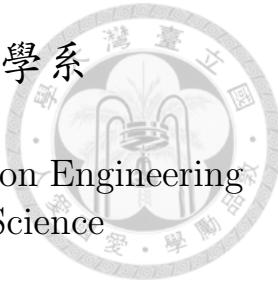


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一套新穎的應用混合實境裝置進行眼振偵測之臨床系統
A Novel Nystagmus Detection System Using A Mixed Reality
Headset

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Abstract

We propose the use of a mixed reality headset, Microsoft®HoloLens2™ to perform nystagmus diagnostic tests. This product has many advantages over current diagnostic tools, e.g., videonystagmography (VNG) device, Frenzel glasses, etc. A friendly user interface was designed to show the filtered waveform of the eye movement during the tests. The nystagmus pattern is detected from the waveform by a rule-based method. In the laboratory, our product has been compared with VNG, the benchmark device of nystagmus detection, and the results and accuracy were comparable in both devices. Furthermore, our product is currently undergoing clinical experiment on patients presenting vertigo/dizziness in clinic.

In experiment 1, we validate the product's accuracy with the VNG device. As for detection algorithm of nystagmus, optokinetic nystagmus (OKN) was utilized as a reference for the pattern of vestibular nystagmus, and the eligibility was approved by an otologist specialized in vertigo/dizziness. In experiment 2, we validate the use of HoloLens2™ to perform the clinical test of nystagmus directly in patients presenting vertigo/dizziness, and the results were compared with those done by the ENT doctors using Frenzel glasses. The conclusion indicates that the product we built in the Hololens2™ is promising in the clinical testing of nystagmus. The whole system, experimental design, and validation methods can be ported to other similar devices if proper modified.

Keywords: *nystagmus detection, mixed reality headset, HoloLens2™, caloric test, optokinetic nystagmus, Dix-Hallpike test, BPPV, videonystagmography (VNG)*

摘要



我們提出使用混合實境裝置，Microsoft®HoloLens2™，來進行眼振檢測的測試。這個產品與現今使用的檢測工具，如影像眼震檢查儀及眼振檢查鏡相比，具有許多優點。我們設計了方便使用的使用者介面來展示測試中經過濾波後的眼睛移動波形圖。其中眼振是經由法則式的演算法從波形中檢測出。在實驗室中，我們去和眼振偵測的標準，影像眼震檢查儀比較，而其結果及準確度和影像眼震檢查儀相近。另外，我們的產品目前正在診間對具有暈眩問題的病患進行臨床實驗。

在實驗一中，我們藉由與影像眼震分析檢查儀記錄的結果比較來驗證裝置的正確性。至於眼振偵測演算法，則是由視動性眼球震顫測試的波形作為典型眼振波形來參考驗證，並由一位專精於暈眩的耳科醫生認證其效力。在實驗二中，我們透過直接對具有暈眩問題的病患進行臨床實驗HoloLens2™在臨床檢測中的使用，並與耳鼻喉科醫師使用眼振檢查鏡之結果相比較。結論顯示了在臨床測試中使用我們在HoloLens2™中設計的產品來測試是非常有可行性的。而整個系統，包括實驗設計、驗證的方式等，可以在經過適當的改動後移植到其他的裝置。

關鍵字: 眼振偵測、混合實境裝置、*HoloLens2™*、溫差實驗、視動性眼振測試、*Dix-Hallpike*測試、良性陣發姿勢性眩暈、影像眼震分析檢查儀



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Chapter 1

Introduction

Nystagmus is defined as “an involuntary, rapid, rhythmic, oscillatory eye movement with at least one slow phase” [Eggers et al., 2019]. It is an objective and widely used sign to diagnose vertigo/dizziness related diseases. Those diseases include benign (paroxysmal) positional vertigo (BPV, or BPPV)[Solomon, 2000], vestibular neuritis (or neuronitis)[Strupp and Brandt, 2009b], and Meniere’s disease[Labuguen, 2006], which are the top three most common causes (93%) of vertigo[Hanley and O’ Dowd, 2002]. There are roughly 2.6 million emergency department (ED) visits for those aged 16 years or older who suffered from dizziness or vertigo, accounting for 3.3% of all ED visits annually in U.S., and it’s a common ED symptom for those older than 50 according to [Newman-Toker et al., 2008]. In National Taiwan University Hospital (NTUH), there are about 1200 visits per month for vertigo/dizziness disorder in only one department (otolaryngology), accounting for 10% of total visits. From the above statistics, we can conclude that the diagnosis of nystagmus plays an important role in the management of the very common vertigo/dizziness disorder.

Different instruments are used to detect and/or analyze nystagmus, among them, videonystagmography (VNG) device and Frenzel glasses, are currently widely used. However, they are not perfect tools in the management of acute nystagmus. As for VNG device, the immobility, high price, and the requirement of experienced operators limit its use to deal with acute patients. A set of VNG costs around NT\$1200,000 to 2000,000. In the otolaryngology department of NTUH, about 150-300 VNG tests are needed weekly, and the reality is only 60 tests per week can be supplied due to lack of facilities and personnel. On the other hand, Frenzel glasses is light, with excellent portability for clinical tests of nystagmus [Solomon, 2000]. However, small nystagmus may be neglected and no objective recording can be made. The credibility of the data lies completely on the experience of the operator. Our product implanted in the Microsoft®HoloLens2™ solves these problems. It is

more portable and costs much less than the VNG device. Unlike Frenzel glasses, it can generate recording of the eye movement during the test, providing an objective result. Moreover, it can be automated, if properly designed with audio and visual aids. A table that compares these devices is provided (table 2.1)

We first compare the data recorded by the VNG device and the HoloLens2TM by performing the same test items in the VNG tests, including Smooth Pursuit, Gaze-Evoked Nystagmus, Saccadic Eye Movement, Optokinetic Nystagmus (OKN) test, and the caloric test. By doing so, we can validate the correctness of data recorded by HoloLens2TM. Smooth Pursuit, Gaze-Evoked Nystagmus, and Saccadic Eye Movement tests demand the eye to pursue the target projected on the screen, utilizing the vestibular and/or visual function. The OKN test demands the eye to follow moving target strips back and forth to mimic a typical nystagmus waveform. It is used to check the nystagmus detection algorithm. Finally, the caloric test is performed to check the capability of HoloLens2TM to properly record the involuntary evoked nystagmus. The subjects participated in the experiment were healthy, and had no vertigo-related medical history.

The second part of the experiments is the standard clinical nystagmus test procedure recorded by our product implanted on HoloLens2TM. These tests are clinical examination to examine the nystagmus, featuring Gaze Nystagmus, Positional Nystagmus, Positioning Nystagmus, and Dix-Hallpike Nystagmus. The whole test includes 15 test items. During the clinical test, Frenzel glasses mounted onto the patient's head, and the doctor observed eye movement of the patient through the lenses. The doctor also changes the patient's posture, such as lying down with head turning to the right or left, to observe the nystagmus triggered by position change. The subject participates in the experiment are the outpatients of ENT clinic of NTUH, all well-informed the content of the experiment and signed the consent form.

This thesis first introduces background medical knowledge and some related works. Then, the two experiments and their results are described in detail respectively. Discussion and conclusion were made in the final portion.

The interest of our project is the utilization and validation of the mixed reality device, Microsoft[®]HoloLens2TM in the nystagmus detection. In addition, the validation process, experimental procedures, program design, and the algorithm of nystagmus detection can all be ported similar devices with eye tracking function if properly modified.



