sensor array in an e-nose are equivalent to the olfactory nerves in the human olfactory system. Various principles of detection can be used for chemical sensing. Figure 2.2 shows the principles of detection and the sensor types regarding the most commonly available sensors. Through one or combinations of mecha-

nisms such as absorption, adsorption, chemisorption, and coordination chemistry, gas sensors can bind odor molecules to the sensing materials' surface and change resistance. The binding mechanism has a critical influence on the selectivity and reversibility of the system. The high binding strength means weak reversibility. Good reversibility requires poor adsorptive, which meantime leads to poor selectivity. While a good sensor would require robustness, reliability, sensitivity, selectivity, and reversibility. Furthermore, the high sensitivity with high reversibility is hard to achieve at the same time. Thus whether users need a tradeoff or detection layer must be regenerated. Many different types of gas sensors are harnessed in the e-nose sensor array, which includes the metal oxide (MOX) sensor, conductivity sensors, conducting polymer composite sensors, piezoelectric sensors, surface acoustic wave sensors, quartz crystal microbalance (QCM) sensor, metal-oxide-semiconductor field-effect transistor sensor and optical fluorescence and amperometric, to name a few. And there are many different types of sensor-coating materials, which can be classified into different additive doping materials, the reversibility of the chemical reactions and running a temperature, etc. As is shown in Table 2.1, which summarizes the types and mechanisms involved with some gas sensors. Besides, to compare the characteristics of sensors, a summary of the pros and cons of e-nose sensor types is also made in Table 2.2.

2.2.4 System Identification Method for E-nose Calibration

Normally a sensor system can be described by a first-order dynamic system. The response of e-nose sensors to odorants is generally regarded as a first-order time

Sensor type	Sensing material	Detection principle
Metal oxides semi-conducting (MOS, Taguchi)	Semi-conducting metal oxides	Resistance variations
Optical sensors	Light-sensitive, photodiode	Optical changes, light modulation
Acoustic sensors: Quartz crystal microbalance (QMB); surface	bulk acoustic wave (SAW, BAW) and Organic or inorganic film layers	Mass change (frequency shift)
Conducting polymer sensors	Modified conducting polymers	Resistance variations
Electrochemical sensors	Solid or liquid electrolytes	Current or voltage change
Catalytic field-effect sensors (MOSFET)	Catalytic metals	Electric field change
Colorimetric sensors	Organic dyes	Color changes, absorbance
Fluorescence sensors	Fluorescence-sensitive detector	Fluorescent-light emissions
Calorimetric; catalytic bead (CB)	Pellistor	Temperature or heat change

Table 2.1 : Types and mechanisms of common e-nose gas sensors [3].

Sensor type	Pros	Cons
Metal oxides semi-conducting (MOS, Taguchi)	High sensitivity, limited sensing range, rapid response and fast recovery time	High temperature operation, high power consumption, sulfur and weak acid poisoning, limited sensor coatings, sensitive to humidity, poor precision
Optical sensors	High sensitivity, can identify individual compounds in mixtures, multi-parameter detection capabilities	Complex sensor systems, expensive to operate, low portability
Quartz crystal microbalance (QMB)	High sensitivity, good precision, diverse sensor coatings	Complex circuitry, poor signal-to-noise ratio, sensitive to temperature and humidity
Surface acoustic wave (SAW)	High sensitivity, fast response time, various sensor coatings, small, cheap, sensitive to virtually all gases	Complex circuitry, sensitive to temperature, specificity to analyte groups affected by polymeric- film sensor coating
Conducting polymer sensors	Sensitive to numerous VOCs, fast response time, ambient temperature operation, diverse sensor coatings, inexpensive, not sensitive to sensor poisoning	Sensitive to temperature and humidity, sensors can be overloaded by certain analytes, sensor life is limited
Electrochemical sensors	Ambient temperature operation, low power consumption, very sensitive to diverse VOCs	Bulky size, limited sensitivity to simple or low mol. wt. gases
Catalytic field-effect sensors (MOSFET)	Small sensor size, low operating costs	Need environmental control, baseline drift, low sensitivity to ammonia and carbon dioxide
Calorimetric or catalytic bead (CB)	Fast response and recovery time, high specificity for oxidized compounds	High temperature operation, only sensitive to oxygen-containing compounds

Table 2.2 : Pros and cons of different types of e-nose sensor [3].

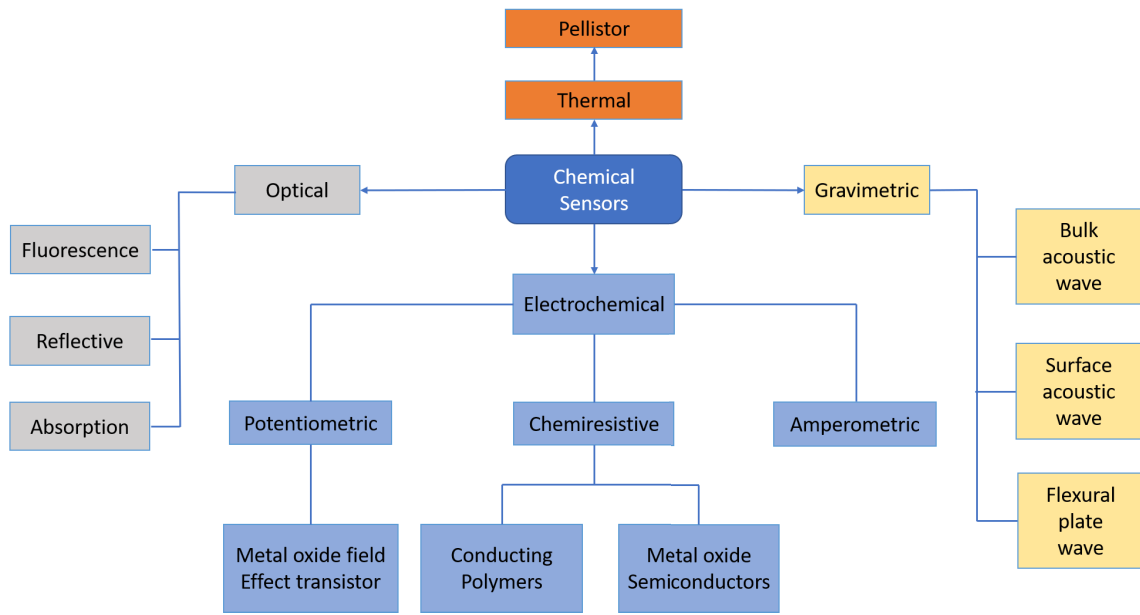


Figure 2.2 : Principle of sensors in e-nose system. *Image source: Semantic Scholar.*

response. To perform more precision control over a sensor system and analyze its characteristics, first, we need to obtain the model description of the system. Since the physical systems and industrial processes are ambiguous regarding sensor systems, it is not easy to analyze the internal mechanism to construct the corresponding model. In contrast, the sensor system model can be achieved by system identification methods, which only require the input and output data of the system. Although the model obtained by this method is not as accurate as the mechanism modeling, however, due to its simplicity and ability to fully reflecting the dynamic properties of a system, at present, most of the fractional-order systems are derived from system identification.

Although both continuous or discrete models can be used to represent existing sensor dynamic systems, however, continuous-time models can describe almost

all the systems [55]. Compared with the discrete model, the parameters of the continuous-time model can be explained from the physical level and reflect the prior knowledge of the system [56, 57]. Besides, with the changing of sampling time, the discrete model of the same dynamic system will change at the same time, but its continuous-time model is constant [58, 59]. Thus, using continuous-time models for system identification can achieve better performance. For the time domain identification, using input and output sampling data of the system, continuous-time model identification can be achieved by indirect or direct methods. The indirect method establishes a discrete model for the system then transforms it into a continuous model. At the same time, direct methods can directly estimate the system parameters based on the continuous-time model. Direct methods mainly have three advantages. First, they can fully depict the physical meaning of a dynamic system. Second, they are good at handling non-uniformly sampled data. Lastly, they can effectively improve the statistical performance of data using pre-filtering.

In this work, we use direct continuous-time model identification for the sensor system. The technical challenge regarding continuous-time model identification is that the differential value of each order of input and output signal cannot be measured. Besides, using the approximate method to calculate the differential value will inevitably amplify the influence of measurement noise on the identification accuracy. Thus, to solve this issue, harness some signal processing techniques to process the input and output signal is a currently available and feasible solution, which can be generally classified into three categories: state variable filter, modulation function method, and integral method. To be specific, state variable filter can avoid calculat-

ing the differential value of the signal [60–62]. Afterward, sampling techniques are proposed, and the data is ready for recursive estimation. The most difficult part of this method is the design of optimal structure and parameters for the filter. The core idea of the modulation function method is to transfer the differentiation of signal to a special function and weaken the impact from initial conditions at the same time [63]. The most common modulation functions include the Gauss function, Poisson function, Hermite function, to name a few [64]. The integral method is to integrate the signal with a certain order, which can eliminate the integral term [65]. This method can be further divided into the numerical integration method and the linear filter integration method. The objects identified by the above-mentioned methods are the continuous-time integer-order system.

2.2.5 Applications and Advances in E-nose Technologies

E-nose technologies have been tested extensively in many real-world applications, spans from food quality testing and control, aerospace and military application, security and safety applications, medical and health applications. For each of these mentioned categories, e-nose is applied in various individual items and products. The details of those items will be reviewed in the following sections.

2.2.5.1 Applications for Food Analysing

E-nose has a broad application in the food industry sector, the main commodities including milk, wine, tea and coffee, fish and meat, plants, etc. The applications

of this area cover from observing the nature and quality of the original ingredients to the supervision of their manufacturing process or to monitor shelf display time. Some studies have successfully using e-nose to detect the meat [66], apples [67], bakery food [68, 69], wheat [70–73], bread [74, 75], red wine [76–78], cheese and milk [79–81].

For meat and fish testing, e-nose mainly focusing on detect meat deterioration, freshness, and types of meat [82], or detecting microbiological contamination [83]. Besides, it can also sniff out the origin [84], taints of meat [85], and the freshness of fish [69, 86, 87]. Traditional methods for spoiled meat detection including total bacterial count (TBC) [88], rancidity measurements with thiobarbituric acid reactive substances assay (TBARS) [89], GC-MS and total volatile basic nitrogen (TVBN) measurements [90], colour evaluation and sensory descriptive analysis can be also useful in the detection of spoiled samples [91]. However, traditional methods are expensive, labor-intensive, and time-consuming. While through detect the volatile organic compounds(VOCs) released from spoilage microorganisms, e-nose can rapidly detect meat deterioration and does not require professional skills. The VOCs changes in the spoiled meat have a close connection with its spoilage process, and according to some research, alcohols, aldehydes, ketones, fatty acids, esters, and sulfur [88] are mostly related odors. In the work of [84], the origin of meats tested by e-nose is studied. [85] developed a e-nose for the detection of boar taint. Through experiments, results show that their self-designed e-nose can reach the classification accuracy to 84.2% in their respective group. [92] proposed an e-nose using colorimetric sensor array was developed for fish freshness evaluation with the clas-

sification accuracy of 87.5%. A novel method using e-nose with 9 MOX gas sensors in combination with electronic tongue (E-tongue) is proposed in [93], the prediction accuracy can reach 93.9% in the testing set.

2.2.5.2 Applications for Environmental Monitoring

Environmental monitoring is becoming increasingly critical in recent years as it is closely related to individuals' health conditions and living quality. Environmental applications for e-nose focus on detecting environmental pollution, toxic chemicals, and off-odors in industrial processes and indoor environments. Some of the important scenarios that e-nose has effectively helped to detect the hazard gas including air quality monitoring [94, 95], outdoor pollution-emission detection [96], chemical plume source mapping [97], industrial factories malodors detection [98], fixed pollution source localization including waste disposal sites and the off-odor generated from decomposition process of kitchens waste [99]. [94] proposed a novel e-nose(MHGD) for indoor air quality monitoring, which can detect and classify the target gases with the accuracy of 70.00%. [95] designed an indoor air quality system including sensor array and web service. In the work of [96], the application of e-nose in outdoor environment and security sectors have been investigated. [97] performed experiments with a mobile robot-based e-nose and demonstrate that using gas distribution mapping methods with e-nose for plume tracking and source localizing. [98] developed a mobile and portable e-nose that can precisely classify and find odor sources in a factory. Using the e-nose FOX 3000, [99] studied laboratory-scale experiments to track the odor changes in household garbage waste.

2.2.5.3 Applications for Disease Diagnosis

Early and accurate disease detection is essential for planning optimal treatment, protecting patients' well-being, and helping to limit healthcare costs and results in fast recovery. Humanity has made tremendous progress in diagnosing and treating disease, and there are a large variety of medical tools to perform disease diagnosis. However, a large fraction of deaths is caused by slowly progressing diseases. We are at a stage where further advancement in health cannot be achieved only by developing new treatments. For most diseases or cancers, the probability of successful treatment strongly depends on when treatment is started. While many diseases are typically only detected once symptoms occur. The problem is that many diseases can remain asymptomatic, hence undetected, for a long period of time. Therefore, there is a persisting need for new ways of detecting disease early, way before any symptoms occur [100]. Although there are various medical tools available to perform screening tests, those methods are often expensive, time-consuming, and cause stress, anxiety, and pain to patients, thus leading to many vulnerable individuals giving up the screening or missing the best treatment time. In contrast, e-nose has been used for diagnostic purposes in many studies and shows its superior ability for a non-invasive, rapid, cheap, and easily accessible diagnosis.

Using cross-reactive e-nose can examine patients' health problems by analyzing the bodily odors emitted from patients, including breath, the skin, the wound, sputum, bodily secretions, etc. In recent years, the feasibility of using e-nose for disease screening and detection through identifying the bio-markers emitted by pa-

tients both in vitro and in vivo [101] has been validated by a variety of publications. Obviously, breath testing is the most straightforward, non-invasive, easily repeatable, and without causing any embarrassment to the patient. [26] perform studies to differentiate COPD patients with and without airway bacterial colonization using Cyranose320 e-nose (Sensigent, Baldwin Park, CA, USA). Experiment results show that e-nose can successfully recognize the existence of airway bacterial colonization in COPD patients. Cyranose320 e-nose is used for the identification of exacerbations of COPD (ECOPD). E-nose shows its effectiveness for differentiating infected from non-infected ECOPD patients [27]. Cyranose320 e-nose shows its applicability for screening and diagnosis of Amyotrophic lateral sclerosis (ALS) disease [28], discriminate patients with malignant mesothelioma (MM) from asbestos-related diseases (ARDs) [29], diagnosing inflammatory joint diseases [102]. Besides, e-nose has also been verified its feasibility in examining VOC mixtures from patients with asthma and healthy control group [30, 103]. Lung-related diseases attract a lot of interest, and a wide range of studies has been investigated on employing e-nose for discriminating between lung diseases, lung cancer, and healthy individuals [31, 32, 34, 37, 104–107].

2.3 Lung Cancer

In this section, more details regarding lung carcinoma are introduced, including histological typing and staging of lung and pleural tumors, the prognosis procedure of lung cancer. For the lung cancer detection part, traditional detection methods

and novel methods using biomarkers from patients are present.

2.3.1 Types and Stages

2.3.1.1 Types

World Health Organization(WHO) classifications of tumors have historically provided a global standard for tumor diagnosis. There are mainly two histological types of lung tumors: small cell lung cancer(SCLC), non-small cell lung cancer(NSCLC). NSCLC is further divided into three main subtypes: adenocarcinoma, squamous cell carcinoma, large cell carcinoma [108]. Adenocarcinoma and squamous cell carcinoma count for most lung cancer patients. About 50% of NSCLC are adenocarcinoma, and this number is gradually increasing in recent years. According to the latest classification of adenocarcinoma of WHO, from 2004 preceded, there are mainly three well-studied major subtypes: classical adenocarcinoma(CA), mucinous adenocarcinoma(MAC), and signet-ring cell carcinoma(SRCC) [109]. SCC of the lung, also known as epidermoid carcinoma, forms in the thin, flat cells lining the inside of the lungs. SCC is more common in men than women.

2.3.1.2 Stages

The staging of lung cancer is essential for helping doctors understand how advanced lung cancer, planning for the optimal treatment, and evaluating the response to treatment. For NSCLC, the staging system named TNM stages is based on the 8th edition American Joint Committee on lung cancer stage classifications [110–112].

TNM stages are based on the values assigned to a patient's lung cancer in three categories: T (tumor), N (node), and M (metastasis) [113–115].

2.3.1.2.1 T (Tumor) Stage T stands for the primary tumor size and whether it has grown into adjacent structures (area of cancer). There are four categories in Stage T: T1, T2, T3, and T4, which are mainly based on the size, quantity, and some other information of cancer tumors.

2.3.1.2.2 N (Node) Stage N is used for confirming whether and how regional lymph nodes are affected by cancer. There are three categories in Stage N: N1, N2, and N3, which are mainly base on the quantity and location of cancer cells in lymph nodes.

2.3.1.2.3 M (Metastasis) Stage M measures if there is distant metastasis. There are two categories: M0 and M1, which are mainly based on whether cancer has spread to other parts of the human body.

2.3.2 Prognosis of Lung Cancer

Prognosis is a medical term that stands for expected development and outcome of lung cancer, including whether the signs and symptoms will improve or worsen, expectations of quality of life, and the likelihood of survival (including life expectancy), etc. [116, 117] Normally, a prognosis is made on the normal course of the disease, the patient's physical and mental conditions, and additional factors. When applied

to large statistical populations, prognostic estimates can be very accurate. Still, the likelihood for the doctor to predict the exact course of the disease is very low at the moment. Basically, the doctor can provide a general prediction about the outlook for patients with the same type and stage of cancer. There are few factors that need to be considered when making a prognosis:

- Outcome of related tests.
- The types and stages of lung cancer.
- Response condition to treatment.
- Other personal factors, such as age, fitness and overall health, gender, smoking history, etc.

2.4 Lung Cancer Detection

This section focuses on lung cancer detection techniques, including conventionally available methods and novel non-invasive methods analysing VOCs from humans to detect lung cancer.

2.4.1 Traditional methods

Conventional methods for lung cancer or pulmonary disease detection normally involves chest X-ray [118], computed tomography(CT) scan [119] of the chest, biopsy, sputum cytology, blood tests, magnetic resonance imaging(MRI) [120], positron

emission tomography(PET) [121] etc. The first step is usually a chest X-ray; if there is evidence of pleural effusion, then a diagnostic thoracentesis can be done to obtain a sample of the pleural fluid. The fluid may contain malignant cells. Through testing, if it does contain malignant cells, that means the lung cancer has invaded into the pleural, which is a hallmark of metastatic cancer and that has a poor prognosis. The cells in the pleural fluid also reflect the type of lung cancer. Cytological or histopathological diagnosis is the gold standard for lung cancer diagnosis. In traditional methods, the tissue is examined through pathology by a microscope to confirm the stages, subtypes, or genetic mutations of lung cancer. But the problem is that the biopsy method is invasive and cause pain, stress, and anxiety to patients, which may lead to patient give up on testing. Besides, this method may also lead to the missing of small nodules. Moreover, under some circumstances, the bleeding caused by a biopsy may lead to a higher risk of morbidity or mortality [122–124].

2.4.2 Lung Cancer Detection using Bio-markers from Human Breath

During the last decade, advances in molecular technologies have shown that the identification of cellular changes at the molecular level can be a promising approach for the early detection of lung-related diseases or lung cancer. Molecular cancer biomarkers can be a supplementary method to conventional diagnosis methods and improve their diagnostic yield [125–132]. In addition, the possibility of measuring cellular changes at an early stage of the development of diseases may allow the

identification of the pathophysiological processes underlying these conditions, which informs the development of the treatment.

Many volatile metabolites have been identified as potential biomarkers of many infectious diseases and for the detection of cancer, including lung cancer. Technological advances produced highly detailed and specific molecular profiles for each patient, both from vapor and liquid samples. Once identified, these biomarkers can serve as reliable indicators for targeted therapies that are more beneficial to the patient.

Although lung cancer can be detected through VOCs, which originate from skin, blood, or the odor in the headspace of cancer cells, our work focuses on detecting VOCs through human breath, which is easily accessible and basically non-depletable. Human breath is composed of five components: nitrogen, oxygen, carbon dioxide, water, and argon. Besides these five, hundreds of other components are present in very low quantity, mostly range from pptv to ppbv [133]. These are called volatile organic compounds(VOCs), and we release hundreds, even thousands of them every time we exhale. Validated by extensive empirical data [134–137] that a large percentage of VOCs spectrum are different among different people, there is only a small group of VOCs sharing a common health condition in a given population [138].

The hypothesis about the underlying relationship between lung cancer with breath analysis is shown in Figure 2.3 [1]. Lung cancer is the result of a combination of genetic and environmental factors. The critical factor that leads to the development of cancer is boosted oxidative stress, and induction of cytochrome p-450 enzymes (CYP450, a group of oxidase enzymes) [139]. Oxidative stress in the body

is related to the general equilibrium between formation and deactivation of reactive oxygen species and free radicals [1]. Some environmental sources such as cigarette smoke, radiation, and pollution can generate reactive oxygen species (ROS) [?]. ROS accumulation in body tissue can attack polyunsaturated fatty acids (PUFA) and proteins, leading to the excretion of ROS and free radicals from cells during oxidative stress. Moreover, ROS can increase cytochrome p-450 enzymes in the tissue, which catalyze the oxidation of organic chemicals [141, 142]. As a result, those processes will reflect in the breath, which will create new VOC combinations [140].