Chapter 2

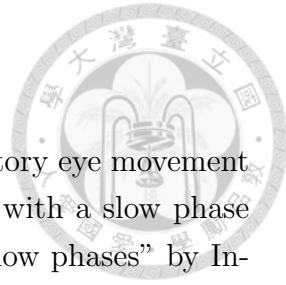
Background

2.1 Physiology

2.1.1 Semicircular Canals

Vestibular system is the system which takes the responsibility of monitoring head and body position and motion. Semicircular canals are one important component [Baloh, 2003]. The semicircular canals comprise three different parts, which are horizontal (or lateral canal), superior (or anterior), and posterior semicircular canal. The horizontal and superior semicircular canal, the utricle, and their afferents compose the superior vestibular labyrinth, while the posterior semicircular canal, the saccule, and their afferents compose the inferior vestibular labyrinth[Jeong et al., 2013] in inner ear. The semicircular canals, filled with endolymph, are in charge of angular acceleration detection. Endolymph is a fluid whose density and viscosity slightly greater than those of water, while its density is the same as the cupula, a bulbous gelatinous mass[Baloh, 2003]. The head movement causes the movement of endolymph, and therefore deflects the cupula. The deflection of cupula then results in the stimulation or inhibition of vestibular nerves attached to hair cells on the cupula[Parnes et al., 2003]. This is how semicircular canals sense the angular acceleration of a human head. The vestibular-ocular reflex (VOR) is an example of how semicircular canals works. VOR is a reflex making things “stay on the fixation while the head is moving”[Gold, 2019]. When semicircular canals sense the movement of head, they pass the information to the ocular motor nuclei through vestibular nuclei, makes the eye move to offset the influence of head movement on the image that eyes can see[Gold, 2019].

2.1.2 Nystagmus



Nystagmus is defined as “an involuntary, rapid, rhythmic, oscillatory eye movement with at least one slow phase. Jerk nystagmus is the nystagmus with a slow phase and a fast phase. Pendular nystagmus is nystagmus with only slow phases” by International Classification of Vestibular Disorders classification group[[Eggers et al., 2019](#)]. Nystagmus may physiologically result from the environmental stimuli (optokinetic nystagmus (OKN)) or the rotation of the head (vestibular-ocular reflex (VOR)), and the type of nystagmus is decided by distinguishing between the jerk and pendular waveform and some additional information of the patient[[Gold, 2019](#)]. In the jerk nystagmus, the direction of slow and fast phase is opposite to each other, whose waveform has “sawtooth” or “ramp-like” appearance[[Eggers et al., 2019](#)]. A slow phase, as its name suggests, is a phase when eye slowly drifts, while fast phase means fast drift of the eye, which is of less importance in diagnosis because it is not the primary result of nystagmus and is just a positional reset of the drift from slow phase[[Gold, 2019](#), [Eggers et al., 2019](#)]. Typically, the direction of fast phase of jerk nystagmus is used to represent its direction [[Eggers et al., 2019](#), [Furman and Wuyts, 2012](#)]. As for pendular nystagmus, there is no fast phase so the vector of it is used for description[[Gold, 2019](#)]. The nystagmus should be presumed to be binocular (happens in both eyes), and conjugate (eyes rotate toward same direction with same amount)[[Eggers et al., 2019](#)].

Nystagmus is a widely used clinical sign to diagnose patients with vestibular and neurological disorders[[Eggers et al., 2019](#)]. Although other evaluation such as history assessment and vestibular tests are equally important, several diseases can be diagnosed by analyzing the parameters of nystagmus. The section [2.1.7](#) introduce several of diseases with typical nystagmus.

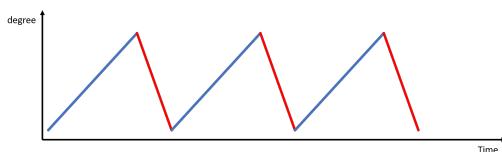


Figure 2.1: Left nystagmus

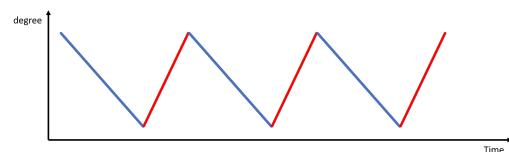


Figure 2.2: Right nystagmus

Figure 2.3: Typical jerk nystagmus waves. The blue line represents the slow phase, and the red line represents the quick phase. Note that the direction of nystagmus is decided by its quick phase. Here the positive of y axis means right, and negative means left.

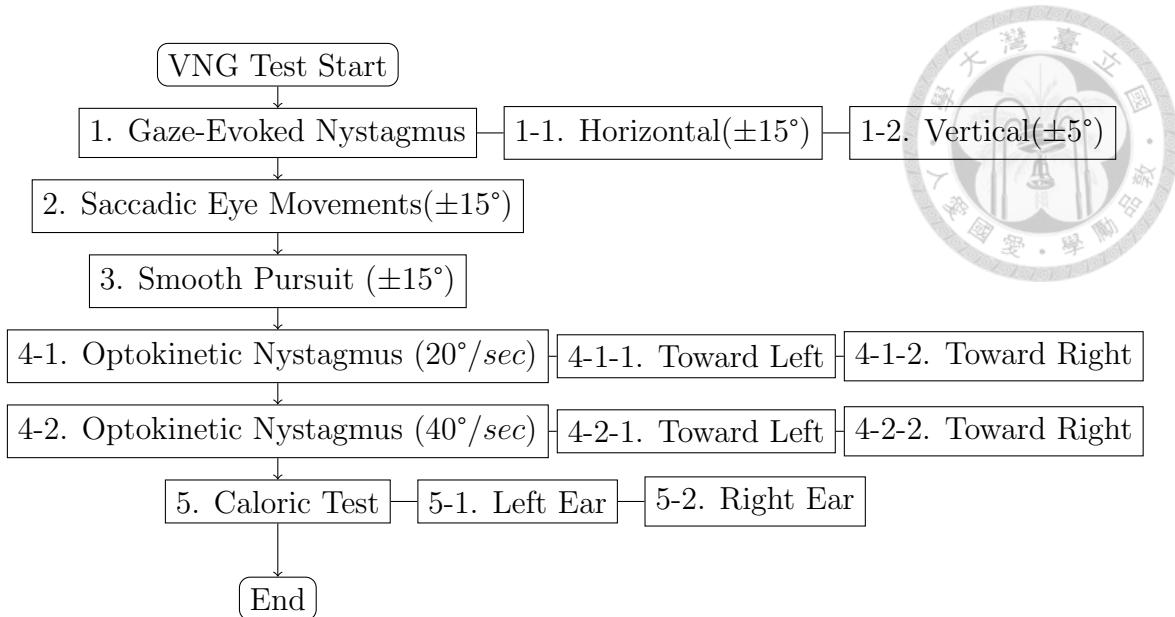


Figure 2.4: VNG test flow, consist of VOMS and caloric tests

2.1.3 Clinical Devices For Eye Movement Diagnosis

There are many kinds of devices or system used to detect/analyze the eye movements. The following lists some of them with brief introduction and description.

1. Videonystagmography (VNG) System:

Videonystagmography (VNG), or video-oculography (VOG), is “a complete diagnostic system for recording, analyzing, and reporting eye movements using video imaging technology, in which hi-tech video goggles with infrared cameras are used”[Mekki, 2014]. Examining the nystagmus in darkness by infrared cameras removes or blocks visual fixation during the tests[Solomon, 2000, Eggers et al., 2019]. In VNG, one side of eye is recorded by infrared cameras, which fully covers the eye like an eye patch, creating a dark environment. Because of the conjugate eye movement, we can record only one eye’s movement instead of both.

A typical VNG tests feature ocular motor function tests(2.1.4), gaze stabilization tests, caloric tests(2.1.5), tests for specific etiologies (e.g. Dix-Hallpike maneuver), and others[Mekki, 2014]. A clinical procedure of caloric tests performed in NTUH is listed at figure 2.4.

2. Frenzel Glasses:

Frenzel glasses (or Frenzel goggles) are glasses with 20 diopter concave lenses with small lights inside[Baba et al., 2004]. The glasses can not only remove visual fixation from the patients, but also make the examiner have magnified

view of eyes[[Eggers et al., 2019](#), [Baba et al., 2004](#)]. Because of its portability and low price, they are widely used in clinical practice and even in ED[[Halmagyi et al., 2020](#), [Baba et al., 2004](#)]. Nowadays there are many new version of they, such as DIY version, even more cheaper version, or video-recording version[[Halmagyi et al., 2020](#)].

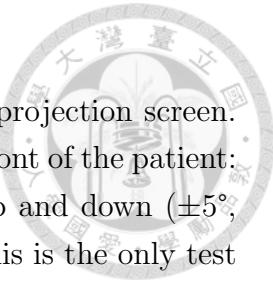
3. Electronystagmography (ENG)

Electronystagmography (ENG), or electro-oculography (EOG) is based on the corneo-retinal dipole potential of the eyeball”[[Furman and Wuyts, 2012](#)]. The eye movement will cause the variation of corneo-retinal potential. Such change of potential is detected by electrodes placed on specific place on the face, and then is amplified and recorded.[[Ganança et al., 2010](#)]. By appropriately placing the electrodes, we can detect different types of eye movement simultaneously[[Ganança et al., 2010](#), [Furman and Wuyts, 2012](#)]. The problem of ENG lies in its instability. Many factors may affect the recorded potential, including eyelid movements, blinks, muscle electrical activities, and ambient electric noises. Among these factors, light affects the most, therefore several calibrations are needed before the test[[Furman and Wuyts, 2012](#), [Ganança et al., 2010](#)].

In this thesis, we introduce the HoloLens2TM to perform the test in order to eliminate the main disadvantage of the devices mentioned above, such as the immobility in VNG device, and the lack of recording of test in Frenzel glasses. The comparison between these devices and the HoloLens2TM is listed in table 2.1.

2.1.4 Vestibular/Ocular Motor Screening (VOMS)

Ocular motor screening (VOMS) is a series of test to “assess vestibular and ocular motor impairments ”, and is often used to examine the symptoms after sport-related concussions[[Mucha et al., 2014](#)]. It is also used to evaluate central nervous system abnormalities and to check the functionality of eye movement before other eye-related tests, such as caloric test[[Furman and Wuyts, 2012](#)]. A typical VOMS assessment includes five domains, which are smooth pursuit, horizontal and vertical saccades, convergence, horizontal vestibular ocular reflex (VOR), and visual motion sensitivity[[Mucha et al., 2014](#)]. The following content describes the VOMS tests recorded by VNG device/system (the introduction of VNG is in section 2.1.3) in NTUH. The VNG system used is VNG Ulmer from ©Synapsys. The test procedures are mostly similar with that described in [[Furman and Wuyts, 2012](#)], but slightly modified.



1. Gaze-Evoked Nystagmus:

The patient is asked to look at the target light dot on the projection screen. The dot, starts from origin (0°), switches between places in front of the patient: 15° left and right ($\pm 15^\circ$, horizontally), and then 5° degree up and down ($\pm 5^\circ$, vertically). The dot switches positions every 16 seconds. This is the only test the vertical eye movement involved.

2. Saccadic Eye Movements:

The patient is asked to look at the target light dot on the projection screen. The dot's movement in this test is the same as the horizontal Gaze-Evoked Nystagmus. The difference lies in the dot switching frequency. The dot changes positions every 2 seconds.

3. Smooth Pursuit:

The patient is asked to follow the trajectory of target light dot on the projection screen. The dot moves left and right 15° periodically, forming a single harmonic motion.

4. Optokinetic Nystagmus (OKN):

The patient is asked to follow the movement of target strips on the projection screen. White and black strips with the same width alternatively appear on the screen with two speed, slow ($20^\circ/\text{sec}$) and quick ($40^\circ/\text{sec}$), toward the left or right end of screen.

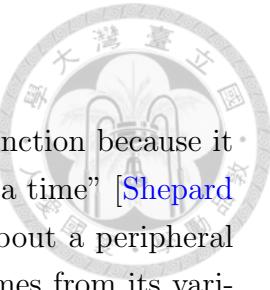
After the four tests, we then perform the caloric test recorded by VNG. The caloric test is described in next section. Figure 2.4 illustrates the whole VNG test flow.

Table 2.1

Comparsion of HoloLens2TM and two nystagmus detection devices.

Device name	HoloLens2 TM	Frenzel Glasses	VNG
Eye Movement Detection	Uses the eye tracking functionality to track the eye position.	A glasses remove the fixation of the subject, providing a magnified view of the eyes.	Records the eye movement by video imaging technology by infared camera.
Pros	<ol style="list-style-type: none"> 1. High portability 2. Can record the whole examination process 3. Can be used in ED and bedside 4. Users can perform the test by themselves if properly designed 	<ol style="list-style-type: none"> 1. High portability 2. Costs the least among these devices 3. Can be used in ED and bedside 	<ol style="list-style-type: none"> 1. Can record the whole examination process. 2. Can analyse the nystagmus 3. Video record of the eye movement provided
Cons	<ol style="list-style-type: none"> 1. The correctness and the effectiveness needs to be validated 2. Can't remove the fixation during the test 3. Sampling rate is relatively low 	<ol style="list-style-type: none"> 1. Can't record the whole process 2. Only subjective result is recorded 3. Requires an experienced doctor while testing 	<ol style="list-style-type: none"> 1. Low portability 2. Costs the most among these devices 3. Requires an experienced staff while testing 4. Some requires the whole set of computer and software. 5. Not suitable for the bedside and ED examination

Note. The content of the table is based on the clinical experienced, the data mentioned in the 2.1.3, and [VestibularFirst].



2.1.5 Caloric Test

The caloric test is a widely used test to evaluate the vestibular function because it can “isolate one peripheral vestibular apparatus for evaluation at a time” [Shepard and Jacobson, 2016], and can “provide lateralizing information about a peripheral vestibular lesion” [Furman and Wuyts, 2012]. The main limit comes from its variability. The result of the test may vary not only from person to person, but may also vary in the same person. Therefore, it is suggested to perform the test on two ears and then evaluate the combined results [Shepard and Jacobson, 2016].

The patient is first asked to lie supinely. Because the horizontal semicircular canals is 30 degree above the horizontal plane [Parnes et al., 2003], in order to make horizontal semicircular canals oriented in the vertical plane, the patient needs to tilt his/her head 30 degree upward [Furman and Wuyts, 2012]. After that, either the water or air enters into the ear as stimulus, inducing the convection current within endolymph in the horizontal semicircular canal [Furman and Wuyts, 2012]. The cold stimulus produces the horizontal nystagmus, with fast phase beating away the stimulated ear, while the warm stimulus produce a nystagmus with opposite direction, beating toward the stimulated ear. A mnemonic, COWS, is coined to describe the reaction, meaning cold opposite, warm the same [Furman and Wuyts, 2012, Baloh and Jen, 2012].

2.1.6 Dizziness and Vertigo

Dizziness and vertigo are common symptoms. The life time prevalence of dizziness and vertigo are about 30% [Hannaford et al., 2005, Neuhauser, 2007]. In [Strupp and Brandt, 2008]. Dizziness “refers either to an unpleasant disturbance of spatial orientation or to the erroneous perception of movement, which is more specifically called ‘vertigo’.” Dizziness is a general term to describe several balance problems, including feeling of unsteadiness, light-headedness or feeling faint, and seeing things moving or spinning [Hannaford et al., 2005]. Vertigo is a more specific term to describe symptom arises from the vestibular system, such as BPPV, Meniere’s disease and vestibular neuritis [Neuhauser, 2007, Solomon, 2000, Thompson and Amedee, 2009]. We focus mainly on the vertigo and these diseases in this paper.