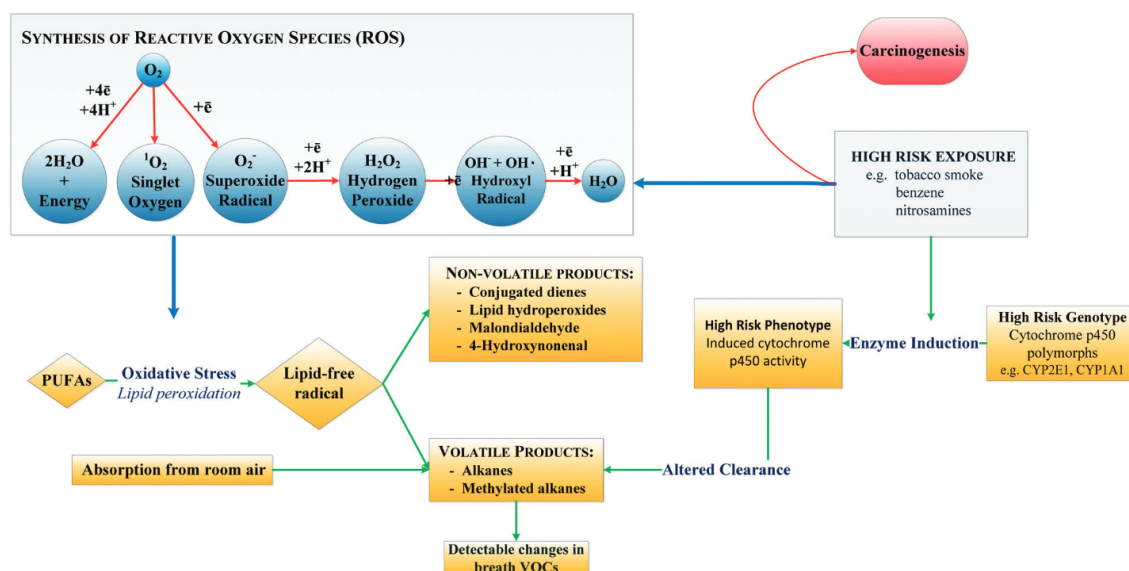


Figure 2.3 : The hypothesis about underlying relationship between lung cancer with breath analysis[1].

Many volatile metabolites of respiration were detected and selected as potential biomarkers of various infectious diseases to detect lung cancer. To be specific, the research found that there are seven main categories of VOCs bio-markers related to lung cancer: hydrocarbon (n-alkanes, branched alkanes, branched alkenes), al-

cohol (primary alcohol, secondary alcohol), aldehydes (branched and straight-chain aldehydes), ketones, esters, aromatic compounds.

2.4.3 Lung Cancer VOCs Detection Techniques

The standard method of metabolomics analyzes normally involves GC-MS analyzes, often in combination with NMR spectroscopy for the identification of the types and quantities of VOMs [143]. More recently, SIFT-MS and FAIMS-analysis are additional tools used to detect and identify candidate biomarkers that may be useful to diseases detection and diagnosis. However, These complex analytical instruments normally are expensive to purchase, operate and maintain. They require labour-intensive operations by highly trained and skilled operating personnel. Such systems are usually not portable for clinical examination rooms, patient care rooms, or emergency field situations.

By contrast, e-nose devices are particularly suited for the field of disease diagnostics because they are sensitive to a wide range of volatile organic compounds (VOCs) and can effectively distinguish between different complex gaseous mixtures via analysis of electronic aroma sensor-array output profiles of volatile metabolites present in the human breath. Metabolites present in human breath. E-nose devices are particularly suitable for the field of disease diagnosis, as they are sensitive to a wide range of volatile organic compounds (VOCs) and can efficiently detect and identify different complex gas mixtures through the analysis of the output profiles of electronic volatile aroma sensors.

2.5 Common ML Classification Algorithms

In the previous section, the details about how to develop an e-nose system are introduced. Then, the background information regarding lung cancer and how to use the e-nose for LC detection is discussed. The classification algorithms are of great importance in an e-nose system. Machine learning algorithms are proposed to discriminate between the gas mixtures collected by the e-nose system. In this section, the pattern recognition algorithm used in the proposed system for gas mixture classification is introduced.

2.5.1 Logistic Regression

Logistic regression is one of the most widely used machine learning (ML) classification algorithms, which utilizes/combines a linear model and sigmoid function to simulate a probability density and works for classification task,

$$y = \sigma(wx + b) = \frac{1}{1 + e^{-wx-b}} = \frac{e^{w^T x + b}}{e^{w^T x + b} + 1} \quad (2.1)$$

in which $\sigma()$ is the sigmoid function, w is the weight, b is the bias, x and y represent the input and output, and usually $y = 0.5$ is set as the decision boundary.

To handle multi-class classification problems using logistic regression, we can use the one versus all technique or multinomial logistic regression [144], which is also known as the softmax regression, a generalization form of logistic regression.

Softmax regression can be formulated as below,

$$h_{w,b}(x) = \begin{bmatrix} P(y = 1|x; w, b) \\ P(y = 2|x; w, b) \\ \vdots \\ P(y = L|x; w, b) \end{bmatrix} = \frac{1}{\sum_{i=1}^L e^{w^{(i)T}x + b^{(i)}}} \begin{bmatrix} e^{w^{(1)T}x + b^{(1)}} \\ e^{w^{(2)T}x + b^{(2)}} \\ \vdots \\ e^{w^{(L)T}x + b^{(L)}} \end{bmatrix} \quad (2.2)$$

in which $h_{w,b}(x)$ is the discriminant function, $y = 1, 2, \dots, L$ is the labels, $w^{(1)}, \dots, w^{(L)}$ and $b^{(1)}, \dots, b^{(L)}$ represent the weight and bias of the softmax regression model. Usually the element of maximum probability is defined as the prediction.

2.5.2 Support Vector Machines

The support vector machines (SVM) is also one of the most widely used ML methods for regression, classification and other tasks. The objective of SVM is to find a hyperplane, which has the maximum margin to separate positive and negative samples [145]. Considering that, any hyperplane is in the form of Eq. (2.3) :

$$w^T x + b = 0 \quad (2.3)$$

where w is the weight, b is the bias, respectively. Then, we need to optimize the values of w and b to find the optimal hyperplane that recognises the different categories with maximum margin.

In addition, the positive slack variable ξ_i is introduced to measure the misclassification degree of the samples. The basic optimization objective and constraints are

expressed as Eq. (2.4) :

$$\min_{w,b} \left\{ \frac{1}{2} \|w\|^2 + C \sum_{i=1}^M \xi_i \right\}$$

$$s.t. \begin{cases} y_n(w^T x^{(i)} + b) \geq 1 - \xi_i, i = 1, 2, \dots, M \\ \xi_i \geq 0 \end{cases} \quad (2.4)$$

where $x^{(i)}$ denotes i - th sample of M -size training set with N -dimensional features. $y^{(i)}$ is the class label of sample $x^{(i)}$ taking the value of $+1$ or -1 , which corresponds to the class 1 or 2. C is a hyper-parameter, which is the trade-off between the first term and the error penalty term, determining the influence of the misclassification on the objective function.

The above-mentioned optimization problem with inequality constraints can be solved by applying Lagrangian Duality technique. So this optimization problem can be deduced by solving Eq. (2.5) :

$$\max_{\alpha} \sum_{i=1}^M \alpha_i - \frac{1}{2} \sum_{i=1}^M \sum_{j=1}^M \alpha_i \alpha_j y^{(i)} y^{(j)} x^{(i)T} x^{(j)}$$

$$s.t. \begin{cases} 0 \leq \alpha_i \leq C \\ \sum_{i=1}^M y^{(i)} \alpha_i = 0, \end{cases} \quad i, j = 1, 2, \dots, M \quad (2.5)$$

the parameter α_i denotes Lagrange multiplier, which can be calculated by the gradient descent algorithm or the sequential minimal optimization (SMO) algorithm [146].

2.5.3 The K-nearest Neighbours

The k-nearest neighbours (kNN) algorithm is a popular ML method, which could be applied for highly nonlinear classification tasks with limited data [147]. For instance, kNN figures out the nearest data samples in the data set and then choose the predominant class among the neighbours. The kNN can also produce a local decision boundary by selecting a proper value to present the asymptotic properties. While the number of data set arises to the infinite, the error probability for the (k=1) NN classifier can be better than twice of the Bayes error, which is the best error that any other classifiers can reach [148].

2.6 Multimodal Learning

2.6.1 Background

Human being's experiences of the ambient environment are multimodal: people get their perceptions about the outside world through sight, sense, smell, taste, and hearing. To design artificial intelligence (AI) to imitate human beings to learn from the surrounding environment, it can be more effective to process multiple modalities. Therefore multimodal learning was developed [149] [150].

One of the critical technical challenges regarding multimodal learning is how to fuse multiple modalities. Commonly used fusion methods include early fusion, late fusion, and hybrid fusion typically [151], as shown in Figure 2.4, 2.5, 2.6. Figure 2.4 shows the early fusion framework, in which the features extracted from multiple

modalities are fused before the final decision procedure. Figure 2.5 shows the late fusion framework, in which the features extracted from multiple modalities are handled by decision models to get decisions, then the decisions are fused for the final decision procedure. Figure 2.6 gives one prototype of the hybrid fusion framework, in which the early fusion techniques and late fusion techniques are used hybrid. Moreover, the correlation, independence, coordinates, alignment, confidence level, and other properties of multiple modalities are considered specifically in the fusion process.

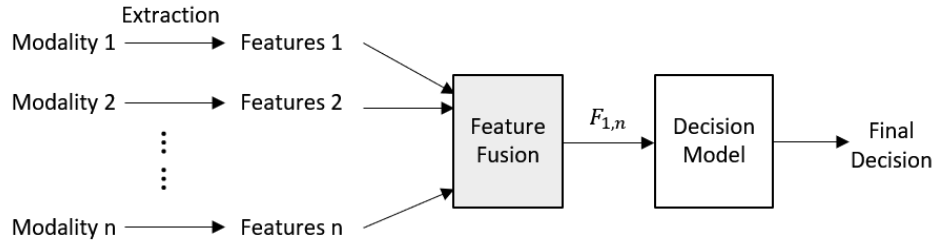


Figure 2.4 : Framework of early fusion. *Image credit: ResearchGate.*

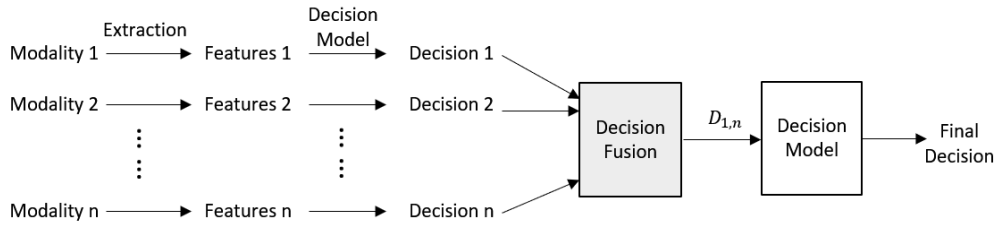


Figure 2.5 : Framework of late fusion. *Image credit: ResearchGate.*

As ML and deep learning (DL) are rising in recent years, multimodal deep learning was proposed as a novel framework using deep learning to learn from extremely complex modalities, such as text, images, video, and audio [152]. And the survey

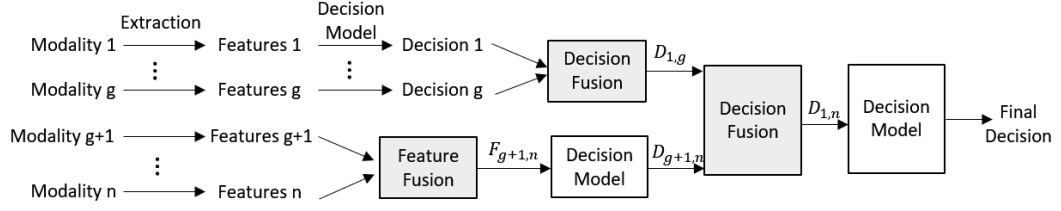


Figure 2.6 : An example for the hybrid fusion framework. *Image credit: Research-Gate.*

[153] explored and identified the new five core challenges of multimodal ML beyond the canonical categorization of early fusion, late fusion, and hybrid fusion. The five challenges are representation, translation, alignment, fusion, and co-learning, in which representation relates to how to learn multiple modalities' representations, translation relates to how to translate or map one modality to another modality, alignment relates to finding the direct relationships between elements of multiple modalities' representations, fusion relates to how to fuse information from multiple modalities for inference, co-learning relates to how to transfer knowledge in multiple modalities, and their representations and predictions.

2.6.2 Multimodal Deep Learning in Cancer Detection and Prognosis

In medical applications, especially cancer detection and prognosis, multiple types of data are related to each patient, including clinical information, radiology images, physician note, gene expression, medication, to name a few. Thus, when data are collected from different sources, the framework of multimodal DL shows its superi-

ority in effectively extracting and understanding more useful information.

There has been some works regarding cancer detection and prognosis domain. The work of [154] proposed a multimodal deep belief network to identify the cancer subtypes with multi-perform genomic data, such as gene expression, miRNA expression, and DNA methylation. Furthermore, the author also analyzes some important factors which are highly correlated with the survival time of cancer patients. The work [155] proposed a multimodal deep convolutional neural network using two modalities of dermoscopy and clinical images for skin disease detection. One of the contribution is to propose a third sub-network to fuse feature maps from the middle layers of the other two modality neural network, which makes the multimodal framework triple-net. And the experiments showed significant improvement over any method based on single-modality. In the work of [156], a multimodal deep learning framework with a hybrid fusion technique was proposed for benign and malignant breast cancer classification. The two modalities are structured data extracted from clinical electronic medical records and pathology images. There are some interesting ideas. For example, the structured data features were repeated 20 times, and the features of pathology images were extracted, and then not just the last layer, the multiple internal layers of the regarding CNN networks were concatenated together. Finally, the experiment results outperformed some other state-of-the-art methods. This work [157] proposed a multimodal deep neural network with data of multiple dimensions, such as copy number, gene expression, and clinical data, to predict the survival time of breast cancer patients into the short term labels and long term labels. The fusion technique is late fusion, with score fusion in the last

step. Experiment results outperformed traditional methods such as SVM, random forest classifier, and logistic regression algorithm. In the work of [158], a multi-modal framework with a graph neural network is used to conduct survival analyze of breast cancer and LC patients. Three modalities are used: gene expression, copy number, and clinical data. The fusion technique is early fusion. The limitation of the above two works is to divide the survival time into just short term and long term, which is a binary classification, not a regression problem, so that the survival time is insufficient in granularity for prognosis and decision making.

2.7 Deep Learning in Medical Imaging

2.7.1 Development History

Medical imaging is a critical tool in medical applications. X-ray is the first medical imaging modality discovered by Roentgen in 1895, which can present the vision of structures inside your body quickly and painlessly. Since then, there have been more medical imaging modalities to be discovered or invented, such as the electrocardiogram (ECG) for heart, computed tomography (CT), ultrasound, magnetic resonance imaging (MRI), electroencephalogram (EEG) for the brain, Positron emission tomography (PET) and so on. These imaging modalities play an important role in assisting doctors to decide how to care for patients from different stages, besides they can also affect many other aspects such as diagnosis, detection, staging, therapy designing, treatment suggestion, prognosis, observation of recurrence, etc.

It is obvious that all the generated medical images were processed by doctors or human experts in the early stage. Then from the 1960s, after the computer was invented, some attempts of using the computer and algorithm to automatically analyze medical images emerged [159–161], in which computer-aided diagnosis (CAD) was proposed to assist radiologists for decision making. Although there has been various researches in CAD, the performance and efficiency of CAD using traditional algorithms can not meet the users’ demand. Not until the success of deep learning [162] in many applications such as computer vision (CV), games, natural language processing (NLP), and so on, the performance and efficiency of CAD based on deep learning made a breakthrough.

The dimension of medical images is ranging from 2-dimension (2D) to 4-dimension (4D). The major tasks regarding those images include segmentation, classification, and object detection. The convolutional neural network (CNN) [162], which is most widely applied to analyze images, was applied and tested on medical imaging. CNN is one specific type of network that uses convolution, a mathematical operation, instead of matrix multiplication, in at least one layer, as shown in Figure 2.7.

To improve the performance of CNNs, a deeper while robust CNNs was required, then some variants of CNN were proposed, such as VGG [163], inception [164], and ResNet [165].

2.7.1.1 3D-ResNet

Specifically, to handle gradient vanishing or exploding problems in deeper neural networks training, especially in computer vision, the residual neural network (ResNet)

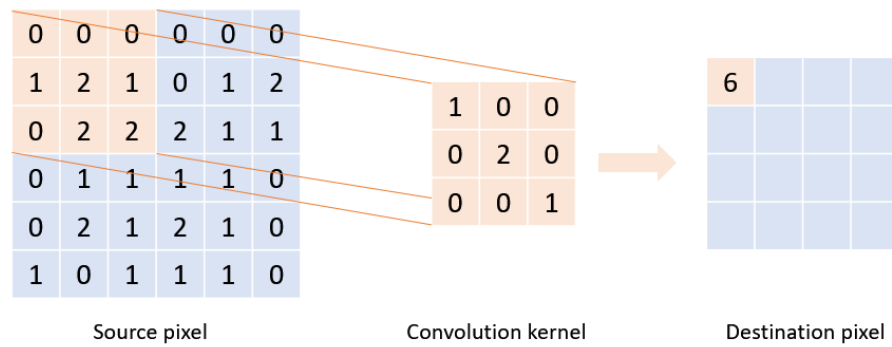


Figure 2.7 : An example of 2D convolution operation *Image source: Towards Data Science*.

[165], a variant of CNN, was proposed. The core concept of ResNet is to construct a basic network block in which the output adds up with input. To handle 3D image input, we can increase kernel shape from 2 dimensions to 3 dimensions (height, length, and depth) in convolution layers.

As shown in Figure 2.8, 3D-ResNets can be built by basic blocks or "bottleneck" building blocks, whose layer number of convolution may vary from 18 to 152 in the whole network. For instance, 3D-ResNet-18 contains four basic blocks, and each block contains four convolutional layers (conv1-conv4). Different from 2D ResNet, 3D filters process features extracted from 3D ResNet, therefore considering the spatial information of height, width, and depth within the tumour volume [166]. It is worth noting that, to eliminate the gradient vanishing and exploding gradients problems in a very deep neural network, the author add extra shortcut connections in the model. The advantage of such residual learning is that it not only addresses the gradient issues during back propagation but fuses the features of different layers. Since the medical dataset is relatively small compared to other general datasets for

image recognition, we use data augmentation techniques before importing the data into the model.

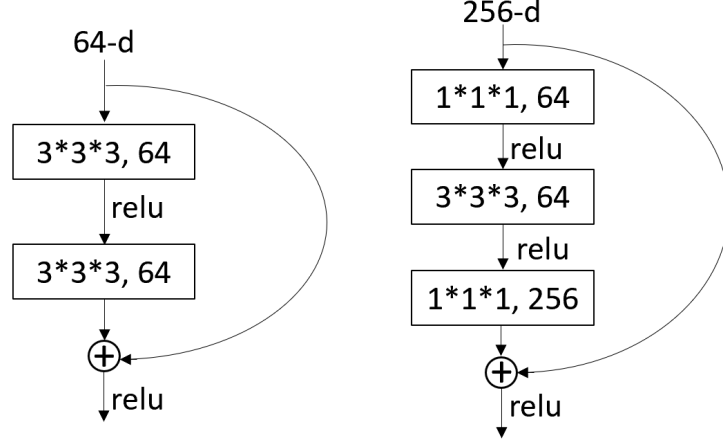


Figure 2.8 : The deep residual function $\mathbf{F}$ of 3D-ResNets. The left figure shows a building block for 3D-ResNets with layers of 18 and 34. The right figure shows a bottleneck building block for 3D-ResNets with layers of 50, 101, and 152.

The residual building block can be formulated as,

$$o = \mathbf{F}(x) + x \quad (2.6)$$

in which x is the input, o is the output, and $\mathbf{F}$ represents the deep residual function.

2.7.2 Deep Learning in Medical Imaging for Cancer

With the rise of ML and DL in recent years, there have been many works about DL in medical imaging for cancer applications, from screening, segmentation, detection, prognosis, etc. In some recent works, for instance, the work of [167] proposed a CAD system to extract features by a deep NN and a classifier to predict lung nodules to

be malignant or benign. The overall accuracy is about 75%, which significantly outperforms the baseline with the model of the belief decision tree. In the work [168], Inception v3 [164] is trained, which designs an inception module inspired by the ResNet, and applied on NSCLC histopathology images to classify NSCLC into two subtypes and normal tissue. The experimental results showed excellent performance with an AUC of 0.97. Furthermore, some commonly mutated genes in one subtype of NSCLC were researched, and some can be empirically predicted. Their work can help pathologists or radiologists to detect the NSCLC types and gene mutations. The work of [169] proposed a deep learning-based CAD system to diagnose breast lesions, including segmentation, detection, and classification from X-ray images. A number of variants of CNN were used, such as YOLO (You Only Look Once) [170], FrCN (full resolution convolutional network) [171], ResNet [165], InceptionResNet-V2 [172], to name a few. The accuracies of those three tasks achieved higher than 95%, which can be applied in clinical practice to assist radiologists. In the work of [173], PET and CT images are processed with SVM and CNN to conduct detection and distinction of lung lesions in the proposed decision support system. The total sensitivity of nodules being detected is significantly 97.2%. Their work also used PET and CT images to automatically analyze the malignant potential of lung nodules [174]. It used cytological images to automatically classify lung cancer with a deep CNN [175].

2.8 Survival Analysis

Survival analysis is the most popular technique for time-to-event data modelling, in which the time until the event is of interest [176], for instance, student dropout, cancer survival, admission to hospital, disease recurrence, etc. The outcome is usually the likelihood of an event of interest within t days.

2.8.1 Time-to-Event Data

The types of time-to-event data are different from the other common data types and normally complicated. Some patients either drop out in the observation time window, or die, or live through the observation time window, or due to other reasons, the actual survival time is unknown. Under this circumstance, such kind of data is called right-censored or censored data [2], as shown in Figure 2.9.

2.8.2 Basic Concepts

There are several important concepts and definitions for survival analysis that will be clarified in this section.