2.1.7 Relation between Nystagmus, Vertigo, and Diseases

The diagnoses of vertigo usually involve thorough history complaint analysis and additional tests [Strupp and Brandt, 2008, Thompson and Amedee, 2009]. BPPV, Meniere’s disease and vestibular neuritis are the top three most common causes

of peripheral vestibular disorders [Hanley and O' Dowd, 2002, Strupp and Brandt, 2009a]. The peripheral vestibular disorders can be differentiated by their characteristic signs and symptoms according to [Strupp and Brandt, 2009a]:

1. Bilateral peripheral loss of vestibular function (bilateral vestibulopathy), characterised by oscillopsia during head movements and instability of gait and posture.
2. Acute/subacute unilateral failure of vestibular function (most often caused by vestibular neuritis), characterised by a rotatory vertigo, oscillopsia, and a tendency to fall toward the affected ear.
3. Paroxysmal, inadequate stimulation or inhibition of the peripheral vestibular system, characterised by attacks of vertigo and oscillopsia.

The examination of nystagmus in peripheral vestibular disorders is suggested to remove the visual fixation because the visual fixation tends to suppress or affect several characteristics of nystagmus [Halmagyi et al., 2020, Eggers et al., 2019]. We will introduce these diseases with their characterized nystagmus respectively in the following sections.

Benign Paroxysmal Positional Vertigo (BPPV)

Benign Paroxysmal Positional Vertigo (BPPV) is the most common cause of vertigo [Solomon, 2000]. A research conducted in Germany reported its lifetime prevalence was estimated at 2.4% [von Brevern et al., 2007]. Another research conducted in Ireland based on clinical diagnoses reported 42.2% of all patients with vertigo, which is the major one [Hanley and O' Dowd, 2002].

The typical symptoms of BPPV are brief attacks of rotational vertigo and concomitant nystagmus induced by sudden head position changes with respect to gravity. The circumstances that trigger BPPV are getting out of the bed, turning over in the bed, bending forward, and looking up [Lee and Kim, 2010, Dieterich, 2004, Strupp and Brandt, 2008]. The main cause of it is primary or idiopathic BPPV (50%-70%) [Parnes et al., 2003].

The mechanism of BPPV is believed to be explained by cupulolithiasis or canalithiasis theory. Canalithiasis describes "free-floating particles within a semicircular canal", and cupulolithiasis describes "particles adherent to the cupula of a semicircular canal" [Parnes et al., 2003]. The density of canalithiasis and cupulolithiasis are not the same as endolymph. When the head moves to "provocative position", the gravitated canalithiasis or cupulolithiasis will then trigger the vertigo, or the so-called BPPV, alongside the "positional", or typical nystagmus [Epley, 1995, Parnes

et al., 2003]. According to [Solomon, 2000], “the direction of nystagmus depends on the stimulated canal and the direction of particle movement”. The detail is listed as table 2.2 The Dix-Hallpike test/maneuver is the clinical diagnostic procedure of BPPV, by examining the nystagmus stimulated by it[DIX and HALLPIKE, 1952].

Table 2.2

Positional tests for horizontal canal BPPV.

Head Position	Nystagmus direction	Affected side	Mechanism
Right ear down	Geotropic(R beat)	Stronger nystagmus with affected ear down	Canalithiasis
Left ear down	Geotropic(R beat)		Canalithiasis
Right ear down	Ageotriopic (L beat)	Stronger nystagmus with affected ear up	Cupuloithiasis
Left ear down	Ageotropic(R beat)		Cupuloithiasis

Note. From “Benign Paroxysmal Positional Vertigo,” by D. Solomon, 2000, Current Treat Options Neurology, 2(5), p.417–428. Copyright ©2000 by Current Science Inc.

Vestibular Neuritis

Vestibular Neuritis (VN) is the second most common cause of vertigo (40.8%) in the research done by [Hanley and O’ Dowd, 2002], and is the most common peripheral etiology of the acute vestibular syndrome[Gold, 2019, Jeong et al., 2013]. It is defined as “acute unilateral peripheral vestibulopathy that manifests with acute spontaneous vertigo, nausea/vomiting, and postural imbalance”[Kim and Kim, 2012]. The symptoms of VN may “last for several days and not associated with auditory or neurologic symptoms”[Baloh and Jen, 2012]. The most popular cause of VN is viral origin (herpes simplex virus 1, or HSV-1), but the evidence of it remains circumstantial[Strupp and Brandt, 2009b, Gold, 2019]. According to this theory, the HSV-1 is assumed to latently infect the vestibular ganglia and later “induces an inflammation and edema, causing secondary cell damage of the vestibular ganglion cells and axons in the bony canals”[Strupp and Brandt, 2009b]. The superior and horizontal semicircular canals are more preferentially affected by the VN because of the anatomic differences between semicircular canals[Strupp and Brandt, 2009b, Kim and Kim, 2012].

Spontaneous nystagmus is one of the key signs and symptoms of VN. The pattern of spontaneous nystagmus depends on the affected semicircular canal[Jeong

et al., 2013]. The nystagmus in VN is usually observed to be horizontally beating toward the non affected ear, with torsional component (the so-called horizontal-torsional nystagmus) because the involvement of horizontal and superior semicircular canal[Jeong et al., 2013, Strupp and Brandt, 2009b] . The proper way to investigate the nystagmus is through Frenzel glasses or infrared video goggles to eliminate the visual fixation. As for the clinical tests of VN, caloric test and head impulse test are one of them [Jeong et al., 2013].

Meniere's disease

Meniere's disease (MD) is the third most common cause of vertigo (10%) in the research done by [Hanley and O' Dowd, 2002]. The frequent symptoms of it are recurrent episodes of vertigo, hearing loss, tinnitus, or aural fullness[Labuguen, 2006, Güneri et al., 2016]. Though there are many tests to diagnose MD, including audiological, vestibular, radiological, clinical, and biochemical tests, we still know little about the actual process of it due to its fluctuated nature[Güneri et al., 2016, Phillips et al., 2021], and the lack of immediate recording [Nakayama et al., 2000]. One wildly accepted theory is the Rupture theory proposed by [Schuknecht, 1968], which explained the cause of the MD. The endolymphatic hydrops in inner ear results in the rupture of the membranous labyrinth. Leaking through these rupture, the neurotoxic potassium in the endolymph first stimulates the vestibular system, and as the concentration of perilymphatic potassium increases, it then injures and reduce the function of the vestibular system.[Nakayama et al., 2000, Yacovino and Finlay, 2016].

Spontaneous nystagmus is a common symptom associated with MD. It was observed in about 75% of MD patients in the research of [Nakayama et al., 2000]. Three phases are classified and defined by the direction of it [Yacovino and Finlay, 2016] or by the change of the vestibular function[Eggers et al., 2019]. In [Yacovino and Finlay, 2016], they are defined as : “ an initial ‘irritative’ phase beating toward the affected ear, the contralateral ‘paralytic’ phase, and the final ‘recovery’ phase beating again toward the affected side”. Caloric test may detect such vestibular hypofunction to some extent[Gold, 2019], about 50 to 67% of the patients [Güneri et al., 2016].

2.2 Algorithm-based Eye Movement Events and Nystagmus Detection

Algorithms to detect special eye movement events and nystagmus in the data collected by clinical devices mentioned in 2.1.3 have been developed over years. Here

we introduce them separately.



2.2.1 Eye Movement Events Detection

The eye movement events of interest include fixation, saccade, smooth pursuit, and blink[Nyström and Holmqvist, 2010]. These events are important in applications such as human-computer interaction and experimental psychology, as well as visual information processing and cognition[Hoppe and Bulling, 2016].

The velocity-based algorithm is one of the most used algorithm. It is sometimes accompanied by analysis of acceleration domain and is usually involved either pre-defined or adaptive threshold of velocity[Nyström and Holmqvist, 2010]. [Smeets and Hooge, 2003] researched on the variability in the execution of saccades, and the saccades are detected by a two stage method, which first located the peak velocity and then search for the onset and offset of them. The algorithm developed by [Nyström and Holmqvist, 2010] used adaptive and data-driven thresholds to lessen the manual setting of algorithm when applied on different situations, which are usually burdens on user. [Asim et al., 2019] developed an event detection algorithm which can performs robustly on dynamic natural simulation and static simulation as well.