2.8.2.0.1 Survival Function Define a function, denoted by $S(t)$, which is the probability of survival time that is longer than time t for an instance.

$$S(t) = P(T \geq t)$$

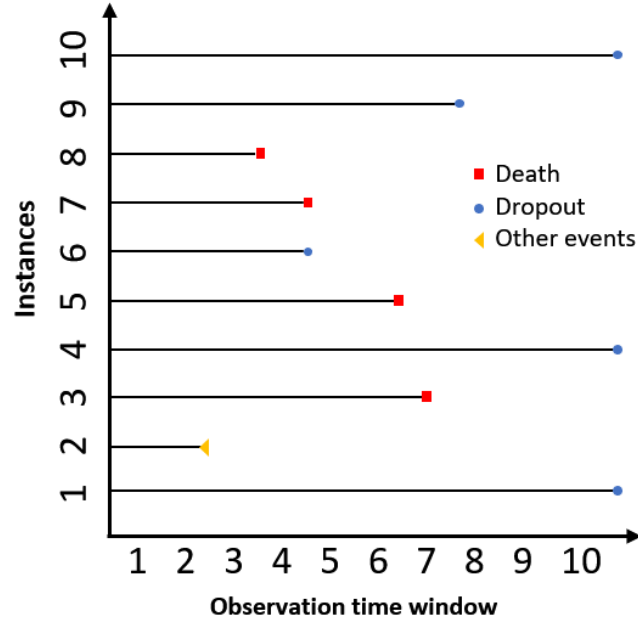


Figure 2.9 : An example for the data type of time-to-event [2].

2.8.2.0.2 Cumulative Density Function Define the probability of the event of interest occurring before t .

$$F(t) = 1 - S(t)$$

2.8.2.0.3 Death Density Function Define the probability density distribution of the event of interest occurring just at time t .

$$f(t) = F'(t) = -S'(t)$$

2.8.2.0.4 Hazard Function Define the conditional probability of the event of interest occurring at the next moment, in case of surviving at time t .

$$h(t) = \frac{f(t)}{S(t)}$$

So the cumulative probability distribution of hazard function is:

$$H(t) = \int_0^t h(x)dx$$

2.8.3 Evaluation Metrics

Because of the existence of censored data in survival analysis (usually right censored), the standard evaluation indexes for regression tasks, such as R^2 , and mean square error (MSE), do not fit for evaluating the performance of a survival analysis model. The most important evaluation index is the concordance index (C-index), which can evaluate uncensored instances and censored instances together.

$$\text{C-index} = \frac{\sum_{i,j} I(\hat{T}_i < \hat{T}_j | e_i = 1, T_i < T_j)}{\sum_{i,j} I(T_i < T_j | e_i = 1)}$$

where T_i is the survival time. $\hat{T}_i$ is the estimated survival time. While e_i is the binary event indicator. $I(\cdot)$ is the indicator function. In binary outcome cases, it can be viewed as the area under the ROC curve (AUC). Usually, 0.5 is considered a random rank, and the value is bigger, the performance is better. Besides, event time as the prediction value, we can apply the mean absolute error (MAE) over uncensored instances to evaluate the performance.

$$\text{MAE} = \frac{1}{\sum_i I(e_i = 1)} \sum_{i=1}^N (e_i | T_i - \hat{T}_i |)$$

There is also an important index called Brier score to evaluate the accuracy of a predicted survival function $\hat{S}_i(t)$ at a given time t . For censored data, it reweights the empirical Brier score by estimating the censoring distribution function $\hat{G}(t) = P(C > t)$ using the Kaplan-Meier method, in which C is the censored time, as shown below.

$$BS(t) = \frac{1}{N} \sum_{i=1}^N \left[(\hat{S}_i(t) - S_i(t))^2 * \left(\frac{I(T_i \leq t, e_i = 1)}{\hat{G}(T_i)} + \frac{I(T_i > t)}{\hat{G}(t)} \right) \right]$$

According to the benchmarks, a good survival function will have $BS(t)$ below 0.25, and the lower, the better. And we usually use Integrated Brier score (IBS) to evaluate the performance of estimated whole survival distribution.

$$IBS = \frac{1}{t_{max}} \int_0^{t_{max}} BS(t) dt$$

2.8.4 Statistical Methods

Traditional statistical methods for survival analysis normally contain three options for modeling the survival function: non-parametric, parametric, and semi-parametric methods.

2.8.4.0.1 Non-parametric Methods Non-parametric methods normally use the data itself to interpret the survival function without assuming any distribution of survival curve, which is efficient in case of no theoretical distributions known, but may produce inaccurate estimates. For example, Kaplan-Meier [177] is often used to estimate the survival function with a large enough life-time data, then plot the survival curve. Nelson-Aalen [178, 179] is often used for estimating the cumulative

probability distribution of the hazard function for incomplete data or censored data.

2.8.4.0.2 Parametric Methods Parametric methods usually pre-define a probability density distribution for the survival data, which is easy, accurate, and efficient if the survival time follows a particular distribution. The common methods include linear regression, lognormal distribution, Weibull distribution, etc. How to choose the proper distribution is the biggest challenge in using parametric methods.

2.8.4.0.3 Semi-parametric Methods Semi-parametric methods are based on both parametric methods and non-parametric methods. And in survival analysis, the Cox proportional hazards model [180] is the most popular method, in which the hazard function $h(t)$ is estimated in non-parametric methods, and the functional form of covariates is estimated in parametric methods, as shown below,

$$h(t, X_i) = h_0(t)e^{X_i\beta}$$

where the β is the parameter to be estimated.

There are still some limitations to the three types of methods. For non-parametric methods, they cannot incorporate covariates, and the survival functions are not smooth. For semi-parametric methods that address the problem of incorporating covariates, such as cox regression, it has to satisfy the linearity between covariates and log-hazard. The downside of parametric methods is that you need the parametric model to be a really good description of the survival data, which is not easy and realistic.

2.8.5 Machine Learning Methods

Recently, with the rising of ML and DL [162], ML methods such as survival trees, ensemble methods, and neural networks, to name a few, have also been applied in survival analysis. For instances, DeepHit [181] used a deep NN to directly learn the probability density distribution of survival time, including cases of competing events and makes significant advance. Cox-time [182] and CoxCC [182] use neural networks to parameterize the relative risk function of the Cox proportional hazards model and model relationships in time and covariates and to get better performance. PC-Hazard [183] discretizes the continuous-time hazard function to be piecewise constant and parameterizes the hazard function with neural networks to outperform the other state-of-the-art methods.

2.8.6 Survival Analysis for NSCLC

Conventional survival analysis for NSCLC is a set of modeling procedures that only harness clinical data, and it measures time to an event. For example, in the specific area of NSCLC survival analysis, [184] studied the variation in prognoses for adult patients with LC within Europe, by age, histology, and country from 1985–1989 with simple statistical methods, such as life-table. The work of [185] shows that tumor size within stage IA is an important indicator of survival with Kaplan-Meier and Cox proportional hazards regression model. [186] examined the survival impact of a specific gene feature for patients with EGFR mutation-positive NSCLC. The work [187] developed an online survival analysis tool for univariate and multivariate

survival analysis (e.g., Kaplan-Meier survival plot, Cox regression analysis) with ten independent data sets, counting 1715 samples. Recently, some works using DL for survival analysis have been proposed. DeepConvSurv [188], which for the first time developed a deep CNN for survival analysis using 2D pathological images. The study of [189] used the random forest model to analyze the manually extracted features from radiology images combined with age to predict a binary classification of survival time. [190] proposed CNN to extract 2D features from CT images in survival analysis. However, learning features from 2D tumor image slices and then averaging features from all image slices for every single patient may cause some problems. [191] used a deep neural network to learn cellular features from biomarkers and Cox proportional hazards model to do survival analysis. DeepLung [192] used 3D CT images and 3D CNN for nodule detection and classification, the success of which inspired us to extract 3D features from CT images for survival analysis.

In conclusion, the early-stage research for NSCLC survival analysis tends to find specific features to predict the survival curve, most of which using Kaplan-Meier and Cox proportional hazards regression model. Then with the rising of DL, deep models tend to be used to analyze more features and more types of data, such as image and text, in NSCLC survival analysis.

Chapter 3

A Pilot Study of Artificial Olfactory System: The Development of Multiple Hazard Gas Detector

3.1 Introduction

The development of system for disease diagnosis/detection using artificial olfactory technology or E-nose is promising. However, there exist several practical and technical challenges that require to be explored to implement e-nose for disease detection: How to build a e-nose detect different kinds of gases? How to choose appropriate sensors for e-nose? How to optimize the sensors? How to design algorithms for e-nose? Therefore, I perform a pilot study to explore the working principle of e-nose system and evaluate the feasibility of using e-nose for gas discrimination.

In this pilot study, I design a robot named Multiple Hazard Gas Detector(MHGD) and test its ability to discriminate gases within and around environment ^{*}.

^{*} Part of the content is from: [List of Publications, Journal 1.](#)

Not only because indoor gases is easy to get but the indoor environment plays an important role in individuals' overall health. The occurrence of a new class of diseases, identified as building-related illnesses (BRI) and sick building syndromes (SBS) rising from long-term occupancy of confined living spaces, like office buildings or homes due to chemical contaminants, particular Volatile Organic Compounds (VOCs), has incurred increasing interest in indoor air quality (IAQ) monitoring [193]. Studies have linked indoor air quality (IAQ) to mental health and illnesses that are not easily noticeable in the short-term but could be major concerns in the long-term [194]. Typically we can find thousands of indoor chemical contaminants, including by-products of the combustion (Nitrogen dioxide(NO_2), Sulfur dioxide (SO_2), Carbon monoxide (CO), etc.), cigarette smoke, particulate matter, rotten meat, mineral fibers and a number of volatile organic compounds. In spite of the very low concentrations, some of these compounds are extremely toxic, like NO_2 or CO ; some others, like benzene and formaldehyde, were proved to be carcinogenic. Therefore, the monitoring of the air quality is of paramount importance to keep safe and healthy conditions.

The objective of this study is to develop a robot (MHGD) using e-nose, which will help vulnerable person groups who have a relatively higher risk to suffer hazardous events than normal people to detect harmful gases more quickly and precisely.

Taking toxic rotten meat as an example, the detection of off-odor in rotten meat is to monitor the deterioration of foods to prevent the misuse of spoiled meat, which may lead to severe diarrhea, amoebiasis and life-threatening intestinal infections of aging people. Detection of inflammable gas such as ethanol aims to provide early

warning of the safety for elders living environment. MHGD will notice the hazardous gas there after taking samples, and then gives the early alarms and declares the gas especially for those who suffer olfactory impairment or movement disorders in case that they cannot smell or find the fire when it starts to burn.

Furthermore, homes with little kids, pregnant women and patients with breathing problems also need such safety guards. Exposure to secondhand smoke causes numerous health problems in infants and children, including more frequent and severe asthma attacks, respiratory infections, ear infections, and sudden infant death syndrome (SIDS) [195]. It is investigated that smoking during pregnancy results in more than 1,000 infant deaths in the USA annually [196]. Thus it is essential to produce a real-time detector to protect the infant and pregnancy from hazard breath. A hazard gas detector may help reassure those people, lessen their risk of hazardous consequences, and thus potentially improve their life quality.

Traditionally ceiling fixed sensors may have a delay when smoke air is far away from the fixed sensors, even fail to detect the hazard smoke due to the low concentration of a gas. The designed MHGD can be set up to be much more sensitively and promptly to the "smell" the smoke than traditional fixed sensors and adjacent to users. Additionally, MHGD also can provide powerful self-designed models such as defining alarm grading systems or only to alarm customers themselves and without disturbing the neighbors.

However, the generated data from e-nose may contain irrelevant information, and moreover, the principles of the new fields could be very complex and even totally unknown. Thus, ML as a powerful tool for advanced data processing, has become a

core technique for e-nose development. A complete ML process is consist of: data preprocessing, feature extraction and dimension reduction, and system modeling [197]. The sensor signals are composed of a large number of variables, after the data preprocessing, feature extracting methods are used to transfer signals from original high dimensional space to a low dimensional feature space or to select "representative" (pertinent) variables to characterize the whole system. Furthermore, ML is utilized to establish models for classification.

In the sensor optimization, we compared three ML methods: support vector machine algorithms (SVMs), k-nearest neighbors algorithm (kNN), multinomial logistic regression (also known as Softmax regression). The experiment results showed that the proposed MHGD system could detect the different gases quickly and classify the odors accurately. At the same time, considering different applications, we also provide three strategies for customers to choose from.

In this study, the contributions of the designed system are reflected in four major parts. First, through the open-source platform, we build a four-wheel tracing car that can automatically track tracing and avoid obstacles based on ultrasonic sensors. It is also equipped with an e-nose system and an information feedback alarm system to perform automatic tracing indoor so as to find out where the potential danger source is, especially for the gases generated hazardous events. Second, by loading the e-nose on a four-wheel tracing car, we can detect the ambient gas composition and classify the detected gas by the ML algorithm to decide whether to send an alarm or not. Third, through the Wi-Fi signal transmission module and buzzer alarm device, it can achieve timely closed-loop feedback on the collected dangerous

information, meanwhile, generate buzz alarm to remind the people of the danger in time and provide them prompt rescue. Forth, an exhaustive strategy is provided to show the trade-off between the cost of the whole system and classification accuracy.

The remainder of this chapter is organized as follows. The next section presents the proposed architecture of the whole system. In Section 3.3, we introduce the ML and data analysis methods used in the work. In Section 3.4, we present the data processing, gas classification, and its associated experimental results. Section 3.5 presents the analysis and discussion based on the experiment results. Finally, Section 3.6 concludes the paper.

3.2 Gas Detection Platform

In order to address the mentioned issues and the potential hazardous events, we designed and implemented a novel, flexible, and portable domestic hazardous odor detection system using an e-nose system, with a small net that consists of micro-controller board Ethernet Shield, hardware interface modules, and the iOS, Android smartphone App, and PC Software. An overview of the proposed detector architecture is shown in Figure 3.1. The model of the proposed detector is shown in Figure 3.2.

As shown in Figure 3.1, the whole system mainly consists of four parts: Stage 1 is sensor optimization, Stage 2 goes through the processes of gathering data with the MHGD, Stage 3 is intended as a data processing work, through what methods are used how the features are gathered, what tools are used, Stage 4 and 5 details

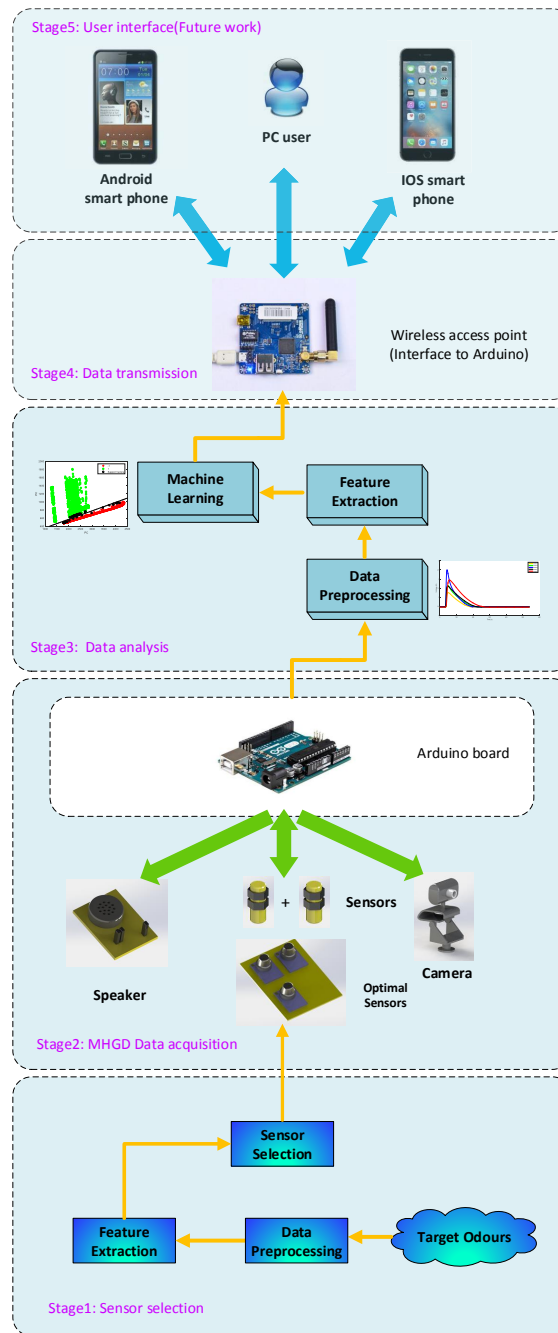


Figure 3.1 : The structure of proposed system

the process of how the data is transmitted to the user interface.

In the first stage, we apply a gas sampling device to do the data gathering work by collecting the dataset under a controlled environment. Those data are used to

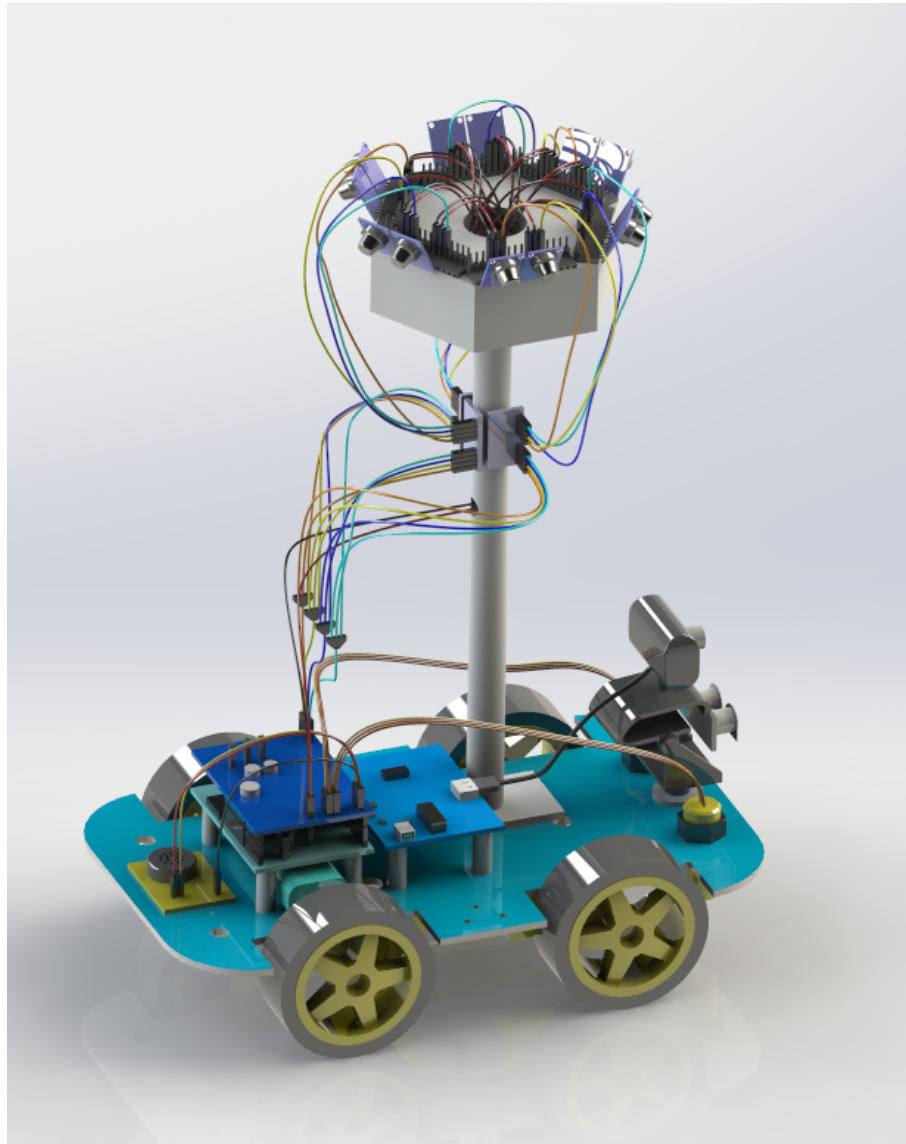


Figure 3.2 : The 3D design of the proposed system

test the sensor responses regarding different odors and verify the feasibility of our hypothesis.

Moving on from the sensor reduction stage, the next stage is intended to briefly shows the hardware components of MHGD. Using the optimised sensor array, we develop a MHGD system with camera, speaker, ultrasonic sensors, infrared sensors,

and MCU that is mounted on a vehicle-based robot that can be remotely controlled.

The third stage shows the data processing. The real data might contains much noise is going through three stages: the first step is data preprocessing, which can eliminate the noise from the real data. The data may still contain the information we do not need, so the next step is feature extraction, which aims to generate data that contains as much information as possible to present the original data. The last step is using ML intend to classify the specific gas.

In the last data transmission stage, the classification result is transmitted to the user interface through a wireless access point.

3.2.1 MHGD System Hardware Development

Mounted on a four-wheel car, this home automation hazard gas detection system consists of three main hardware components, including the main board, the customer interface, and the e-nose system. The main hardware is composed of a simple open hardware design for the Arduino board with an Atmel AVR processor and onboard I/O support, while the software side of the Arduino consists of a standard programming language and a boot-loader which runs on the board. One of the main advantages of the MGHD is its flexibility for mobile olfaction tasks. The mechanical design of the MHGD opens a variety of possible configurations. It can work either as a conventional home gas detector, smelling for the possible hazard gases, or as a mixed hazardous gas detector by replacing different combinations of sensors array on the specially designed socket which uses bionics on the top of the device to focus on

detecting and classifying some specific gases. In our system, the hardware interface modules are directly interfaced with every single module with wires. In order to make our system more scalable, we use ADS1015 to connect the main board with the e-nose system. The ADS1015 device incorporates a low-drift voltage reference and an oscillator, a programmable gain amplifier (PGA), and a digital comparator. These features, along with a wide operating supply range, make the ADS1015 well suited for our system, which is a powerful and space-constrained sensor measurement application. In the proposed system, we could use three ADS1015 chips, so our system can have up to 12 different gas sensors, as shown in Figure 3.2.

3.2.2 Software Development

The system shown in stage 4 and stage 5 consists of an application developed using the Android and iOS platforms and a micro-controller board Ethernet-based wireless access point. The open-source micro-controller is the main controller that hosts the micro web-server and performs the necessary actions. The sensors and actuators (motors) are directly interfaced to the OS controller. The multiple hazard gas detector can be controlled and monitored from a remote location using the smart home application, which will communicate with the micro web-server via the wireless access point.