Recently, the application of machine learning in event detection is trending, and some are aiming to eliminate the involvement of manual setting of the detector. [Hoppe and Bulling, 2016] developed a convolutional neural networks (CNN) based method that learns a single eye movement events detector directly from the continuous gaze data stream. [Bellet et al., 2019] proposed U'n'Eye, a CNN inspired by U-Net[Ronneberger et al., 2015] which “detect saccades at human-level accuracy and with minimal training examples”. [Zemblys et al., 2019] developed gazeNet, an end-to-end supervised learning approach to classify the raw eye tracking input into events, to eliminate the necessity for hand-crafted features or thresholding.

2.2.2 Nystagmus Detection

As mentioned in 2.1.2 and 2.1.7, nystagmus is an important event which can be used to diagnosed many diseases. Researchers have inspected different devices and algorithms, hoping to find a better and more convenient way to detect its occurrence. Note that most of the nystagmus detection algorithm focus on the horizontal nystagmus. The devices used to record the eye movement range from low-cost camera[Tsai et al., 2020, Turuwhenua et al., 2014] to commercially available VOG devices [Juhola et al., 2011]. Because of the difference between devices, the preprocessing

(including filtering of signal, deletion of interruption of eye blink or head movement, interpolation of empty frames, and upsampling) of the signal is important and needs modification. As mentioned in 2.1.2, the slow phase of nystagmus is more important in diagnosis, however, it is more difficult to detect it in the waveform of eye movements than the quick phase, whose velocity has a ‘delta function-like’ features[Turuwhenua et al., 2014].

[Juhola et al., 2011] proposed an algorithm to analyse and model three-dimensional (horizontal, vertical, and torsional) nystagmus in signals recorded by VOG device. [Turuwhenua et al., 2014] first estimate the limbal velocity from the optic flow derived velocity, and then check the presence and direction of OKN by finding the velocity peak, which is highly related to the quick phase of nystagmus. [Punuganti and PhD, 2020] proposed automatic nystagmus detection and quantification method based on clustering of pre-detected velocity peaks, and is evaluated on data from patients underwent Dix-Hallpike maneuver recorded by VOG device, and publicly available saccade dataset.

[Newman et al., 2019] focus on the detection of nystagmus in the long-term monitoring by feature extraction and classification, and in the caloric test by dynamically finding the best-fit lines that fits the saw-tooth like pattern of nystagmus. Lalanne et al. [2020] proposed the use of machine learning tool, convolutional sparse coding, to detect the nystagmus in synthetic and real dataset. Slama et al. [2016] proposed an approach to assess the vestibular disorder by first select the most useful features in OKN and caloric tests by Fisher linear discriminant analysis, and then classified these features by multi neural network and statistical study.



Chapter 3

Device, Data, and Methodology

3.1 Specification of HoloLens2TM

The detailed specification of HoloLens2TM can be found at online official document. We only introduce those related to eye tracking function.

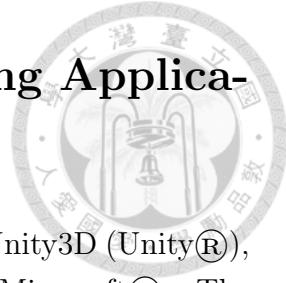
We use HoloLens2TM's eye tracking functionality to detect and analyze the eye movement. Here we address some problems encountered during development.

According to the official document: <https://docs.microsoft.com/en-us/windows/mixed-reality/design/eye-tracking>, “developers get access to a single eye-gaze ray (gaze origin and direction) at approximately 30 FPS (30 Hz)”. In our application, the real frame per second (FPS) of data is about 30 to 60, with a average 46.

According to another document: <https://docs.microsoft.com/en-us/windows/mixed-reality/develop/native/gaze-in-directx>, “Eye-gaze represents the direction that the user’s eyes are looking towards. The origin is located between the user’s eyes”. We think this may generate instability and inaccuracy in the data, but the impact is not significant compared with the data recorded by VNG device after filtering the signal.

Although it’s suggested that when performing caloric test and Dix-Hallpike test, the fixation should be removed to avoid the suppression of the nystagmus, the mechanism of HoloLens2TM's eye tracking function makes it difficult for complete avoidance. We have tried removing the fixation by covering the glasses of it, which resulted in the invalid output. Because of that, visual fixation is only partially removed during our tests.

3.2 Design of Eye Movement Recording Application



The screenshot of the application is as figure 3.1. It is built with Unity3D (Unity®), using the Mixed Reality Toolkit (MRTK-Unity) developed by Microsoft®. The application is separated into VOMS test section and caloric test section. The arrow icons at the left and right are for sub-test selection. The panel at the front is to show the information of sub-test. From up to the bottom is: name of the sub-test, the direction of test, the duration of test and a count-down timer showing remaining time before next sub-test starts. This count-down timer provides the user with a brief resting time. When the count-down timer goes to zero, the next sub-test begins automatically. The button at the bottom left panel is the exit button, and the one at the right bottom is button toggles the start and stop of the countdown timer.

After the application starts, the user can either select the sub-test by clicking the arrow on the left or right, or wait until the test automatically begins. During the tests, there is nothing showing on the screen of HoloLens2™ because we perform the test with the target shown by the VNG device on a projection screen. A brief audio instruction notifies the beginning and the end of the sub-test. The whole automatic process pauses after finishing the VOMS test to provide sufficient time for the preparation of caloric test.

After every sub-tests finishes, a csv file which stores the data of the sub-test will be generated. The file is downloaded from the HoloLens2™ and then analysed by the program which is further described in the section 3.4.2.



Figure 3.1: The screenshot (captured in the editor) of application records the eye movement in HoloLens2™. The application is built with Unity3D (Unity®), using the Mixed Reality Toolkit (MRTK-Unity) developed by Microsoft®.

3.3 Data



The HoloLens2TM api provides several information about eyes and head, including the direction and the origin of eye gaze, head origin and head direction, as normalized vectors.

3.3.1 Data Representation

Here we calculate the representation of eye rotation by the following process: (1) Calculate the x, y, and z projection of eye gaze direction to the coordinate of head, \overrightarrow{EyeX} , \overrightarrow{EyeY} , and \overrightarrow{EyeZ} , by projecting the eye gaze vector to the $\overrightarrow{HeadRight}$, \overrightarrow{HeadUp} , and $\overrightarrow{HeadForward}$ respectively. (2) Represent the rotation along the x and y axis, θ_x and θ_y by calculating the arctan ($EyeX/EyeZ$) and arctan ($EyeY/EyeZ$). Here $EyeX$, $EyeY$, and $EyeZ$ are the magnitude of \overrightarrow{EyeX} , \overrightarrow{EyeY} , and \overrightarrow{EyeZ} . We validate this representation by comparing the data of VNG device in the section 5. Note that the positive of θ_x is right, negative is left, and the positive of θ_y is up, negative is down.

3.3.2 Challenges With Data

Missing Data The missing data (Fig 3.2) is found in the data, tend to locate at the beginning of it. We assumed it is because that the device did not find the eye at the beginning of the test, and fixed it afterward. Moreover, few invalid data is found in the rest part of data, we assumed that they are caused by the eye blink. We skip and annotate these invalid data.