In stage 5, the data from wireless access point is transmitted to the users' devices through an Internet connection via Wi-Fi. Currently, we only have a simple user interface. In the future, we will design with real-time home hazardous gas interface installed three different software platforms for users. The present simple smartphone

application, as well as the PC software, provides a graphical user interface (GUI) for accessing and controlling the device. The iOS application is created by the X-code. Most of the programming in this paper are implemented using Cocoa Touch and Objective-C code. For the Android App, Android Studio or Eclipse is used to create the application. The PC application was based on .NET 4.5 framework. Visual Studio is used to create the software. Then we created a solution.SLN file. The main project consists of four parts, including the main interface initialization, system settings, video stream settings, and servo angle settings.

3.3 Data Analysis

The sampling signals are analyzed for the benefit of fast and robust recognition in our application. The data analysis process is composed of three parts: data preprocessing, feature extraction, and pattern recognition. The signals obtained from our device normally contain noise, and data preprocessing is used to eliminate those noise then features with certain geometric definition were utilized to represent the entire signal. Those sets of parameters are served as input to a classification process for sample identifying.

3.3.1 Signal Pre-processing

Signal preprocessing is an essential element in e-nose instruments. In order to increase the signal-to-noise ratio (S/N) and reduce the sensor drift, the analysis of the first raw sensor signals originating from the chemical sensor array requires a

data preprocessing stage. Herein, we apply median filter, mean filter, and normalization in data preprocessing. The formula for the normalization in this study is as followings,

$$x_i = \frac{x_i - x_{min}}{x_{max} - x_{min}}$$

where x_i is the response value of a certain point in the response curve, x_{max} and x_{min} represent the maximum and minimum value, respectively.

Time parameters of 1st-order and 2nd-order derivatives are sensitive to noise. In order to eliminate noise and improve accuracy, mean filter and medium filter are adopted in this paper. A median filter is used to remove the outliers of the data. After that, the curve becomes stepped, so the mean filter was adopted to smoothing the result of the median filter. Then, normalization is adopted in this paper to reduce the effect of sensor drift.

3.3.2 Feature Generation

"Gas print" collected from e-nose is converted into an electrical signal, which is more suitable for data analysis. However, due to the properties and limitation of current sensors, this may cause the distortion of available information. In order to reflect different information of the reaction kinetics at different aspects [198] and obtain much more information from the multivariate time responses of sensor arrays, we propose a feature extraction method. Integrals, differences, primary derivatives and secondary derivatives at a certain interval (as shown in Table 3.1) from the response curves were extracted as shown in Figures 3.3, 3.4 and 3.5.

Those features were chosen according to the characteristics of the sensors' response curves. We extracted 9 features from each sample [199, 200], as is shown in Table 3.1.

Type	Features	Description
Response based features	f1	The maximum response value
Derivative-based features	f2	Maximum 1st-order derivatives
Derivative-based features	f4	Maximum 2nd-order derivatives
Derivative-based features	f5	Minimum 2nd-order derivatives
Time parameter	f6	response time
Time parameter	f7	Time interval from tg to td1 max
Time parameter	f9	Time interval from tg to td2 max
Time parameter	f8	Time interval from tg to td2 min
Integral	f3	Integral from gas-on to peak

Table 3.1 : Feature types and descriptions used in gas classification

3.3.3 Machine Learning Techniques

The last step of data analysis is to establish models for classification. The features extracted are served into subsequent classification tasks. Three kinds of classification algorithms are applied for target gas detection and used to process the recorded data for identifying gas mixture components and contamination estimation. In this section, we illustrate the basic principles and some important details of three selected

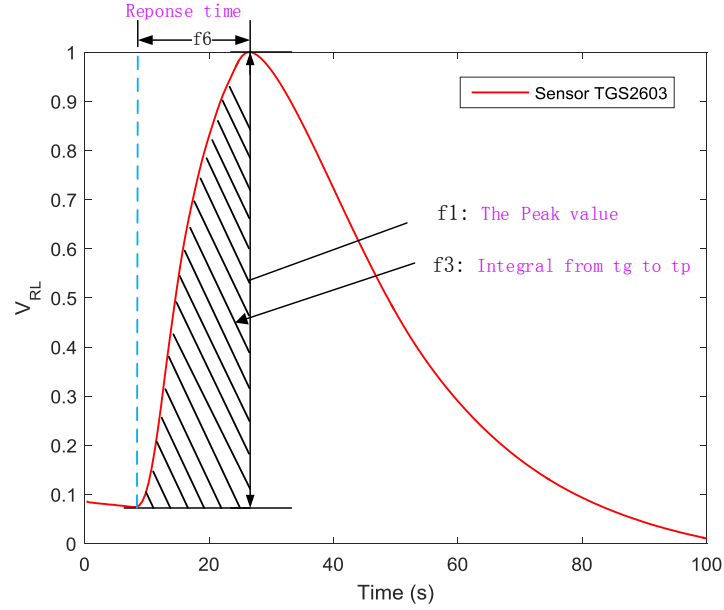


Figure 3.3 : Feature f1, f3 and f6 extracted from Sensor TGS2603's original response curve.

algorithms, including kNN, SVM, and Softmax.

3.4 Experiment and Analysis

To realize the low-cost and efficient-responding properties of the whole system, the experiment system was designed in two parts: sensor array optimization in a closed environment and target odors detection in an open environment. In the first step, sensor optimization is carried out on a stationary e-nose device with a sealed sensor chamber, aiming to test the selected sensors are capable of changing their behavior differently when exposed to volatile substances released by three selected analytes.

The samples tested in the experiment are three threaten gases: the odor from

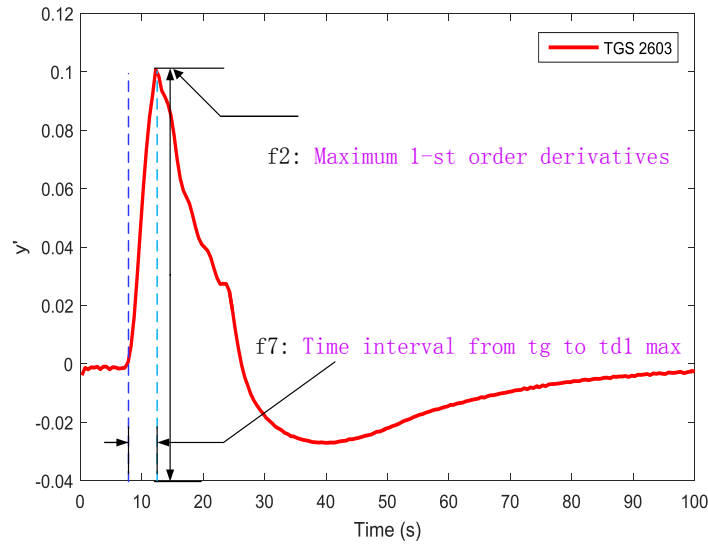


Figure 3.4 : Feature f2 and f7 extracted from the first-order derivative from Sensor TGS2603's response curve.

spoiled rotten meat, the inflammable gas ethanol as well as smoke from a burning cigarette, particularly, emissions of volatiles from cigarette tobacco comprise a wide range of chemical components making up a complex odor [201], thus, analysing the samples from a burning cigarette in our work focus on analysing the volatile compounds released by tobaccos and cigarettes samples. Real samples have been used in our experiments. In all experiments, the weight of spoiled meat is 4g. The volume of ethanol liquid is 2ml. 3g burning tobacco in a headspace bottle is served as a sample for cigarette smoke. The absolute value of the concentration cannot be accurately controlled in our experiment. The odor is injected into the sealed e-nose chamber with a sampling needle; afterthat, clean air was pumped into the chamber. The sensor array used in the experiments of gas recognition is composed

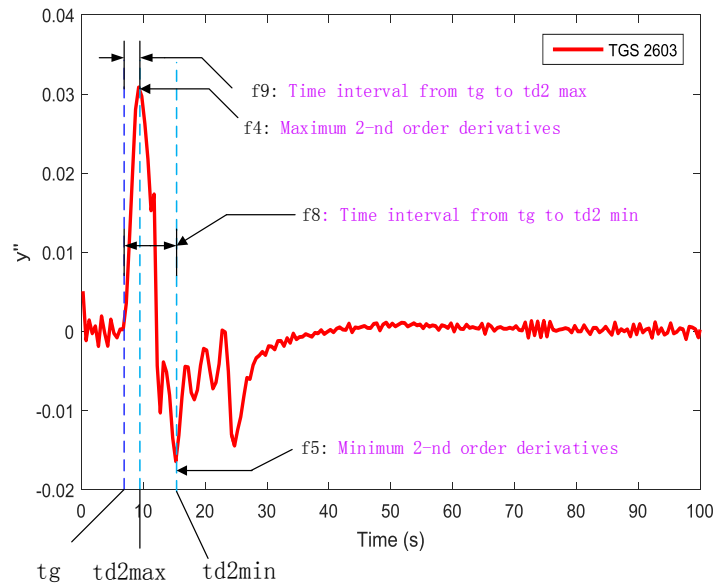


Figure 3.5 : Feature f4, f5, f8 and f9 extracted from the second-order derivative form of Sensor TGS2603's response curve.

of three elaborately selected gas sensors: TGS2620, TGS2603, and TGS2600. The response characteristics of these sensors are listed in Table 3.2. Sampling is done in three phases: baseline phase, sampling phase, and recovery phase. Each test lasts for 1150 seconds. All the measurement data will be stored in the computer for future process and analysis. The gases are collected under a closed and controlled environment where the ambient temperature of 25-27 degrees Celsius and 50% RH ambient humidity. The experiment for three odors was carried out 150 times. We have 150 datasets, and each odor has 50 datasets.

In the second step, the optimised sensor array is installed on the MHGD to detect target odors. Since the sensor array is direct exposure to the room environment, this condition is referred to as an open environment. According to the previous

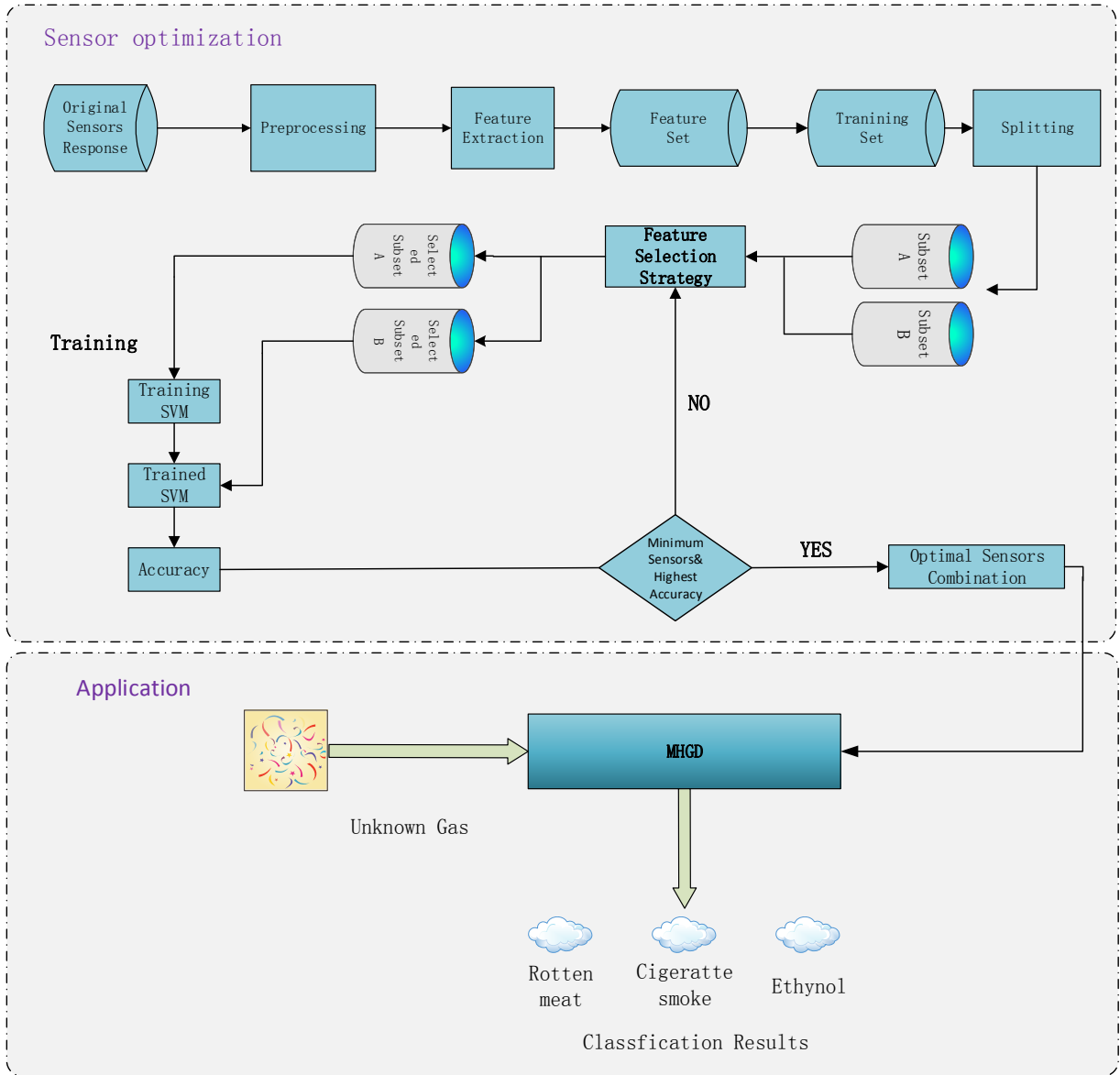


Figure 3.6 : The data flow diagram of MHGD.

study [202], the features mentioned in Table 3.1 will be influenced in a moving condition (i.e. moving sensing device or moving gas source). Therefore, all gases are collected under closed controlled environment, that is, no-wind and stationary platform conditions. All experiments are carried out at the room temperature. In

Sensors	Gas type	Type	Producer
TGS2620	Ethanol, Hydrogen, Iso-butane, Carbon monoxide, Methane, etc.	MOS	Figaro (Japan)
TGS2603	Trimethylamine, Methyl mercaptan, etc.	MOS	Figaro (Japan)
TGS2600	Methane, Carbon monoxide, Iso-butane, Ethanol, Hydrogen, etc.	MOS	Figaro (Japan)

^a The response of sensors is non-specific they also sensitive to other gases, which are not listed in the table.

Table 3.2 : Gas sensors sensitivity characteristics ^a.

this way, the testing system could get rid of the interferences in ambient, so that the repeatability of the response curves collected by MHGD is guaranteed. Spoiled meat and gas ethanol are adopted in the experiment. For sample delivery, we take the cigarette smoke as an example, 3g burning tobacco in a headspace bottle is served as a sample for cigarette smoke. Before testing, the distance between the headspace bottle with burning tobacco and MHGD is 15cm. Testing repeats ten times for each sample. Each test lasts for 300 seconds, getting 20 groups of data sets in total.

3.4.1 Data Analysis

In each test, the responses of gas sensors are obtained. Three different hazard odors were prepared, tests were performed one hundred and fifty times. The data flow diagram is presented in Figure 3.6. Considering that the trend of sensor array curves collected from the same gas are similar, thus, only one measurement of each gas is selected for illustrating the original data and effect of data preprocessing. The response curves are shown in Figures 3.7, 3.8 and 3.9. Individually, Figures 3.7a, 3.8a, 3.9a show the raw response curve of sensor array and the Figures 3.7b, 3.8b, 3.9b present the curves after filtering and normalizing. To better illustrate the

variability and problematics that can appear in a real scenario, the response curves in the second experiment are shown in Figure 3.10a, 3.11a and 3.12a. And the data after preprocessing are shown in Figure 3.10b, 3.11b and 3.12b respectively.

As is shown in the figures, a lot of noises have appeared in the raw data. In order to eliminate those noises, make it more representative and revealing the real response curve of the sensor, median filter and mean filter are adopted. The major advantage of the median filter is that it can eliminate the effect of input noise values with extremely large magnitudes [203]. Meanwhile, the mean filter was more likely to remove the impulse noise [204]. After filtering, the curves became smooth. Since the signal is voltage, the magnitude is very small but some with high variation. Thus, we implement the normalization technique, the range scale, which sets the limits at $[0, 1]$. It is shown that curves after preprocessing are becoming smoother than raw data.

The random shuffling of datasets was performed on Matlab. After that, each dataset is divided into two equal subsets before training. For 27 features from three gases, we apply three classification schemes. A two-fold cross validation (2-CV) method (75 samples for training and 75 for testing) is repeated 300 times. Of the two subsets, one subset is retained as the testing set, and the other subset consists of the training set. All dataset is used for both training and testing, which ensures that each sample is used for validation. The confusion matrix is calculated 300 times for evaluation of three classification schemes and seven sensor combinations as is shown in the confusion matrix of the result in Tables 3.3 and 3.4.

After data preprocessing, we apply three classifiers, SVM, kNN, and Softmax,

Classifier	Odor	TGS2620					TGS2603					TGS2600				
		Ethanol	Meat	Cigarette	Sen.	Spe.	Ethanol	Meat	Cigarette	Sen.	Spe.	Ethanol	Meat	Cigarette	Sen.	Spe.
SVM	Ethanol	14950	2	48			15000	0	0			14901	10	89		
	Meat	0	14900	100	0.9867	0.9934	0	14802	198	0.9333	0.9667	0	15000	0	0.9888	0.9944
	Cigarette	0	448	14552			0	2803	12197			0	405	14595		
kNN	Ethanol	14880	70	50			14892	52	56			14700	201	99		
	Meat	0	10202	4798	0.8733	0.9367	0	13500	1500	0.9600	0.9800	15	14605	380	0.9767	0.9884
	Cigarette	0	783	14217			0	192	14808			2	351	14647		
Softmax	Ethanol	14885	108	7			14900	25	75			14933	0	67		
	Meat	3	14701	296	0.9533	0.9767	100	14799	101	0.9333	0.9667	50	14890	60	0.9867	0.9934
	Cigarette	5	1682	13313			0	2700	12300			3	418	14579		

^a Results for 300*2-fold cross validation (2-CV) using single sensor. Sen denotes sensitivity and Spe denotes specificity.

Table 3.3 : Confusion matrix of single sensor ^a.

Classifier	Odor	TGS2620+TGS2603					TGS2603 +TGS2600					TGS2620+TGS2600					TGS2620+TGS2603 +TGS2600				
		Ethanol	Meat	Cigarette	Sen.	Spe.	Ethanol	Meat	Cigarette	Sen.	Spe.	Ethanol	Meat	Cigarette	Sen.	Spe.	Ethanol	Meat	Cigarette	Sen.	Spe.
SVM	Ethanol	14739	261	0			15000	0	0			14812	188	0			14712	288	0		
	Meat	0	15000	0	0.9833	0.9916	0	15000	0	0.9976	0.9988	0	15000	0	0.9888	0.9944	0	15000	0	0.9888	0.9944
	Cigarette	0	491	14509			0	109	14891			0	315	14685			0	214	14786		
kNN	Ethanol	13821	360	819			15000	0	0			14800	200	0			14799	201	0		
	Meat	0	15000	0	0.9467	0.9733	0	15000	0	0.9933	0.9966	0	15000	0	0.9867	0.9934	0	15000	0	0.9933	0.9966
	Cigarette	0	1220	13780			0	302	14698			0	398	14602			0	102	14898		
Softmax	Ethanol	14298	0	702			15000	0	0			14461	0	539			14575	0	425		
	Meat	0	15000	0	0.9733	0.9866	0	15000	0	0.9856	0.9928	0	15000	0	0.9856	0.9928	0	15000	0	0.9856	0.9928
	Cigarette	0	500	14500			0	649	14351			0	111	14889			0	224	14776		

^a Results for 300*2-fold cross validation (2-CV) using 4 sensor combination. Sen denotes sensitivity and Spe denotes specificity.

Table 3.4 : Confusion matrix of sensor combination ^a

to analyze the data. There are three sensors in the original sensor array. In order to balance the number and the classification sensitivity of sensors, we trained three classifiers for all seven sensor combinations and found the best parameters for each classifier.

Table 3.3 shows the confusion matrix of three single sensors. Table 3.4 shows the confusion matrix of sensors array combination.

3.5 Results Analysis and Discussion

In this study, three classifiers are trained for different sensor combinations. First, the feature set generated from the sensor array from e-nose was provided to the algorithms as input vectors. Then, the training process of SVM, kNN, and Softmax, are executed automatically using Matlab. Herein, we compare three strategies for customers to choose from.

In order to reduce the cost of the system, we train the data from a single sensor separately and find the best parameter for each classifier. As is shown in Table 3.3: for TGS2620, SVM has the highest sensitivity and specificity for 98.67% and 99.34% respectively. For TGS2603, kNN has the highest sensitivity for 96% and specificity for 98.00%. As for TGS2600, the highest sensitivity is achieved by SVM for 98.88% with the highest specificity for 99.44%. Thus, in terms of low-cost, using TGS2600 with SVM shows excellent performance.

The results of classification accuracy with all sensors with three classifiers are shown in Table 3.4. It is observed that all classifiers show excellent performance. The best performance is achieved by kNN of 99.33% with specificity for 99.66%. And it means that any classifier can achieve high accuracy, and there is no need to implement different classifiers and find one with the highest performance under this circumstance.

The results of classification accuracy with two sensors with all classifiers are also shown in Table 3.4. Under this circumstance, the highest classification accuracy is achieved by SVM with sensor TGS2603 and TGS2600, which is higher than a single

Odor	TGS2620+TGS2600		
	Meat (Predicted)	Cigarette(Predicted)	Ethanol(Predicted)
Meat (Label)	9	0	1
Cigarette (Label)	0	4	6
Ethanol (Label)	1	1	8

Table 3.5 : Confusion matrix under open environment.

sensor, and the cost for all the systems is also lower than that of all three sensors. Thus, in terms of the universal application, TGS2602 and TGS2600 show the best result.