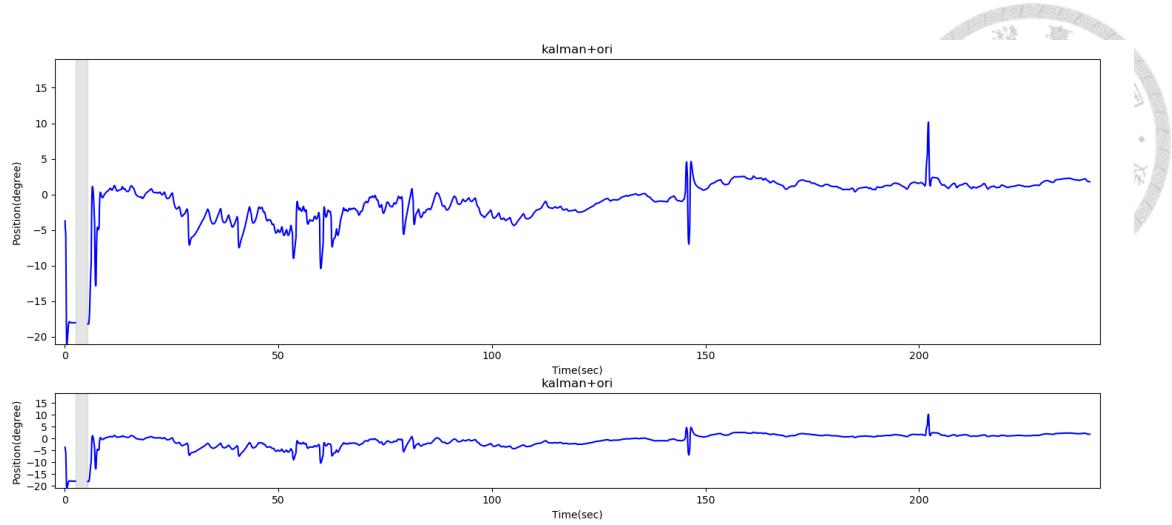


Figure 3.2: The gray part in the figure represents the missing data, which may be caused by frequent blink.

Bad Tracking The original signal is shown as figure 3.3a. We found out that the signal shows a step-like features when the eye moves slowly, especially in the result of smooth pursuit and optokinetic nystagmus tests. We assumed this results from the bad eye tracking, since the eye tracking origin in HoloLens2TM, as mentioned in section 3.1, is from the middle of two eyes instead of the pupils, the waveform may be affected. Another reason may be the low sampling rate. Since it is an universal phenomenon in the results, we applied the Kalman filter [Kalman, 1960], implemented by *FilterPy* [Labbe, 2015], to all data for optimization. As shown in figure 3.3b, the signal filtered looks more realistic and more similar to the wave we expect to appear in the corresponding tests.

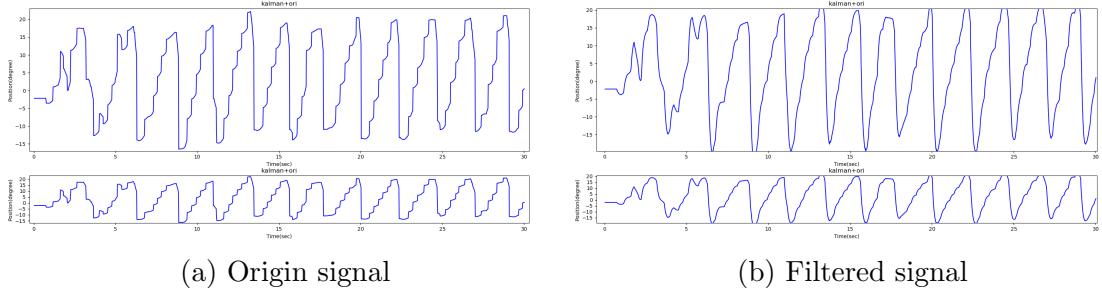


Figure 3.3: Bad Tracking Result: This happens whenever eye moves slowly, continuously toward the same direction, we apply Kalman filter to predict the real eye-movement wave.

3.4 Methodology

The methodology is divided into two parts, the nystagmus analysis and user interface of analysis program.



3.4.1 Nystagmus Analysis

Our nystagmus detection method is mainly based on [Punuganti and PhD, 2020] and [Turuwhenua et al., 2014]. Moreover, the method is adjusted and modified by the suggestion from an otolaryngologic specialist.

SPV Baseline Estimation and Peak Finding

We try to find the velocity peaks, which are highly related to the quick phase of the nystagmus. A slow phase velocity (SPV)[Punuganti and PhD, 2020] baseline is calculated by the following steps:

1. Calculate the velocity of data by applying a moving average on the data [Engbert and Kliegl, 2003] as

$$V_i = \frac{F_s}{6}(P_{i+1} + P_{i+2} - P_{i-1} - P_{i-2})$$

where

V_i is the velocity at time i

F_s is the average sampling frequency of the data.

P_i is the x or y rotation of eye at time i

2. Estimate the SPV baseline by applying a moving median filter on the absolute value of the velocity in a rolling window of 1s, with the highest 5% velocity in the window excluded.

The peaks then found by `find_peaks()` in the *SciPy*[Virtanen et al., 2020], with the parameter `height` set as the mean of the less 50% of velocity. Then, those velocity are larger than SPV baseline are selected. The parameter is set to not only avoid picking the small peak near the baseline, but also avoid the influence of extreme values which may make small nystagmus be ignored.

Peak Selection

The peak is then selected by the following process:

1. Check if the peaks pass through zero in velocity.

A typical nystagmus is formed by a combination of slow phase and quick phase, whose direction are different. Therefore, a velocity peak must pass through zero to show the direction change between the slow and quick phase[[Turuwhenua et al., 2014](#)].

2. Delete peaks whose duration is too long.

Since the velocity peaks indicate the quick phase, which is a quick revise of the eye position, it should not last too long[[Turuwhenua et al., 2014](#)]. However, as the clinical experience of the doctor provides, sometimes it do takes long time to revise the eye position if the shift of the eye is large. According to this claim, we relax our rules to let the peaks whose duration are long but with large shift survive.

3. Combine peaks that are overlapping.

Here we delete peaks that are overlapping. Because the *find_peaks()* may select peaks that are too closed to be two different peaks, we should combine such peaks into a single one.

4. Delete isolated peaks.

A nystagmus typically features two or more slow and quick phase sets. Thus, we delete those isolated from others[[Turuwhenua et al., 2014](#)].

Nystagmus Finding and Analysis

After finding all valid quick phases, we then detect the accompanying slow phases by finding the first direction change in the slow phases right before the quick phases. The dominant nystagmus is decided by the COWS (detailed in section [2.1.5](#)), and then the corresponding features of nystagmus are calculated:

SPV (slow phase velocity): The SPV of *i*th nystagmus, SPV_i , is decided as:

$$SPV_i = \frac{\Delta Position_i}{\Delta Time_{SP,i}}$$

where

$\Delta Position_i$ is the position change between the onset and the offset of the slow phase of the ith nystagmus.



$\Delta Time_{SP,i}$ is the duration of time between the onset and the offset of the slow phase of the ith nystagmus.

3.4.2 Design of Viewing Program 1

In order to easily check the signal, detected nystagmus, and other features, a viewing program is designed using *Tkinter* [Lundh \[1999\]](#) and *Matplotlib* [Hunter, 2007](#) with *Python*. The UI of program is shown in figure 3.4.

After selecting the desired file, one can check the result of the algorithm before-mentioned. The program features the following functions:

1. Eye-movement wave.
2. Nystagmus labels: The nystagmus detected by the algorithm is labeled. Note that the direction of nystagmus here can be decided by the test itself.
3. SPV: Shown as line chart.

The user can toggle the visibility of every figure by simply clicking the buttons above. With the toolbar provided by *Matplotlib*, one can scale or pan the axis to get a detailed view on the range of interest.