SVM outperformed other classifiers in the first experiment. Therefore, we adopted SVM as the classification model in the second experiment. Due to the limited number of samples, we applied Leave-One-Out (LOO) strategy to train and test the classification model. The experiment of MHGD in an open environment achieved an acceptable result, which reached an accuracy of 70% (21/30). The confusion matrix is shown in Table 3.5.

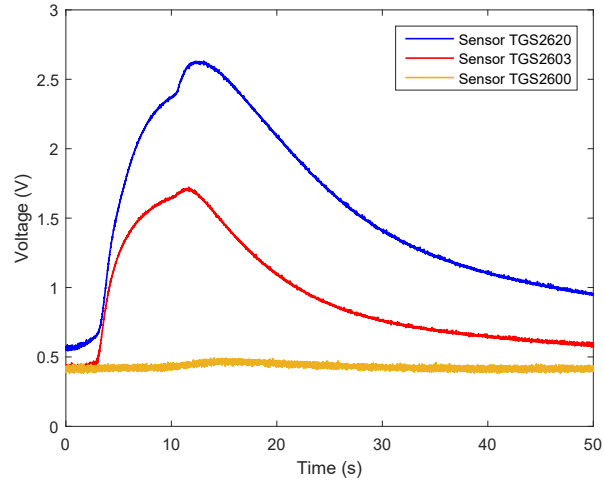
3.6 Conclusions

By integrating mobile devices, wireless communication, data acquisition, and analysis system, we design and validate a multi-functional hazard gas detection system. It allows the users to detect various gases by using mobile devices or PCs. Using

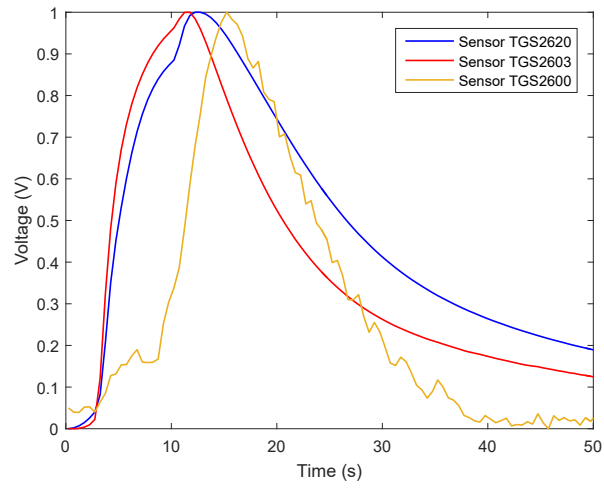
this system as a framework, it can be extended to various other applications such as home air quality monitoring, fire detection, as well as hazard gases detection in a chemical plant for better decision-making. To demonstrate the feasibility and effectiveness of the proposed solution, the system is tested for its capability to perform the operations of sensing and classifying the source of hazardous gas under a laboratory environment. Experimental results show that the proposed odor classification algorithm received desired classification sensitivity and specificity.

The proposed system enhances the current air quality monitoring systems in residential buildings in terms of high classification accuracy, ease of deployment, and integration into existing security and safety systems.

Future work will include further improvement in the addition of extra features, such as seamless integration into existing infrastructure, development of a more intelligent user interface, enhancing the robustness of the system, performing sensing tasks under more sophisticated environments, taking different combinations of features into consideration to find the feature sets with best and reproducible performance, simplification of hardware, reduction of power consumption, and miniaturization and integration into the Internet of Things.

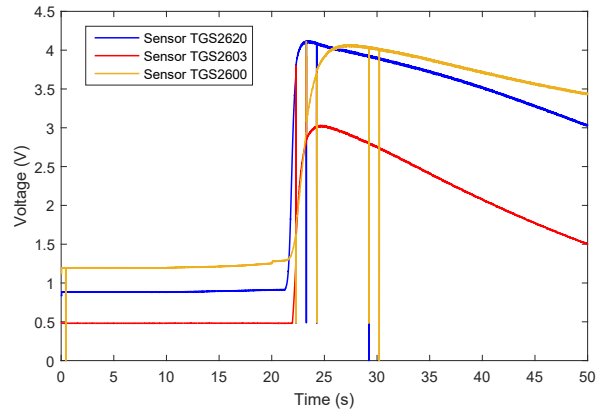


(a)

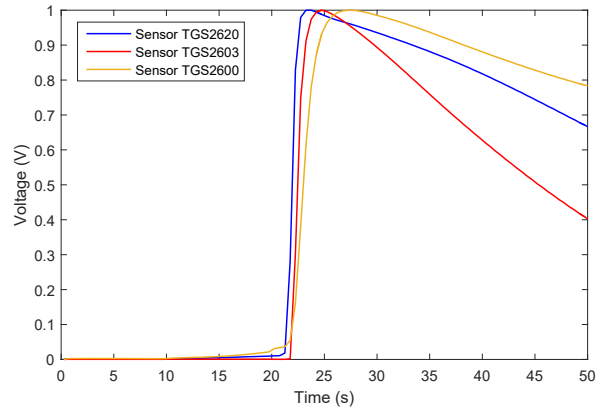


(b)

Figure 3.7 : The response curves of Sensor TGS2620, TGS2603, and TGS2600 for gas ethanol, in which Figure 3.7a is of the raw time series data, and Figure 3.7b is of the preprocessed time series data.

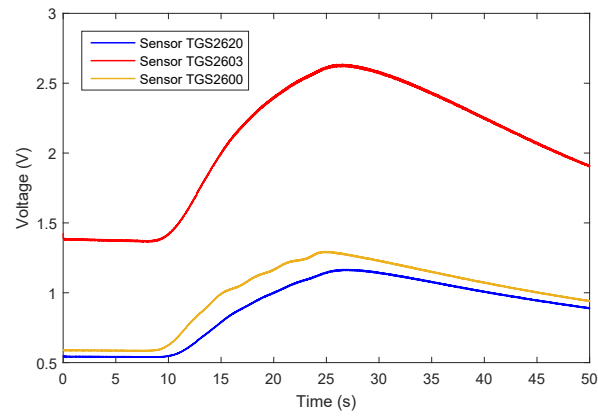


(a)

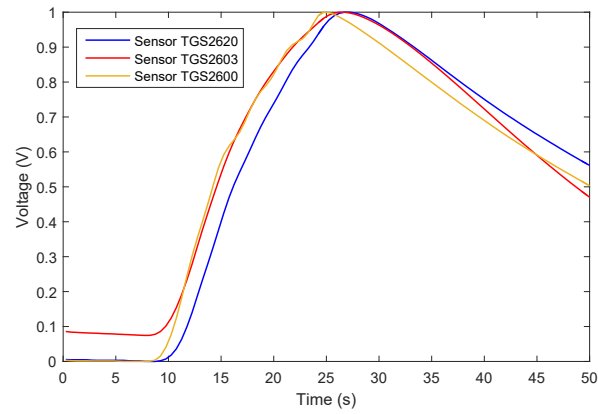


(b)

Figure 3.8 : The response curves of Sensor TGS2620, TGS2603, and TGS2600 for rotten meat odors, in which Figure 3.8a is of the raw time series data, and Figure 3.8b is of the preprocessed time series data.

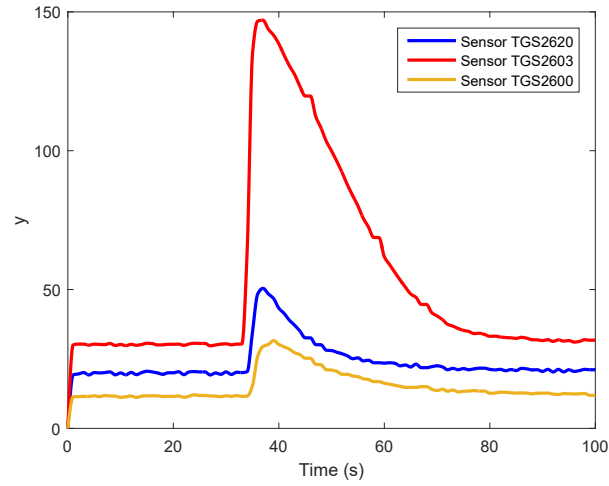


(a)

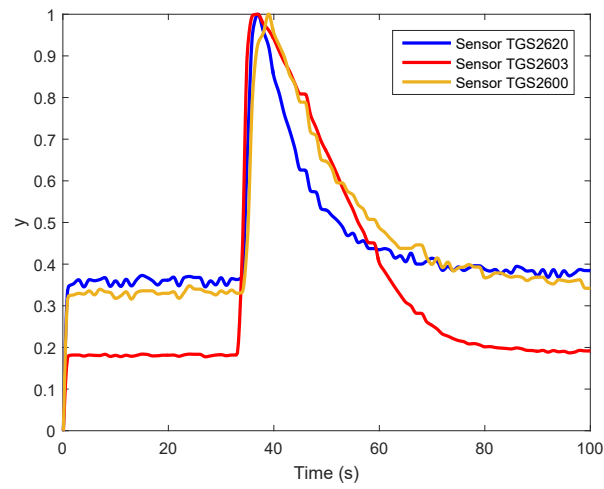


(b)

Figure 3.9 : The response curves of Sensor TGS2620, TGS2603, and TGS2600 for burning cigarette gases, in which Figure 3.9a is of the raw time series data, and Figure 3.9b is of the preprocessed time series data.

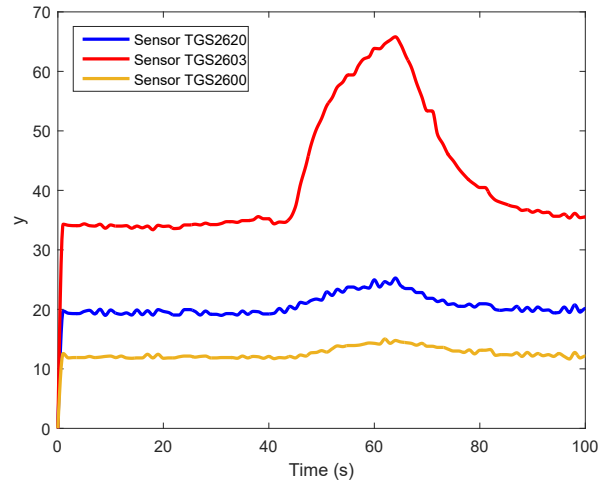


(a)

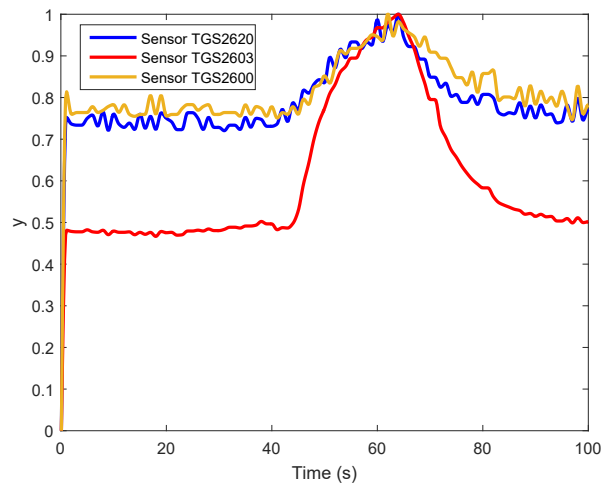


(b)

Figure 3.10 : The response curves of Sensor TGS2620, TGS2603, and TGS2600 for gas ethanol in the second experiment, in which Figure 3.10a is of the raw time series data, and Figure 3.10a is of the preprocessed time series data.

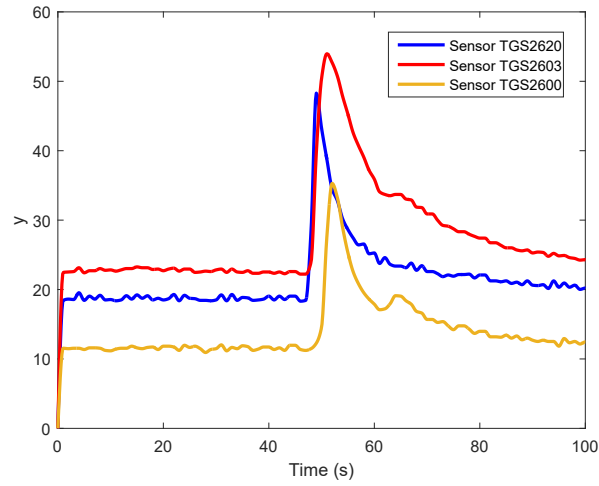


(a)

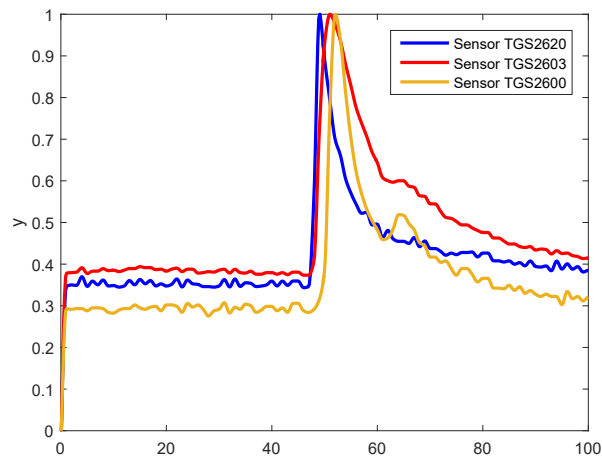


(b)

Figure 3.11 : The response curves of Sensor TGS2620, TGS2603, and TGS2600 for rotten meat odors in the second experiment, in which Figure 3.11a is of the raw time series data, and Figure 3.11b is of the preprocessed time series data.



(a)



(b)

Figure 3.12 : The response curves of Sensor TGS2620, TGS2603, and TGS2600 for burning cigarette gases in the second experiment, in which Figure 3.12a is of the raw time series data, and Figure 3.12b is of the preprocessed time series data.

Chapter 4

Rapid Disease Detection System

4.1 Introduction

Cancer is the second leading cause of death worldwide and is responsible for an estimated 9.6 million deaths in 2018 [205]. Globally, about 1 in 6 deaths is due to cancer [206]. Late-stage presentation and inaccessible diagnosis and treatment are common [207]. The probability for successful treatment strongly depends on when treatment is started, and the mortality can be reduced if cases are detected and treated early. The major problem for current delayed diagnosis is that most diseases can remain asymptomatic, therefore undetected, for a long period of time.

The research found that many diseases are linked to variations in human breath. There are hundreds of volatile organic compounds in human breath, and we release hundreds, even thousands of them every time we exhale. The analysis of these volatile organic compounds in our breath is called breath analysis. E-nose as a new frontier in disease detection has shown its great potential in non-invasive, rapid, and inexpensive analytical of volatile organic compounds from human breath.

Traditional standard volatile-compound detection methods techniques such as spectrometry and spectroscopy have been verified in clinical trials for diagnosing illnesses including cancer, multiple sclerosis, Parkinson’s disease, tuberculosis, diabetes, and more via breath tests. These complex analytical instruments usually are expensive to purchase, operate and maintain. They require labor-intensive operations by highly trained and skilled operating personnel. Such systems are usually not portable for use in clinical examination rooms, patient care rooms, or for emergency field situations. By contrast, the cheaper and more portable diagnostic devices, such as electronic-nose, can sense changes and differences in VOCs metabolite signatures (profiles) in diseased patients, compared with those of normal healthy individuals, to diagnose many different types of diseases. Thus it is worth developing a non-invasive, easy to access, and inexpensive electronic-nose system that patients can administer at home for early disease detection.

To overcome many of the deficiencies associated with the currently available diagnostic methods for lung cancer and facilitate clinical diagnostic processes. Our goal is to develop a cheaper, easy-to-use, portable e-nose system that can analyze the volatile organic compounds in human breath to discriminate lung cancer patients from healthy individuals rapidly and sensitively. Our system offers a potential means for non-invasive early diagnosis of LC, allowing earlier, more effective treatments, more rapid patient recovery, and shorter, less expensive stays for hospital care. The model of the proposed RDDS system is shown in [Figure 4.1](#).

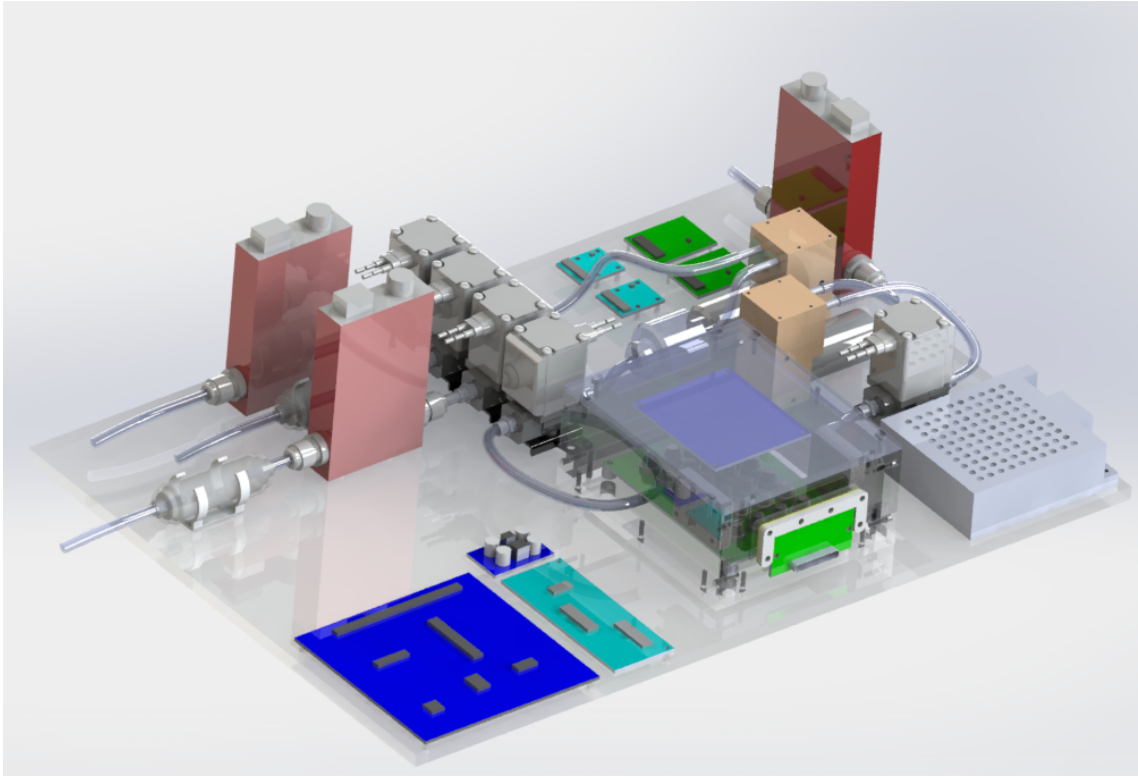


Figure 4.1 : The model of proposed RDDS system.

4.2 Overall System Architecture

The proposed architecture is based on the concept of mimicking the mechanism of the human respiratory system by a modular design that comprises several modules/function blocks in the e-nose. All modules can be controlled via a user interface to perform the instructions send by customers regardless of the electrical characteristics of each module, which makes it easy to use and does not require professional skills. Moreover, our design can provide extra auxiliary functionalities through ample reserved peripheral interfaces—for example, wireless communications module, camera, non-gas-related-sensors, and many more. RDDS is mainly for medical ap-

plications but not limited to only one application, which can be applied to other applications since the ideal all-purpose e-nose does not exist [19]. All the modules can be installed or uninstalled from the system, including the sensor array, which is the most significant part. With our self-designed sensor board, each sensor can be connected or disconnected from the e-nose in a plug-and-play fashion, enabling customized configuration based on the requirement.

The development of RDDS mainly comprises the following two aspects: hardware design and software design. The hardware architecture is the physical component in our platform, the design of which considers all of the system's present and foreseeable requirements. At the same time, the software serves as the interface between users and e-nose, which is intended as data acquiring from the system and transferring the information from users to control the system or adjust the work states of the system.

The functional block diagram of RDDS is shown in Figure 4.2. As is shown in Figure 4.2, the physical structure of RDDS has six parts: Power module, driver module, mechanical module, micro control unit (MCU) module, sample module, and sensor array module. The power module converts AC voltage into DC voltage, which supplies to the whole system. The drive module contains different kinds of driver circuits that are used to drive the mechanical parts, such as electronic valves, micro pumps, to name just a few. The mechanical module comprises by a series of physical actuators that perform actions to change the system status between the gas introduction, gas transferring, and gas exhaling. The MCU module is designed in the system, which serves as an instructor between e-nose and users.

Main components	Brand	Model
Power	Meanwell	LRS-35-12
Driver	RYHF	L298N
ADC	TI	ADS1115
MCU	STM	STM32F103
DCDC	SWIRFE	TPS5450
Valve	SMC	VX210CZ1D
Temperature/humidity/pressure sensor	APSM	BME280
Micro mini pump	XW Fluid	XW-802-BLDC

Table 4.1 : The brand and model of the main hardware models.

Specifically speaking, the MCU module controls the RDDS platform changing working status through setting operation parameters. Besides, it also provides a USB interface between the e-nose and personal computers. The sample module includes an analog-digital converter array, which acquires analog signals from sensors, converts them into digital signals, and sends them to the MCU module. The MCU module automatically collects these data and sends the data to personal computers. The sensor array module is the core part of the whole system, as it can produce related voltage signals regarding mixtures in different combinations and concentrations. The sensor array module and chamber design will be discussed in detail as a separate part in the following section. The brand and model of the main hardware models are listed in Table 4.1.

In the software design, two blocks will be discussed. The first part works in the e-nose platform, which is proposed to control whole hardware, gather data from sensors and send it to the user interface. Besides, the calibration algorithm is integrated to enhance the reliability of the system. The second part is on the personal computer that serves as a client terminal, from which the sensor response curves will be visualized for users.