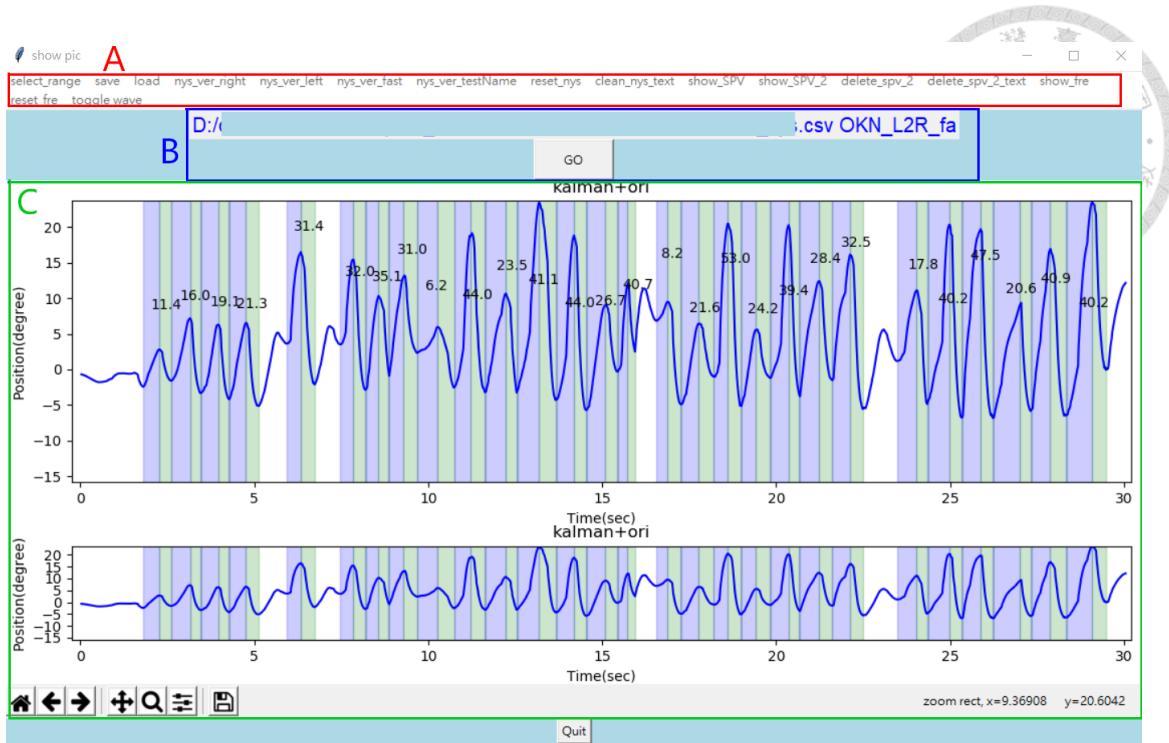


Figure 3.4: The viewing program. The region label A is the toolbox section, which provides several functions such as toggling the visibility of wave and SPV. B is the file selecting section. By clicking the “GO” button, one can select the file from the file browser, and the file name and its test name will be shown here. C is the data viewing window. The numbers labeled on the data are SPV value of each possible nystagmus wave. The *Matplotlib* toolbar is provided, too.



Chapter 4

Experiment 1

There are three main purposes in first experiment. The first is to validate the data of HoloLens2TM by performing the VOMS test. The second is to validate the nystagmus detection algorithm in OKN test. The last is to evaluate the use of HoloLens2TM and the nystagmus detection algorithm in the caloric test. We compare the result of HoloLens2TM with that of VNG device, and validate the data and results. Moreover, the participant is asked to answer to the questionnaire about the HoloLens2TM and the process.

The experiment is separated into two stages. The first stage is to perform the VNG test items with HoloLens2TM, and the other is to perform the same VNG test with VNG device (VNG Ulmer from ©Synapsys) by the same participant. The detailed process of the VNG test is listed in figure 2.4. The target light spot used in the tests is all generated by the VNG device, ensuring the fairness of two stages. The setting of tests, including the distance between the projection screen and the participant, the brightness of the experimental environment, and the examiners, are the same in the two stages. The only difference is the setting of the caloric test. With HoloLens2TM, the participant sits in the chair with head hyperextended, while in the second part, the participant undergoes the test on the bed. This is because the shape of HoloLens2TM makes it difficult for subject to lie down for caloric test, therefore, the part with HoloLens2TM is performed with subject sitting in the chair instead. This difference does not affect the results since the angle of participant's head is kept in the angle (30° upward) in both exams.

The data of the first stage of the test is recorded by the HoloLens2TM with the application (figure 3.1) designed and built with Unity3D (Unity®). Here we describe the process of the first stage in detail:

1. The participant is asked to go through the automatically started eye-calibration

function. This eye-calibration is a built-in program of HoloLens2TM, which ensures the accuracy of the eye-tracking function of it. If not calibrated, the output data are regarded invalid.

2. The application is activated either by the participant or by the examiner.
3. The process of the typical VOMS test (step 1. to 4-2. in figure 2.4) then automatically proceeds, with audio instruction notifying the participant and the examiner when the test begins and ends. There are 10 seconds between each sub-test of the VOMS test. The examiner operates the VNG device to display the target on the screen.
4. After finishing the VOMS test, the caloric test is prepared. The participant is asked to adjust head position to ensure that the head is 30° upward.
5. For caloric test, 10 ml water of room temperature (around 22-25 degree Celsius) is administered into test ear moderately with a syringe. Because the caloric test may induce severe vertigo, headache, and even vomiting, the participant is fully educated and informed beforehand. Note that the participant can quit the experiment whenever they can't proceed.

The second stage is the typical VNG test done by the VNG device, which is already listed in figure 2.4, so we skip the detailed process here.

After finishing the whole test, the participant is asked to filled in a short questionnaire. The results are listed in section 5.4. The content of it is as follow:

- What's the difficulty to operate the application during the test?

Answer options:

- Easy
- Normal
- Hard

- Is there any problem when operating the application?

Answer options:

- Yes
- No

- Your opinion on the process of test, application, and the device(HoloLens2TM) itself? (This question is free-answer question)

This study was approved by National University Hospital Institutional Review Board. The participants (n=19) are all healthy and without vertigo related disease history. All participants are well informed with the whole test process and potential symptoms (such as severe vertigo after caloric test). The data collected during the test is de-identified and will be deleted after the project finished. NT\$500 is offered to the participant as the reward of participation. The experiment is conducted with four experts supervising, including an experienced otolaryngologist.



Chapter 5

Result of Experiment 1

5.1 VOMS tests

Some results of VOMS tests are presented in figure 5.1 and 5.2. Note that because there are difference in vestibulo-ocular reflex of participants, the results may vary to some degree. Moreover, as we applied a filter on the original signal, there may be some artifacts generated by it. Here we do not mention the results of vertical Gaze Nystagmus, since in practice the horizontal eye movement is the main focus. After comparing our results with those from VNG device, we draw the following conclusions:

1. The representation of data is similar to that of the VNG device, and the target of the test: Though the beginning position may not be at zero for all tests, we find that the shift (or amplitude) in every test is as expected, e.g., the average shift in the horizontal Gaze-Evoked Nystagmus is 14.5° of the result from HoloLens2TM, while that of VNG device is 12.62° , and the original setting of the test is 15° . The results are shown in the table 5.1.
2. The overshoot artifacts appear in the filtered waves: Since the Kalman filter is applied on signal, the overshoot artifacts are generated and obvious in the results of the first three tests. However, the results are not severely affected by it judging from the data. We avoid these artifacts when calculating the results of HoloLens2TM.
3. About the Smooth Pursuit: As we can see, the quality of the wave recorded by the VNG device is better than that of HoloLens2TM. This is because the problem mentioned in section 3.3.2. Though the wave is not very smooth, the statistical results still give an acceptable calculation of parameters.

4. About the VOMS test: The VOMS test is relatively stable because the test is not involved with fast eye pursuit, which can be concluded from the small standard deviation of the results among different subjects.