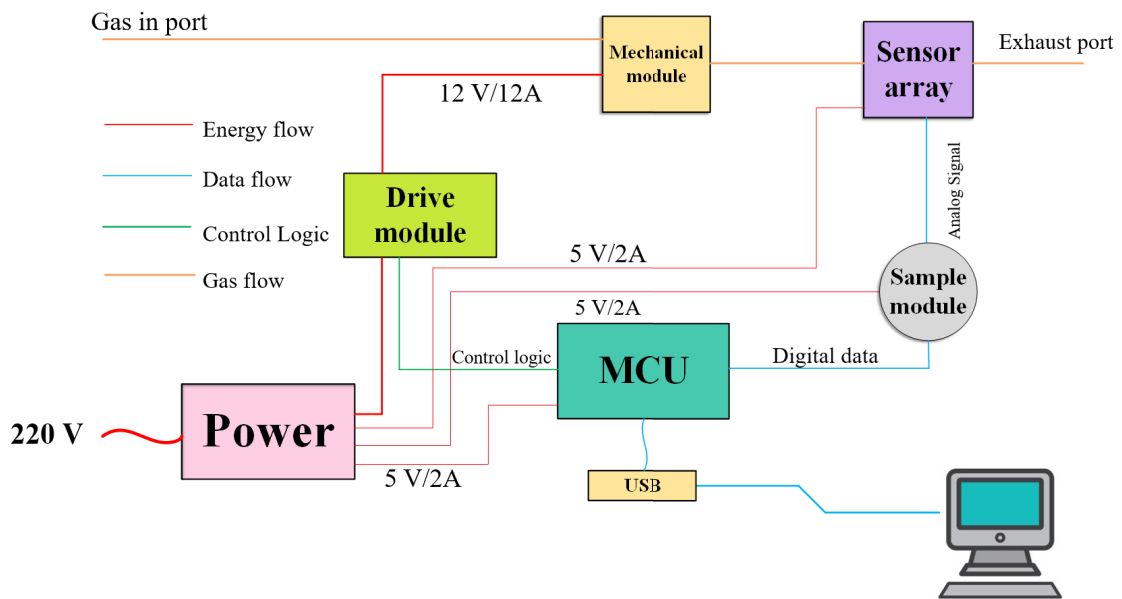


Figure 4.2 : Functional block diagram of RDDS.

4.3 MOS Sensor Array and Sampling Chamber

E-noses employ different types of electronic gas sensors, one of the most important modules in the whole system. There are mainly three types of gas sensors that have been widely used and investigated in e-nose: metal-oxide-semiconductor (MOS)

based gas sensors, surface acoustic wave(SAW) sensors, quartz crystal microbalance (QCM) sensors. MOS sensors, characterized by their fast response, small size, low cost, etc., have been commonly used in e-nose systems and the RDDS system. In this section, I will introduce the working principle for MOS sensors and sensor arrays. Then I will introduce the details about the selection of sensor array based on the lung cancer biomarkers. After that, I propose a signal detection circuit for sensor signal collection. Finally, the design of the detection chamber is introduced.

4.3.1 Working Principle of MOS Sensor and Sensor Array

Semiconductor sensors, also known as metal-oxide-semiconductor sensors (MOS sensors) [208], can detect gases by a chemical reaction between sensing material and target gases. MOS sensors have been viewed as one of the most promising sensor candidates for the e-nose system. This is due to the whole fabrication process of MOS-based gas sensors is inexpensive, while it has a high sensitivity, low power consumption, and a fast response/recovery rate. Normally sensors require heating up before testing. The electrical resistance of sensors is relatively high after heat up, but the sensor's resistance is decreased when it comes in contact with target gas. The change in resistance is used to calculate the gas concentration. Different metal oxide semiconductor materials mainly cause the properties of different sensors—the most common material used in semiconductor sensors including Tin, Sn, Zn, W, etc. The sensing properties of MOS sensors can be further enhanced by mixing various metal materials such as Pd, Pt, Ag, etc. At the same time, the selectivity and sensitivity will change accordingly. The sensors utilized in this work include TGS,

MQ series, and MOS sensors using the SnO_2 as the sensing material.

As is shown in Figure 4.3, the change in resistance of the MOS material caused by the target gas can be measured with a simple voltage divider circuit and a reference resistor.

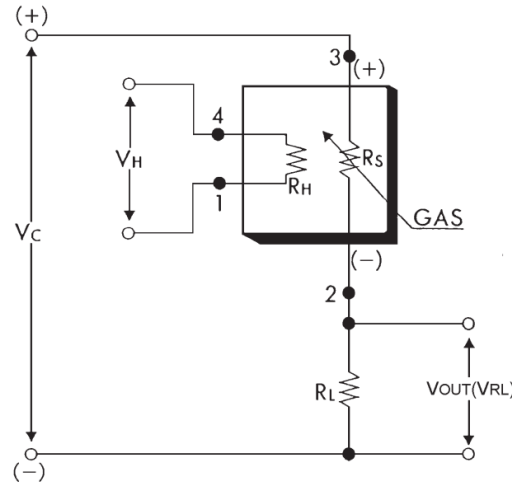


Figure 4.3 : Basic measuring circuit of MOS sensors.

where V_h denotes heater voltage and V_c is the circuit voltage. Normally $V_h = V_c = 5V$, R_s is sensor resistance. Circuit voltage (V_c) is applied to allow measurement of voltage (V_{out}) across a load resistor (R_L) which is connected in series with the sensor. Thus, measuring the resistance of the sensor (V_c) can be calculated by Eq. 4.1 using the value of V_{out} .

$$V_{out} = \frac{R_L}{R_L + R_s} \cdot V_C \quad (4.1)$$

4.3.2 The Design of Sensor Array and Sampling Chamber

The chamber and sensor array placed within the chamber is one of the most important modules in the whole system. It is the "Lab" inside the e-nose, and signals are collected from this module. Data generated from this module has a significant influence on the pattern recognition algorithm. Using cross-reactive sensor arrays with pattern recognition algorithms, a robust odor-discrimination system can be created.

MOS sensor array typically consists of a few individual sensors. Using cross-reactive, it can generate more information than a single sensor. The selection of sensor array for RDDS is critical. It should be sensitive enough to detect the presence of biomarkers related to disease while responding swiftly to slight changes in the concentration and combination in gas mixtures. Besides, it should also provide a consistent output that is specific to a given volatile organic compound. Ideally, the sensing module in e-nose for medical diagnosis on human breath should be extremely sensitive at a very low concentration of disease-related volatile organic compounds. After the sampling procedure, the volatile organic compounds are exhausted from the sensor array, and sensors should be quickly returned to the baseline and ready for the next test. The type and number of sensors should be carefully considered to ensure the information from biomarkers can be fully collected. This is because insufficient sensors may lead to the loss of important information; therefore, the algorithm developed based on the sensor array may not work under certain circumstances. It is worth noting that even combining all kinds of available sensors,

Sensor	Response characteristics	Type	Producer (Country)
TGS813	Methane, propane, ethanol, hydrogen, carbon monoxide	MOS	Figaro (Japan)
TGS822	Organic solvents such as methanol, ethanol, etc.	MOS	Figaro (Japan)
TGS2600	Air pollutants, cigarette smoke, methane, ethanol	MOS	Figaro (Japan)
TGS2602	Air pollutants, VOCs, ammonia, hydrogen sulfide	MOS	Figaro (Japan)
TGS2610C	Methane, ethane and other combustible gases	MOS	Figaro (Japan)
TGS2611C	Methane, ethane, carbon monoxide and other combustible gases	MOS	Figaro (Japan)
TGS2611E	Methane, propane, isobutane	MOS	Figaro (Japan)
TGS2620	VOCs, ethanol, organic solvent vapor	MOS	Figaro (Japan)

Table 4.2 : Response characteristics of eight metal-oxide semiconductor gas sensors.

there are still limits to the useful dimensions of the array. While redundant sensors raise the sensitivity, unimportant information amplifies the noise, which may lead to the poor performance of the pattern recognition algorithm. Considering the factors mentioned above, we choose 8 MOS sensors for our applications. The sensitivity characteristic of the sensors are listed in Table 4.2.

Considering the complexity and uncertainty in the clinical trial, we design a flexible sensor board(Figure 4.4) for the sensor array, which can be personalised for different gas sensors combinations to meet requirements that may arise during the experiment. Figure 4.5 shows the PCB design for our sensor board. These self-designed sensor array circuits can place up to 12 sensors on one board. Multiple boards can be used in the chamber, and due to the space limitation in our chamber, we only use two boards and up to 24 sensors in our system. Moreover, to monitor the inside of the chamber, humidity, temperature, and pressure sensor were used. The prototype of the sensor board is shown in Figure 4.6.

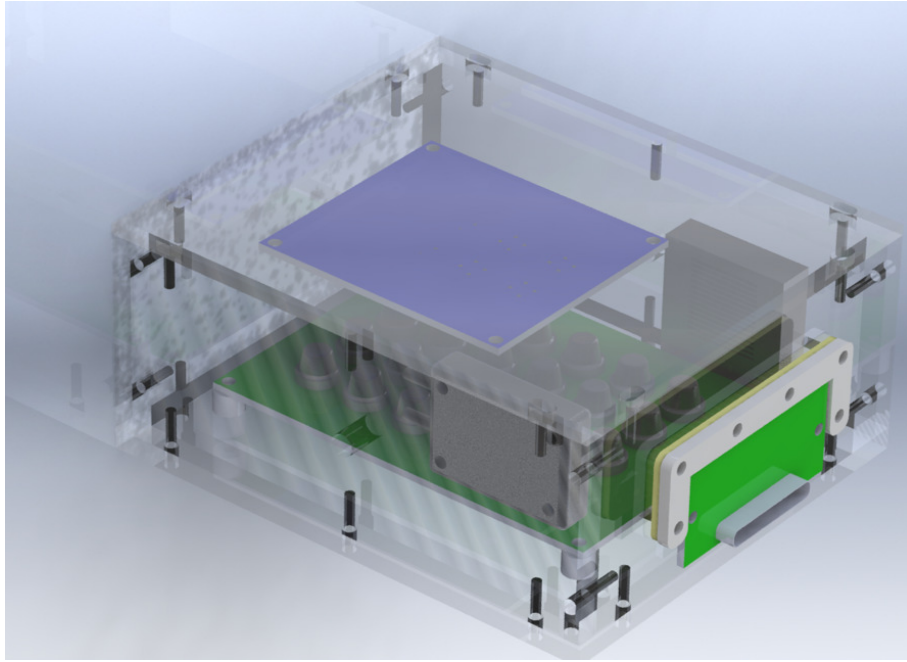


Figure 4.4 : Chamber design.

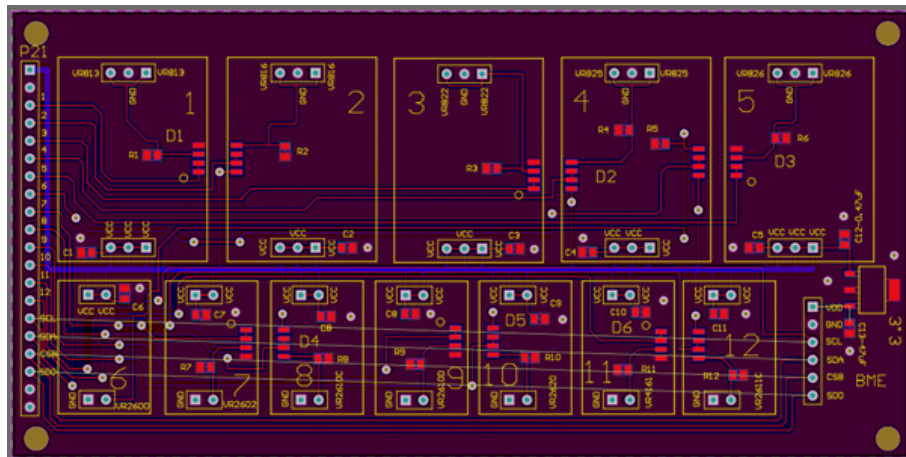


Figure 4.5 : PCB design for sensor board.

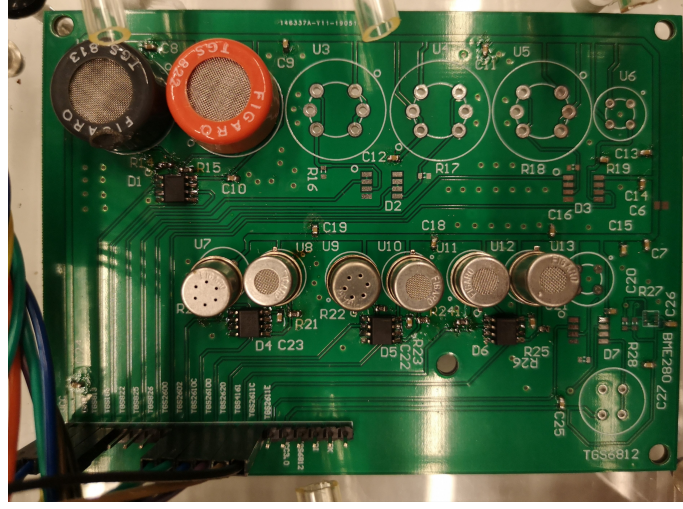


Figure 4.6 : The prototype of sensor board.

4.4 The Hardware Development of RDDS

In terms of hardware design, RDDS mainly consists of six parts: power module, drive module, mechanical module, micro control unit (MCU) module, sample module, and sensor array module. The hardware design of each module of RDDS will be discussed in detail.

4.4.1 Power-supply Design

Power-supply design and management for RDDS is an important part of the overall system. RDDS has a user-friendly design. Considering the power requirements for each module, the power supply module of RDDS can directly convert 110 220V AC voltage into 12V/5V DC voltage. 12V DC voltage is used to supply the drive module. The 5V DC voltage is used to supply the MCU module, sensor array

module, sample module. The current out ability is considered, which is designed to 12A for the driver module and 2A for the other five modules. The power supply module is shown in Figure 4.7.

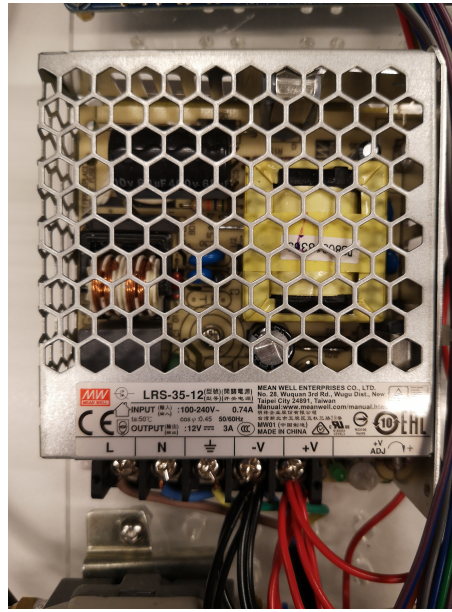


Figure 4.7 : Power-supply Design.

4.4.2 Driver Module Design

This part is focusing on the design of the driver module. Considering the voltage-current requirement of each mechanical part, the driver module is designed with a large nMOS transistor. nMOS transistor serves as a switch under the control signal from MCU. The power supply for nMOS is 12V DC. There are two working conditions for the nMOS. First, when the control signal is low, the nMOS will shut down, and there is no output. Second, when the control signal is a high voltage, the transistor will work as a small resistor, and the 12V DC supply voltage will directly

float into the mechanical module. Besides, to prevent overload and overcurrent problems, protection circuits are integrated. Figure 4.8 shows the final design.

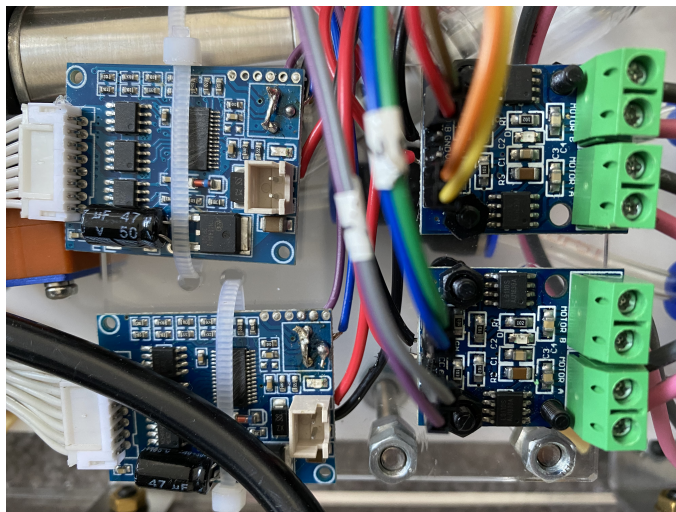


Figure 4.8 : Driver module design.

4.4.3 Mechanical Module Design

The mechanical module is intended for gas compounds delivery, which in combination with control logic, has a critical influence on how the airflow from the source of volatile aromatic molecules is transferred and interact with the sensor array and therefore affects the performance of following pattern recognition algorithms. Specifically, there are mainly four stages before the volatile aromatic molecules transfer to the sensing module. First, gas is introduced into the system, and then gas is pumped into the "airway" of our RDDS to ensure the stability of the mixtures. After that, the mixture will flow into the chamber and interact with the sensor array, and the data will be sent to the user interface for further analysis. Lastly, the gas will be

”exhaled”. Those procedures can be achieved by various valves, pumps, and mass flow controllers. The mechanical connection topology designed in this work is shown in Figure 4.9. In this work, five solenoid valves, two MFCs, three vacuum pumps are used. The control signals can be sent to each mechanical component with our user interface according to the customer control logic. The experiment results show that all mechanical parts can work properly regarding various requirements as expected.

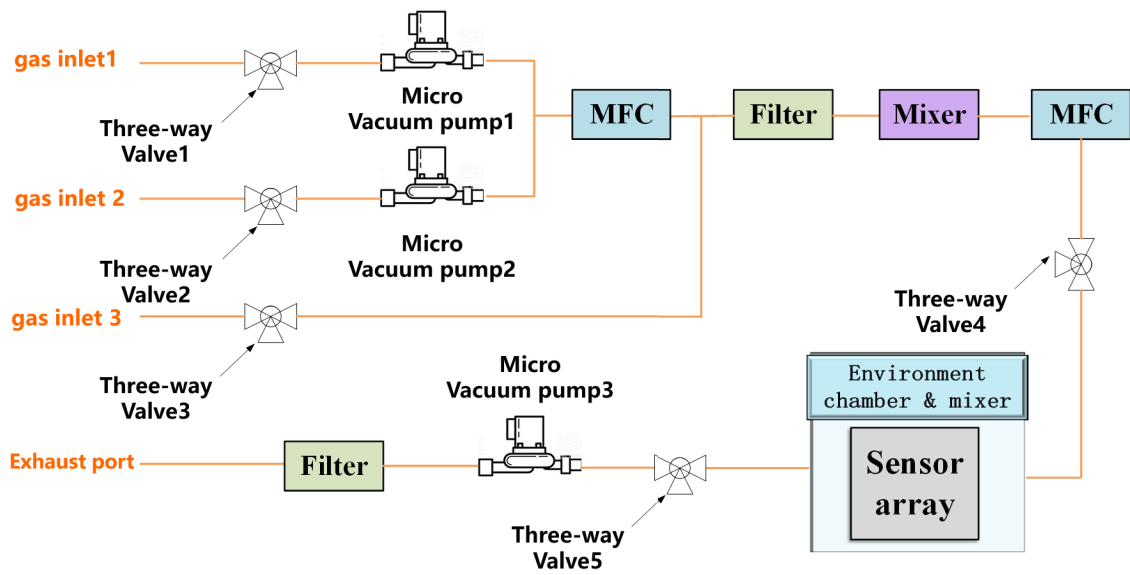


Figure 4.9 : Mechanical module design.

4.4.4 MCU Module and Sample Module

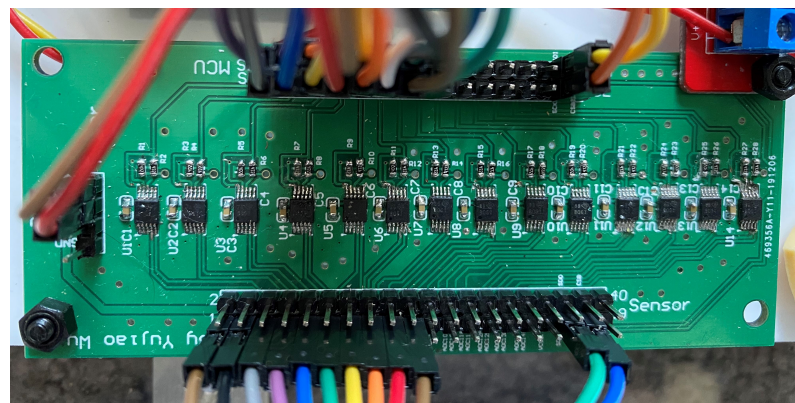
Regarding MCU design, to incorporate all the hardware sources designed in the system and prepare enough for the possible supplementary parts, we use the STM32F101 micro-controller in our work. This micro-control unit can control all modules required in the RDDS as well as provides numerous peripheral interfaces. We use

RS-232 as the communication protocol between MCU and the user operating system. Since most personal computers have a USB port, a USB to RS232 chip is used to make it easier for users.

For the sample module, fourteen ads1115 chips were designed in sample module. Every ADC can be configured in different modes to meet the requirements regarding multiple application scenarios. The final design is shown in Figure 4.10.



(a)



(b)

Figure 4.10 : Figure 4.10a shows the design of MCU module. Figure 4.10b shows the the design of sample module.

4.5 The Software Development of RDDS

The software design of RDDS will be introduced from two aspects: one is on the user interface, and another is in MCU. The software structure is shown in Figure 4.11.

The first part is designed on the personal computer and served as a user interface. RDDS can be easily controlled through the user interface. Just by a simple click on the user interface, the instructions will be sent to RDDS. Meanwhile, it also can be used as a monitor to keep track of the real-time working conditions of e-nose and make changes accordingly. Finally, once the sampling procedure is finished, the user interface will automatically receive and record the data.

The second part is designed on MCU, and it can be further categorized into three functions: mechanical driver function, sampling control function, and data transfer function. The mechanical driver function is intended to receive the parameters configured from the user and work accordingly. The sampling control function is mainly for the sensor array configuration. The data transfer function uses the universal asynchronous receiver transmitter (UART) protocol along with a UART to USB chip.

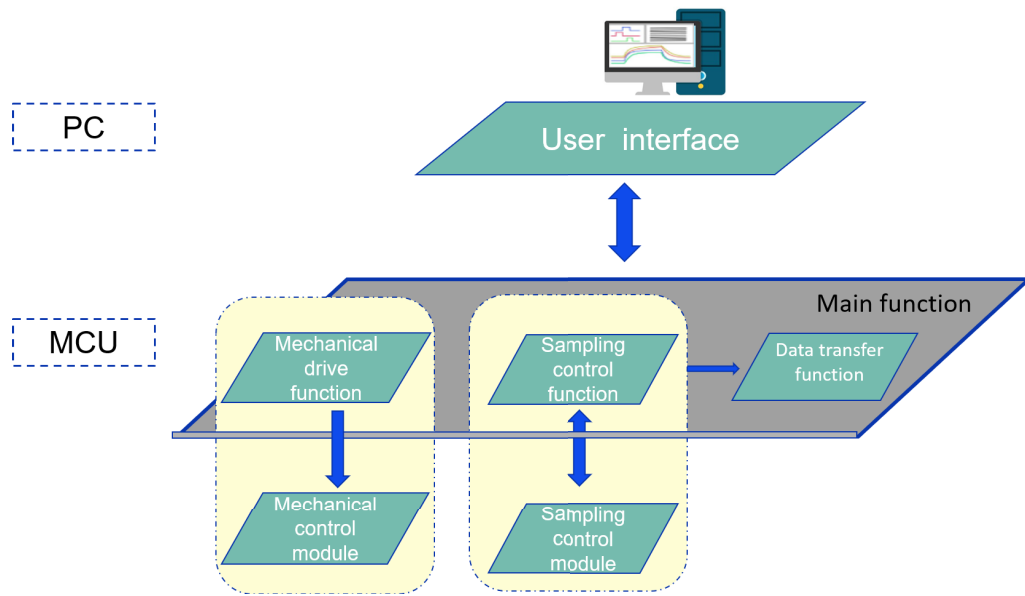


Figure 4.11 : Mechanical module design.

4.6 A Simple Calibration Method for E-nose System

After the realization of the RDDS system, the first step is to perform system calibration. The reason for calibration is that since RDDS is designed for breath analysis in the medical field, however, in real-world clinical practice, multiple devices based on the identical design will be used in different clinics. Thus, it is essential to perform instrument calibration before the sampling procedure to ensure the data is reproducible and reliable in future analysis. To be specific, there are mainly three reasons:

- To alleviate the effect from the inherent variability of sensors.
- To improve reproducibility and standardization by drift counteraction.

- To minimize the measurement uncertainty and ensuring the accuracy of the device.

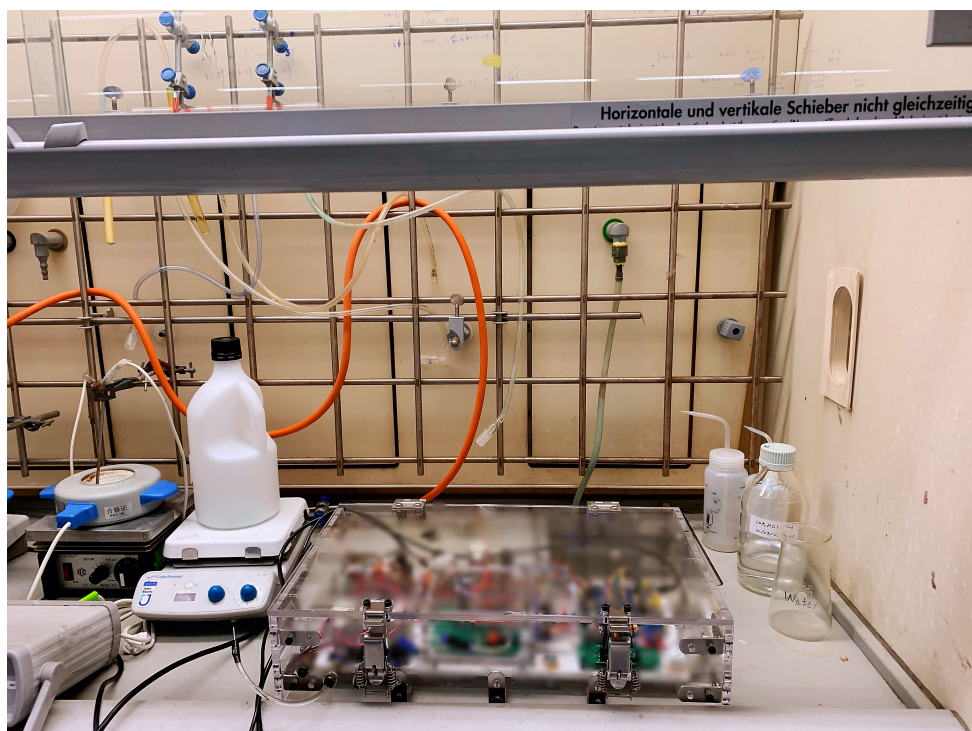


Figure 4.12 : The experiment regarding RDDS system is performed in UTS chemical lab.

As is shown in Figure 4.12, we perform the experiments regarding the RDDS system in UTS science chemical lab and collect the data accordingly.

4.6.1 Experimental Setup

We design an experimental procedure for RDDS to acquire continuous responses of an 8-sensor array while the gas conditions are controlled. First, we need to prepare the standard gases. While standard gas is prepared well and ready for further

measurement, the RDDS instrument requires heating up before testing. Then, we set up the time interval for each sampling stage on the user interface then the sampling procedure starts. The whole system is fully operated by a computerized environment that can generate more accurate and reproducible data. The sensors' responses were acquired continuously at 50Hz throughout the complete experiment. After the instrument finishes the whole testing procedure, gathered data is automatically uploaded to the user, and the last step is the system cleaning and preparing for the next test.

4.6.2 Calibration Theory – Time Response of Sensor System

A sensor system can be described by a first-order dynamic system. The basic form of a first-order dynamic system $G(s)$ is given by:

$$\tau \dot{y}(t) + y(t) = ku(t) \quad (4.2)$$

$$G(s) = \frac{Y(s)}{U(s)} = \frac{k}{\tau s + 1} \quad (4.3)$$

where τ is the time constant, k is DC gain.

To determine a sensor system is good or bad is mainly based on two criteria. First, the dynamic response should be fast. Second, the steady-state error should be small. Based on the dynamic and steady-state properties, a sensor system can be fully described. As is shown in Figure 4.13, for the input, we normally adopt a step

input. Based on the step input, we can observe the properties of the corresponding step response. And the step response can also reflect the characteristics of a sensor, so we can know how fast the system is, when the peak time is, we can also know what the steady-state gain is. Normally, if the sensor is good enough, the steady-state gain should be 1, and the time constant is short.

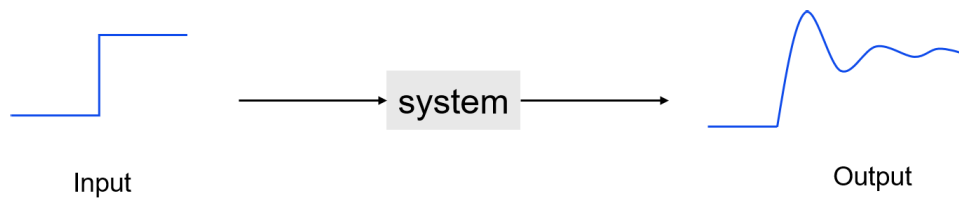


Figure 4.13 : The experiment regarding RDDS system is performed in UTS science chemical lab.

Through experiments, we can get the steady-state response. Based on the steady-state response, we can get the two parameters: time constant and DC gain. The time constant can describe the response time, as is shown in Figure 4.14, which is a first-order model τ stands for the time constant, we want to τ to be as small as possible, at the same time we also calculate the dc gain which in this Figure 4.14 is K .

However, sometimes the system has some delays. Let $G(s)$ be a first-order system with time delay:

$$G(s) = k \frac{1}{\tau s + 1} e^{-\theta s} \quad (4.4)$$

where k is the gain, τ is the time constant, and θ is the time delay in the system.

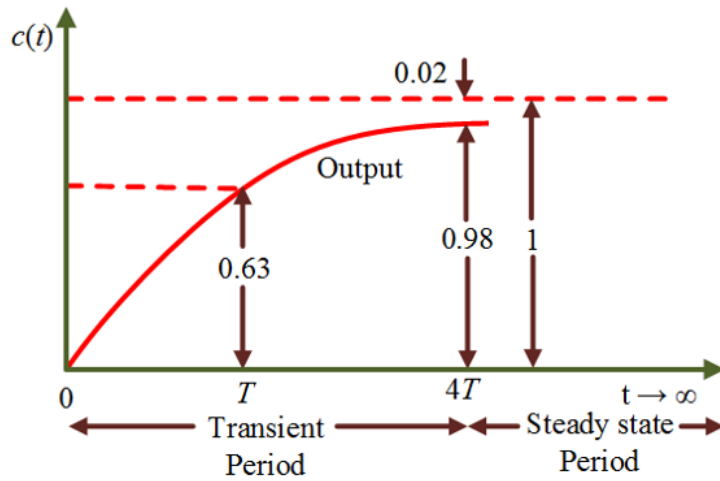


Figure 4.14 : Unit step input time response of a first order system. *Image source: ElectricalWorkbook*

To be specific, there is a gas path in our e-nose system, and it will take some time before the sample gases arrived at the sensor chamber. And this delay is not the fundamental response of the sensors, as it is related to many other types of equipment within the e-nose. In this case, for a system, we also need to know the θ , but θ is not sufficiently related to sensors. If the sensor is designed well, the θ can be very small, which can be negligible. In our work, we get the model, and we calculate the delay, but we will only identify it because it is not related to the sensor. Figure 4.15 shows a step response specification of the RDDS system.

4.6.3 Results and Conclusions

We perform all the experimental data on the system identification in Matlab to identify the two parameters. As is shown in Table 4.3, we can finally get the time

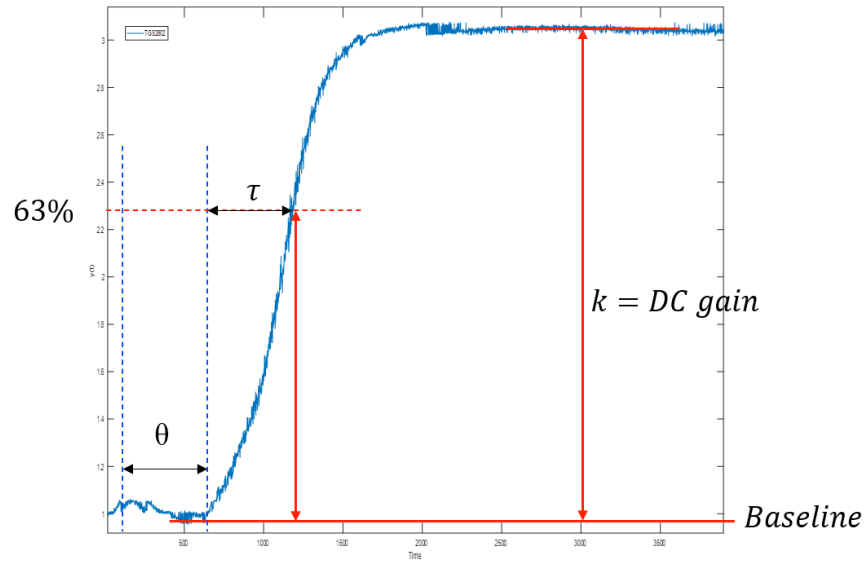


Figure 4.15 : The step response specification of RDDS system.

	τ	k	$G(s)$
Sensor1	10.021	3.026	$G(s) = \frac{3.026}{10.021s+1}e^{-\theta s}$
Sensor2	8.523	2.9591	$G(s) = \frac{2.9591}{8.523s+1}e^{-\theta s}$
Sensor3	9.02	1.0257	$G(s) = \frac{1.0257}{9.02s+1}e^{-\theta s}$

Table 4.3 : The step response specification of RDDS system.

constant and steady-state gain and also the transfer function for each sensor.

4.7 Summary

In this chapter, to address the many deficiencies associated with the currently available e-nose system, further explore the diagnostic potential existing in e-nose, an

original rapid disease detection system named RDDS is developed. RDDS is a fully automatic, non-invasive, and portable e-nose system to analyze volatile organic compounds in exhaled breath. Although, due to Covid-19, we are unable to perform clinical trials to validate our system, RDDS has the potential to provide a complementary method for a non-invasive and inexpensive way to detect lung cancer and lung-related disease. Besides, regarding RDDS, we proposed a simple calibration to ensure the reproducibility of experimental data from multi-clinics. The prototype of the RDDS system is shown in Figure 4.16. Furthermore, there are several potential problems of the proposed system that need to be improved:

- Despite the fact that the current e-nose system can perform well under laboratory circumstances, the variation of VOCs humidity, especially relative humidity (RH) variation, imposes numerous problems for analysing real-world breath samples. For example, it may result in a decrease in detection accuracy. Therefore, dehumidification techniques and algorithms will be proposed in the system. In the future, algorithms will be developed to ensure the stability of classification accuracy with the RH changes. Moreover, it can be generalised to other e-nose systems that are severely affected by variations in humidity.
- As the concentration of many breath samples is in the ppbv to pptv level, future accurate breath testing systems will incorporate modules that can amplify the signals generated by the disease biomarkers. Moreover, under practical clinical conditions, there are a great variety of different sampling conditions that greatly influence the response of disease biomarkers. Therefore, to main-

tain detection accuracy, ambient environment noise elimination as well as the broad range of sampling conditions and protocols standardisation are key issues which need to be addressed.

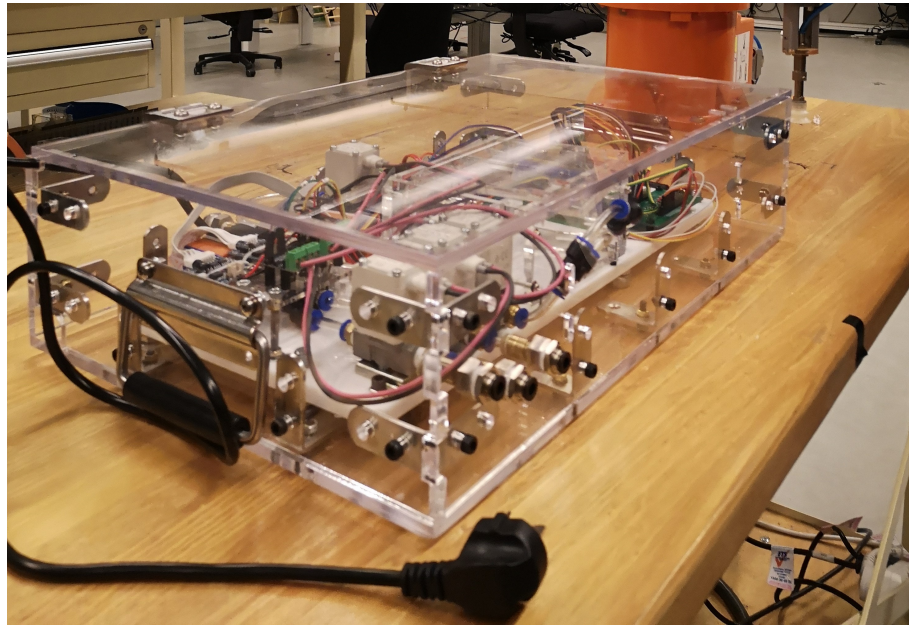


Figure 4.16 : The prototype of RDDS system.

Chapter 5

DeepMMSA: A Novel Multimodal Deep Learning Framework for Non-small Cell Lung Cancer Survival Analysis

Lung cancer is the leading cause of cancer death worldwide. The critical reason for the deaths is delayed diagnosis and poor prognosis. With the accelerated development of deep learning techniques, it has been successfully applied extensively in many real-world applications, including health sectors such as medical image interpretation and disease diagnosis. By combining more modalities that being engaged in the processing of information, multimodal learning can extract better features and improve predictive ability. The conventional methods for lung cancer survival analysis normally utilize clinical data and only provide a statistical probability. To improve the survival prediction accuracy and help prognostic decision-making in clinical practice for medical experts, we for the first time propose a multimodal deep learning method for non-small cell lung cancer (NSCLC) survival analysis, named DeepMMSA. This method leverages CT images in combination with clinical

data, enabling the abundant information hold within medical images to be associate with lung cancer survival information. We validate our method on the data of 422 NSCLC patients from The Cancer Imaging Archive (TCIA). Experimental results support our hypothesis that there is an underlying relationship between prognostic information and radiomic images. Besides, quantitative results showing that the established multimodal model can be applied to traditional method and has the potential to break bottleneck of existing methods and increase the the percentage of concordant pairs(right predicted pairs) in overall population by 4%.

5.1 Introduction

Lung cancer is the leading cancer killer in both men and women in the world, representing 19.4%–27% of all deaths from cancer [209]. It can be broadly classified into non-small cell lung cancer (NSCLC), counting for 85% and small cell lung cancer (SCLC), counting for the remaining 15%. Lung cancer has a poor prognosis. The lung cancer five-year survival rate is lower than many other leading cancer sites, such as colorectal (64.5%), breast (89.6%), and prostate (98.2%) [11]. More than half of people with lung cancer die within one year of being diagnosed [11]. Accurate assessment of the disease stage and survival time of lung cancer is essential in deciding the optimal plan and timing treatment for the clinicians.

Nowadays, a large fraction of interpretation of medical information is performed by medical experts. In terms of image interpretation by human experts, a lot of diagnostic errors appear in radiology. Approximately 20 million radiology reports

contain clinically significant errors each year [44]. This limitation is mainly due to the subjectivity, the fatigue of the expert, the complexity of the image, as well as the extensive variations across different interpreters [210]. Moreover, 2/3 of the world population lacks adequate access to radiology specialists; this would translate to 4.7 billion people.

Artificial intelligence (AI) is a promising tool that has shown its efficacy for diagnostic purposes[192, 211, 212]. With the rapid development in deep learning-based computer vision, its ability to recognize images or diagnose pictures even exceeds human ability [213–215]. The CNN is the most frequently used deep learning technique. In the last few years, image analysis by deep learning or CNNs has been utilized in low-dose lung CT for early diagnosis, which dramatically decreases the lung cancer mortality rate. To be specific, it enabled computer vision models to assist the doctors to detect suspicious pulmonary nodules or identify the location of the nodule, evaluate whole-lung/pulmonary malignancy, classify candidate nodules into benign or malignant, and predict the risk of lung cancer [192, 216–222]; in some cases, the models have reached competitive performance to doctors, and the accuracy even exceeds the doctors[212, 223–226].

Although AI in combination with CT scans is a promising tool that has shown its utility for diagnostic purposes, it has rarely been used in predicting death, and possibly even determining death, which is a unique and challenging area that could be fraught with the same biases that affect analog physician-patient interactions. Current research for NSCLC survival analysis is largely based on the statistical analysis of clinical data. Traditional approaches generally utilize clinical information

such as age, clinical TNM stage, gender information, etc. In the work of [190], which uses CT images in survival analysis. But the model only learns 2D features from each tumor image slice separately, afterward, the averaged features from all image slices are calculated for every single patient and overlook the third-dimensional properties of the tumor. Moreover, the overall performance of currently available works for survival analysis is considerably low.

By contrast, deep learning has the potential to reduce diagnostic errors and overcome human limitations. Thus, it is worth developing a fully automated deep learning framework for NSCLC survival prediction based on CT images and clinical data to explore whether the deep learning techniques have the ability to extract useful information from CT images and clinical data to predict death. In our work, considering the 3D nature of CT images, in order to reveal the underlying relation between prognostic information and CT images, to fully utilize the potential of the prognostic power existing in the radiomic data, we design a 3D multimodal Resnet framework for NSCLC survival analysis. Since combining CT image and clinical data could provide comprehensive and supplementary information to describe the cancer status, this framework could indicate a more accurate overall trend of survival. To our best knowledge, this is the first time to develop a multimodal deep learning framework based on 3D features extracted from lung CT images fused with features extracted from clinical data for death prediction. Quantitative results on the NSCLC- Radiomics data show that the proposed method could surpass the state-of-the-art methods by 4% on concordance, revealing that our method could provide more accurate diagnosis and prognostic decision-making in future clinical

practice. The results of ablation experiments show that using multiple modalities improves the biggest marginal performance compared with using a single modality.

After we designed the model, we use the concordance statistic to evaluate our method. Concordance, or synonymously the C-index, is one of the most popular performance measures in accessing survival models [227–229]. It measures the discrimination ability of a model in survival analysis[230]. C-index refers to the proportion of pairs whose predicted results are consistent with actual results among all patient pairs. For instance, the C-index is increased by 1% implies that if a survival analysis is made for a population of one million people, the correct prediction will increase the number of people by four thousand. Quantitative results show that the established multimodal model can be applied to the traditional method and it has the potential to break the bottleneck of existing methods and increase the percentage of concordant pairs (right predicted pairs) in the overall population by 4%. Revealing that discrimination of proposed model is improved. And can provide a more accurate prognostic decision-making in future clinical practice. The results of ablation experiments show that using multiple modalities improves the biggest marginal performance compared with using a single modality.

To conclude, we mainly have the following contributions:

- The proposed method overcomes the weakness of traditional non-parametric methods (KM etc.), which cannot incorporate multiple variables.
- Experiment results show that our method could surpass the SOTA methods (Cox-Time etc.) by 4% on concordance.

- To our best knowledge, this is the first attempt to reconstruct a deep 3D convolutional-based model and using images for survival analysis.
- Experiment results support our hypothesis and reveal the underlying relation between prognostic information and radiomic images.
- Our multimodal framework can provide more accurate survival analysis with sufficient granularity for personalised prognosis and decision-making compared to SOTA methods.

5.2 Methodology

In this section, we describe details about the proposed DeepMMSA. As far as we know, this is the first work to use a multimodal deep learning framework to process CT images together with clinical information for NSCLC survival analysis.

5.2.1 The Structure of DeepMMSA

Inspired by the recent successful applications of CNNs in NSCLC diagnosis and other image recognition tasks, we proposed a DeepMMSA that harnesses the strategies of analysing the combined information from multiple modalities. As shown in Figure 5.1, we use the tumor region of interests (ROIs), which is the lesions on CT scans as low-level image input. Motivated by the work of [192], 3D CNNs were used to extract features from all three-dimensional directions within the tumor volume. Meanwhile, we integrate the clinical information through a 27-dimension high-level clinical layer,

the input of which includes screening test results such as clinical TNM stage, overall stage, histology, gender, age of the patient. The clinical layer is embedded in the hidden layer directly.

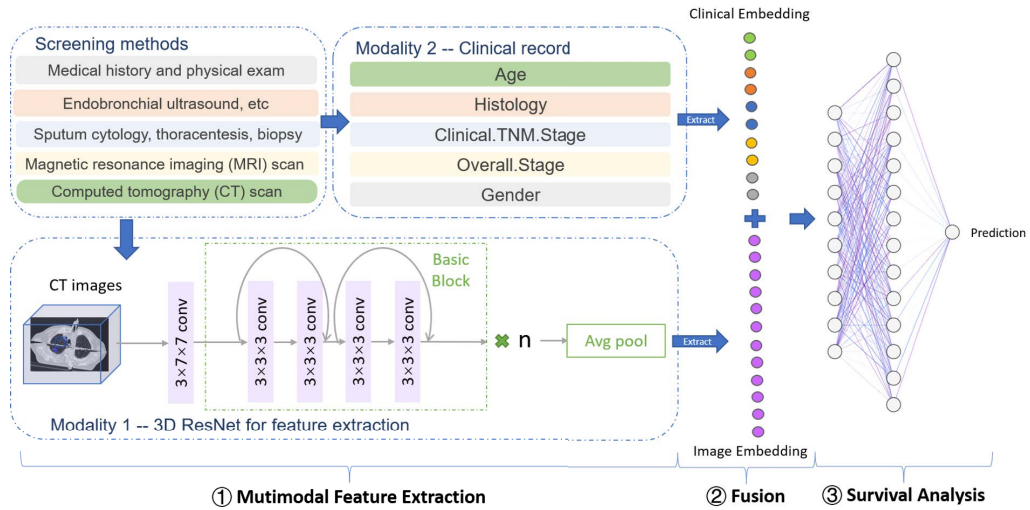


Figure 5.1 : The framework of deepMMSA. DeepMMSA mainly has three modules: (1)First, it employs the 3D-ResNet in combination with plain networks for multimodal feature extraction; (2) Then, it uses simple feature fusion method (early fusion) for multimodal fusion; (3) Lastly, during decision making stage, multiple-layers Perceptron (MLP) is designed for the survival prediction.

DeepMMSA framework consists of three modules:

- Multimodal feature (CT image features and Clinical record features) extraction.
- Multimodal feature fusion.
- Survival analysis.

5.2.1.1 Multimodal Feature Extraction

5.2.1.1.1 CT Images Feature Extraction with 3D-ResNet As is shown in Figure.5.1 our framework requires two multimodal inputs, CT images, and clinical data from the regarding patients. To be specific, CT images are introduced to the radiomics embedding layer and clinical data are introduced to the clinical embedding layer. We adopt 3D-ResNets as our network structure for the low-level image feature learning. As shown in Figure 5.1, 3D-ResNets can be built by basic blocks or "bottleneck" building blocks, the number of which may vary from 18 to 152 in the whole network. For instance, 3D-ResNet-18 contains four basic blocks, and each block contains four convolutional layers (conv1-conv4). Compared with 2D ResNet, features are extracted in all three-dimensional directions within the tumor volume with 3D ResNet, therefore taking the third-dimensional spatial information into consideration [166]. It is worth noting that, in order to eliminate the gradient vanishing and exploding problems in the very deep neural network, extra shortcut connections were added in the model. The advantage of such residual learning is that it enables the reuse of features. Since the dataset is relatively small compared to other general datasets for image recognition, data augmentation techniques were used before importing the data into the model.

The formulation of the residual building block is,

$$o = \mathbf{F}(x) + x \quad (5.1)$$

in which $\mathbf{F}$ is the deep residual function, x, o are the input and output.

5.2.1.1.2 Clinical Record Feature Extraction The clinical embedding layers introduce clinical data to the network separately aims to capture the survival information indicated within clinical data. For clinical data, a neural network with two hidden layers was proposed to extract features. As is shown in Figure.5.1, the 27-dimension non-image features were extracted by a network, which in combination with the image features is processed in the later fusion stage.

5.2.1.2 Multimodal Feature Fusion

During the feature fusion stage, multimodal features from CT images and clinical records are difficult to be directly fused together. This is due to the features from different modalities have different scales or statistical properties. Thus, to solve this problem, the Batch Normalization (BN) technique is used to adjust extracted features in each modality before the fusion procedure. Given the features $z_1, z_2, \dots, z_m$ over a batch, $\hat{z}_i$ is calculated as:

$$\hat{z}_i = \gamma_i \frac{z_i - \mu_i}{\sqrt{\sigma_i^2 + \epsilon}} + \beta_i \quad (5.2)$$

where γ_i, β_i are the parameters to be learned, μ_i is the mean value of z_i over the batch, σ_i is the standard deviation of z_i over the batch, ϵ is set to a very small number such as 10^{-8} .

5.2.1.3 Survival Analysis

Survival analysis is the last module in the framework and is intended as an overall feature analysis to get the final survival time prediction. In this module, to meet

the requirements for a specific problem, any survival analysis model can be used. It can be models either from traditional statistical methods, such as the Kaplan-Meier model, Cox regression model, or from novel ML methods, such as survival trees, and deep neural networks. All the mentioned models can be used to analyze the input from multimodal features in our proposed fusion layer. In this work, we define the survival time as the label, and use the one hidden layer neural network with one dimension output layer for the regression setting and overall optimization convenience. Additionally, in order to achieve the same scale between ground truth and the output in our model, the Sigmoid function is used as a normalization technique to process the output.

$$\hat{T}_i = \frac{1}{1 + e^{-f(x_i)}} \quad (5.3)$$

and we use MSE loss function and $L2$ regularization penalty term as the objective function, which is defined as:

$$\text{minimize } L = \frac{1}{N} \sum_{i=1}^N (T_i - \hat{T}_i)^2 + \lambda \sum_{j=1}^M w_j^2 \quad (5.4)$$

where w_j is the model parameter and the total number is M . λ is the penalty coefficient.

5.3 Experiments

Extensive experiments are conducted based on NSCLC patients from TCIA to validate the performance of the DeepMMSA with several state-of-the-art methods in

terms of the prediction accuracy for the survival time for patient. Besides, concordance is used to evaluate the prediction result. Afterward, we perform several ablation experiments regarding different network structures to determine the best structure.

5.3.1 Dataset

The proposed method was trained and tested with the data of 422 NSCLC patients from The Cancer Imaging Archive to evaluate the performance. For these patients' pretreatment CT scans, manual delineation by a radiation oncologist of the 3D volume of the gross tumor volume and clinical outcome data are available [231]. The corresponding clinical data are also available in the same collection. The patients who had neither survival time nor event status were excluded from this work.

5.3.2 Data Preprocessing

For CT images, we resize the raw data, which is the 3D volume of the primary gross tumor volume into $96 * 96 * 8$. After that, we transform the range linearity into $[0,1]$. Then, to prevent overfitting, we perform data augmentation, which includes three methods: rotate, swap, and flip. Then we get $422 * 8 = 3376$ samples, among which there are $373 * 8 = 2984$ uncensored samples and $49 * 8 = 392$ censored samples.

Clinical data contains categorical data and non-categorical data. Firstly, missing value is a common problem in medical data and may pose difficulties for data analysing and modeling. Specifically, in our dataset, the "age" category contains a

few missing values. After observing the data, we find that the age of patients in the dataset is close to each other. Thus, we impute the mean value and fill it into the missing value. Afterward, in order to fit into the model, one-hot representation is used to digitizes the categorical data, so that the data could be easily processed by the network.

Then, we use the min-max feature scaling method and standard score method to perform data normalization, such as age and survival time. For input x , the min-max feature scaling method's output is:

$$x' = \frac{x - x_{min}}{x_{max} - x_{min}} \quad (5.5)$$

and the standard score method's output is:

$$x'' = \frac{x - mean(x)}{std(x)} \quad (5.6)$$

where std is the standard deviation.

For a single patient with multiple tumors, we select the primary gross tumor volume ("GTV-1") to be processed in our work, while other tumors such as secondary tumor volumes denoted as "GTV2", "GTV3" to name just a few, which were occasionally presented, were not considered in the dataset.

5.3.3 Experiment Setup

We train and evaluate the framework on the NSCLC-Radiomic dataset following 5-fold cross-validation with the patient-level split. We divided the dataset into training, validation, and testing data into 6:2:2 respectively. For hyperparameters

tuning, such as the penalty coefficient[232], we use the validation dataset to fine-tune and get the optimised hyperparameters. In the training process, we use 200 epochs in total with Adam[233] as the optimizer. The batch size parameter is set as 64. The initial learning rate[234] is set as 0.001, then the learning rate is decayed by 0.5 in every 40 epochs.

Since we use survival time as the label, not cumulative hazard, in the training and validation process, we only use the uncensored data for precise survival time and objective function calculation, and in the testing process, we use all data for concordance evaluation and uncensored data for MAE evaluation.

Since this is the first work to use a multimodal framework for NSCLC survival analysis, we implement several state-of-the-art survival analysis methods as baselines to compare with our work. The baseline methods include Cox-time [182]), DeepHit [181], CoxCC [182], PC-Hazard [183] and the regular cox regression.

5.3.4 Ablation Study

To find an optimal network for our problem, we consider performing ablation experiments based on the following four aspects of network architecture:

- Whether multiple modalities outperform single modality?
- How the depth of Resnet affect the performance? Which 3D structure is the best?
- What is the best ratio set between image data and clinical data in the fusion

stage?

- Whether hidden layers should be added in the survival analysis stage?

Firstly, the evaluation of different depths of Resnet and whether multiple modalities are better than a single modality are conducted. By using one hidden layer in the survival analysis network and fixing the ratio of multiples modalities features in the fusion stage to 512:27, four different structures were tested. Table 5.1 shows that our model of r3d34 structure with multiple modalities achieves the best performance. All ablation results support our assumption and show the effectiveness of using multiple modalities in survival analysis.

Moreover, using the best structure r3d34, we step further to investigate the effects of changing the ratio between modalities with and without the hidden layer. It can be done by changing the number of perceptrons for image and non-image features. The comparison results listed in Table 5.2 shows that setting the ratio between images and non-image modalities as 25:27 achieves the best performance. Besides, adding hidden layers in the survival analysis module can further improve the performance. From ablation experiments, the best framework architecture of using r3d34 structure, setting the ratio between multiple modalities as 25:27 with one hidden layer outperform the other structures in this work.

The results indicate that NSCLC prognosis information can be learned from CT images. Using a multimodal structure, more information can be jointly extracted and learned from various information sources and non-linearly transformed into a deep network, therefore improve the overall prediction accuracy. Furthermore, using

	CT images		Multi-modality	
	Loss	C-index	Loss	C-index
r3d18	0.1023	0.5782	0.0847	0.6287
r3d34	0.0975	0.5942	0.0757	0.6490
r3d50	0.1026	0.5804	0.0760	0.6375
r3d101	0.1071	0.5660	0.0795	0.6142

Table 5.1 : To evaluate the performance of different ResNet structure and effect of whether using multiple modalities.

multiple modalities improves the biggest marginal performance compared with using single modality.

5.3.5 Results

The losses in the training and testing are shown in Figure 5.2. For a fair comparison, five state-of-the-art methods are performed as baseline methods from previous works for survival analysis. As shown in Table 5.3, we compare our framework and with the other five baseline models. The results show that our framework achieves the best performance. Besides, the results verify that compared to the methods(Cox-time, DeepHit, etc.) which simply use clinical data, DeepMMSA shows its superiority of effectively extracting the supplementary information from multiple modalities and can significantly improve the prediction accuracy.

	Hidden		No hidden	
	Loss	C-index	Loss	C-index
512:27	0.0757	0.6490	0.0760	0.6376
100:27	0.0745	0.6512	0.0755	0.6421
25:27	0.0739	0.6580	0.0761	0.6450
5:27	0.0765	0.6403	0.0793	0.6215

Table 5.2 : To evaluate the effects of different ratios between modalities features in fusion procedure and the performance of survival analysis neural network with or without hidden layer.

Model	MAE	C-index
Cox-time	0.183	0.6152
Cox regression	0.204	0.6009
CoxCC	0.183	0.6120
PC-Hazard	0.191	0.6094
DeepHit	0.183	0.6133
DeepMMSA	0.162	0.6580

Table 5.3 : Result vs baselines.

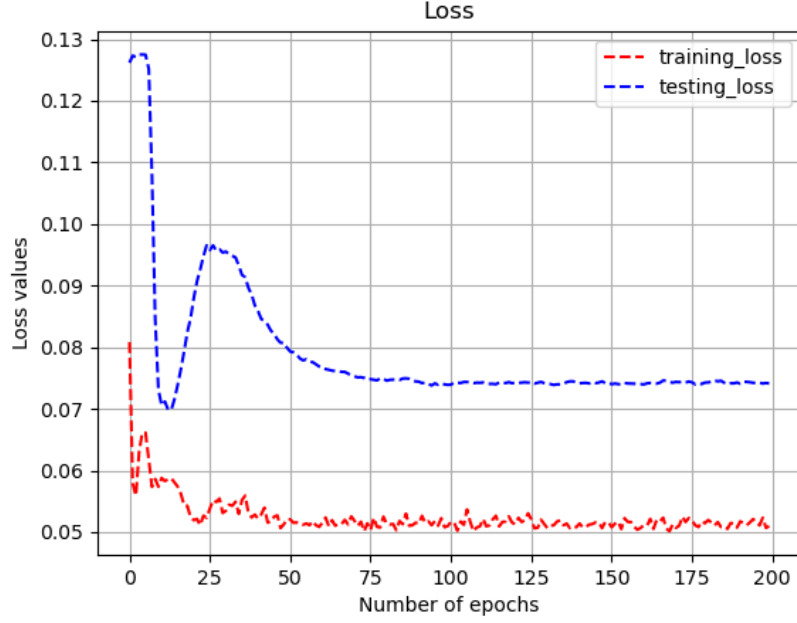


Figure 5.2 : Training and testing process.

5.4 Conclusion and Future Work

In this work, we proposed a fully automated end-to-end multimodal deep network framework for NSCLC survival analysis. Our framework can learn complementary representations from the CT image and non-image clinical data modalities. Extensive experimental results show that DeepMMSA outperforms conventional methods that use a single source of information alone. But there are still some future works to do. There are some potential ways to improve the performance of the proposed framework. Since there are three basic modules for multimodal deep learning survival analysis framework, we consider to make improvements based on the following three aspects:

- Provide more complementary information by adding more modalities to im-

prove the performance, such as e-nose based diagnosis [235] time series data, etc., and try to fully exploit the inherent correlations across multiple modalities.

- Perform different multimodal fusion approaches, such as decision fusion and hybrid fusion method, etc.
- In the survival analysis module, theoretically, we can use any survival analysis model, such as cox-time, deepsurv, to improve the performance of our proposed framework.

5.5 Summary

In this chapter, an accurate and individualised LC prognosis system is constructed. In this chapter, to our best knowledge, we are the first time propose a multimodal deep learning framework using a 3D modality for NSCLC prognosis. The input contains multiple modalities, which include 3D CT images of tumors and clinical records. The high-level representation of 3D CT images is extracted by 3D ResNet. Then the representations of multiple modalities are fused by the early fusion technique. Finally, we use a neural network to predict the survival time. In this framework, techniques such as batch normalization, regularization, and prediction normalization are used. In the validation stage, firstly, we conduct the ablation study to find the relatively best and robust structure for the DeepMMSA, then we compare the optimised DeepMMSA framework with some state-of-the-art methods of survival analysis as baselines. Finally, the results show the performance of our

framework significantly outperforms the baselines in both C-index and MAE, which validates the superiority of our framework.

Although the performance of this work has outperformed many state-of-the-art methods, one more modality can be added into this framework, which is the time series data from e-nose. Adding data from e-nose as one modality in this framework has the potential to further enhance the performance. However, due to the COVID-19, we cannot perform the planned clinical trial of e-nose based time series modality. But in the future, we planned to perform experiments on NSCLC patients using RDDS with the hope to extract more prognosis related features from e-nose and enhance the performance of DeepMMSA.

Chapter 6

Dissertation Conclusions and Future Works

6.1 Summary of Dissertation

In this dissertation, a novel e-nose systems for non-invasive, rapid, low-cost lung cancer detection is proposed. In addition, an advanced AI-based framework design for LC prognosis is presented. The novel artificial intelligence e-nose system is named MHGD and it seeks to protect vulnerable groups from indoor hazard. The significance of MHGD not only lies in its contribution to environmental monitoring but also in its capacity to give us a deeper understanding of e-nose system. It provides a strong foundation for our next goal that the designing of an e-nose prototype which can be used in a range of medical fields. Based on MHGD, we are enabled to move forward to develop the RDDS system which aims to discriminate lung cancer patients from healthy individuals. Compared to the first prototype, this system is more robust and flexible. In addition, it is able to provide more reliable testing results due to the specialised control logic and the closed gas path. In order to prepare RDDS for multi-clinic testing, a calibration method is proposed. After this, a framework named DeepMMSA is proposed for the rapid LC prognosis system. By

using multiple techniques such as multimodal deep learning, 3D CNN, and survival analysis, the DeepMMSA displays superior performance in NSCLC survival analysis through experimentation. To the best of our knowledge, this is the first time that a multimodal deep learning framework with multiple modalities, including 3D CT images for NSCLC prognosis of survival analysis, has been proposed. In the validation process, the framework with its optimised ablation structure, significantly outperforms other state-of-the-art methods of survival analysis, both in the MAE and C-index.

It is important to mention that due to COVID-19, we were unable to conduct clinical trial experiments on LC patients using our e-nose system. In future, we plan to combine more modalities, including an e-nose based diagnosis time series modality, in the DeepMMSA framework. By adding LC-related VOCs information collected from the e-nose system to the DeepMMSA, we believe that this framework has the potential to become a multi-function end-to-end framework for rapid and non-invasive LC detection and prognosis.

6.2 Summary of Contributions

The contributions of this dissertation are as follows:

- (1) Detail the construction of a novel artificial intelligent e-nose system. Employing an open-source platform based on ultrasonic sensors, this system can automatically track, trace and avoid obstacles. Using the gas sensors and an information feedback alarm system, MHGD can perform automatic tracing

indoors and accurate identification of where the potential danger source is, especially for gas-generated hazardous events.

- (2) Detail the development of a rapid disease detection system for LC detection.

Using the MHGD, mechanical components such as valves and pumps are able to be added to the RDDS for precise airflow control and reducing the influences from the ambient environment. This ensures stability through the whole testing procedure and more reproducible experiment results. Added to this, the sensors are calibrated in RDDS.

- (3) A novel framework for personalised NSCLC prognosis is proposed. DeepMMSA is the first framework which uses 3D features from CT images with clinical data for prognostic analysis. Compared to other SOTA methods, it can more accurately make survival predictions.

6.3 Future Works

There is much work that will be explored based on our current project.

- For the MHGD, we can add extra features, such as seamless integration into existing infrastructures and the development of a more intelligent user interface.
- For the RDDS system, we plan to recruit 20 LC patients in the clinical trial to verify the efficacy of the device.
- For the input multiple modalities, we can combine more modalities, such as

the e-nose based diagnosis time series data [235], biomarker information, and genetic information. This will improve the data quality and quantity, and the final performance.

- For the multimodal deep learning framework, we can try to fully exploit the inherent correlations across multiple modalities or their representations, such as alignment, correlation, hierarchical relationship, and so on. Then we can explore more fusion techniques to enhance the framework performance. Finally, more state-of-the-art survival analysis algorithms can be applied, such as cox-time, DeepSurv, to improve the overall performance.

To sum up, in combination with the gas information extracted from the e-nose system, the information extracted from the clinical data as well as 3d information from medical images, our system could track volatile organic metabolite changes in the human body. It could also detect tumour abnormalities and provide more accurate diagnosis and prognostic decision-making in future clinical practice. This final structure is shown in Figure 6.1.

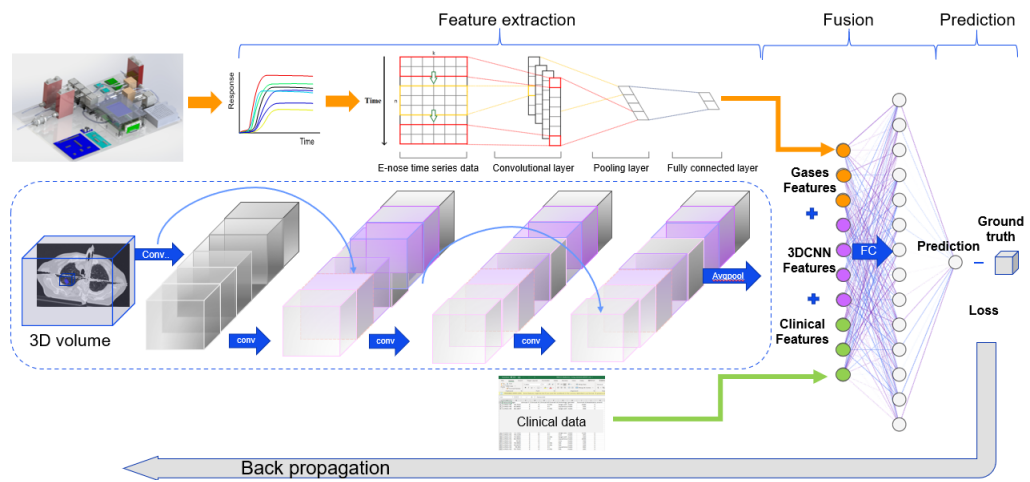


Figure 6.1 : Future multimodal framework for rapid LC detection and accurate prognosis.

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