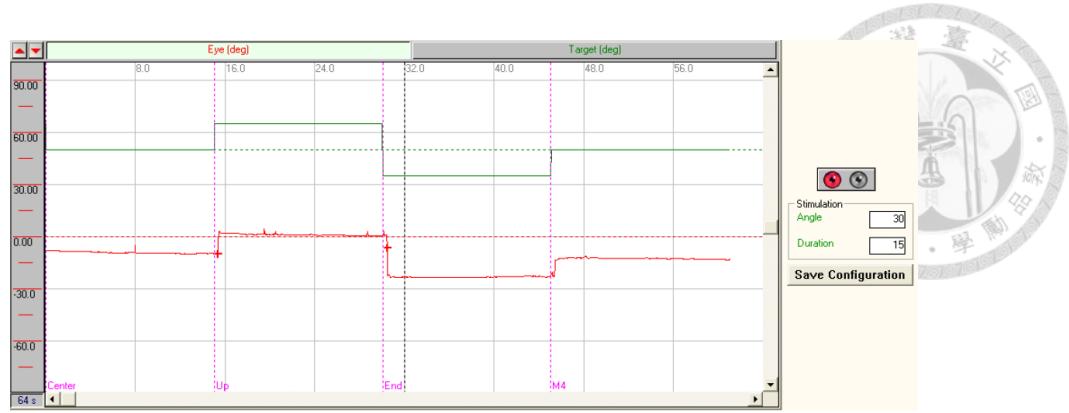
Table 5.1

The average and the standard deviation of VOMS test in experiment 1 with different device, and its original setting.

Test Name	Device	Setting
	HoloLens2 TM VNG Ulmer from ©Synapsys	N/A
Gaze Nystagmus (Horizontal)	$14.5 \pm 2.02^\circ$	$12.62 \pm 1.77^\circ$
Saccadic Eye Movement	$15.1 \pm 1.51^\circ$	$15.51 \pm 1.55^\circ$
Pursuit(Gain ^a)	0.69 ± 0.1	0.72 ± 0.12

^a Gain is defined as eye velocity divided by target velocity[[Fooken et al., 2018](#)].

Note. This table shows the result from HoloLens2TM, VNG Ulmer from ©Synapsys, and the target of the test. The result is the average of the data collected from the subjects. The result of vertical Gaze Nystagmus is omitted here.



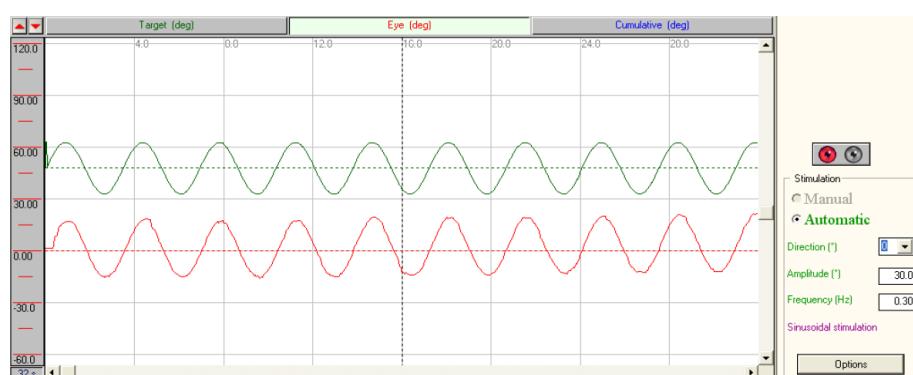
(a) Gaze-Evoked Nystagmus (Horizontal)



(b) Gaze-Evoked Nystagmus (Vertical)

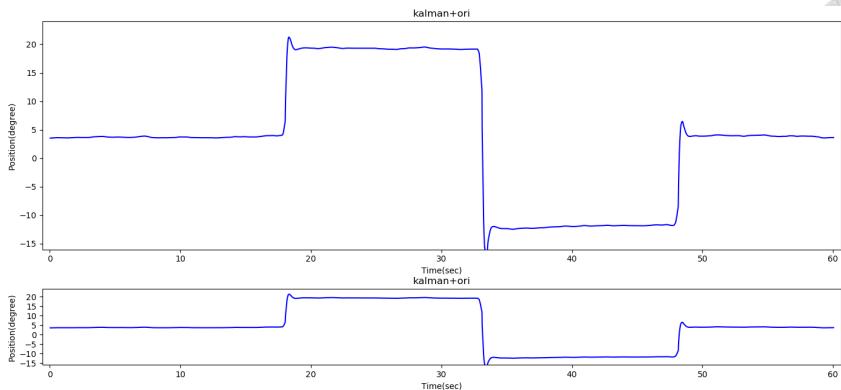
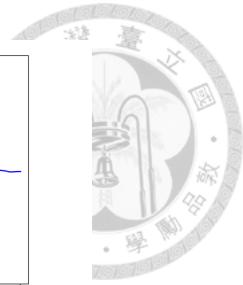


(c) Saccadic Eye Movements

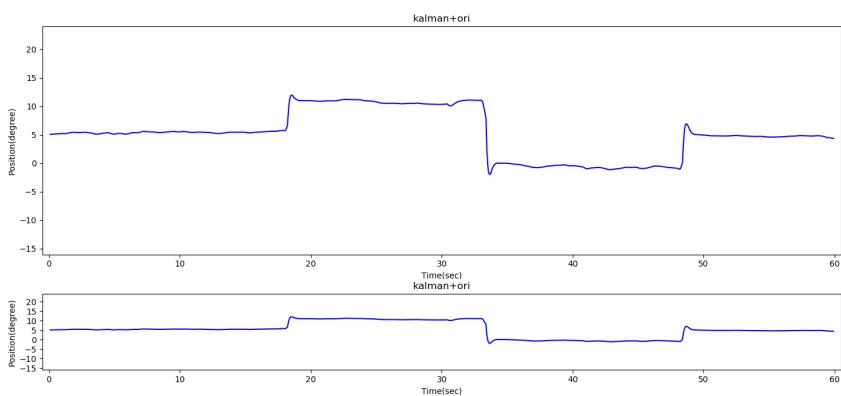


(d) Smooth Pursuit

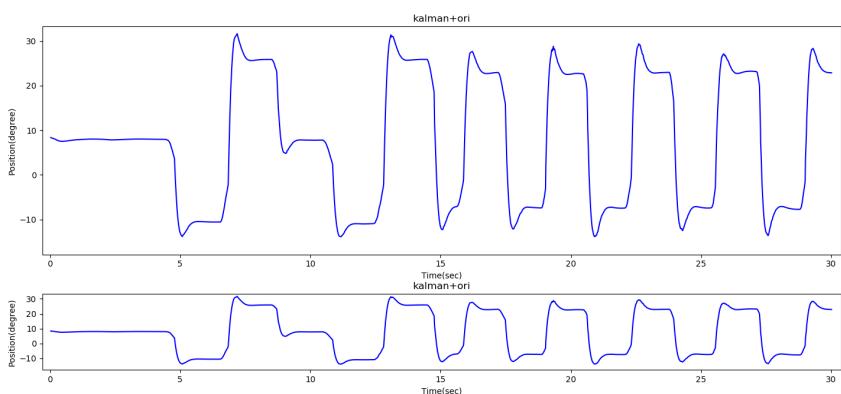
Figure 5.1: Result of VOMS test in VNG device



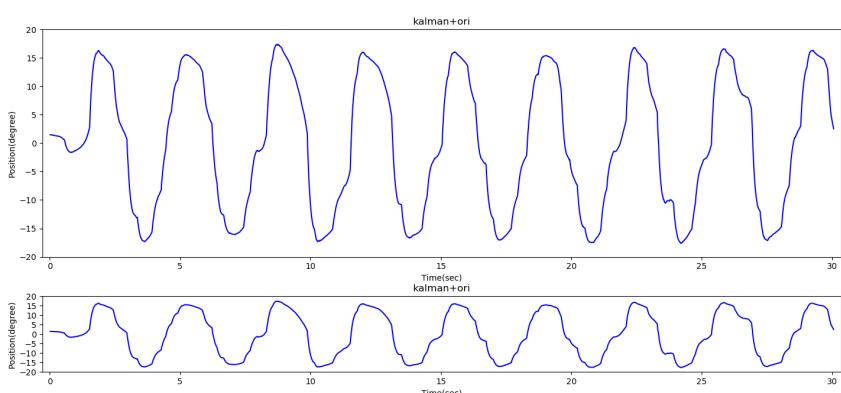
(a) Gaze-Evoked Nystagmus (Horizontal)



(b) Gaze-Evoked Nystagmus (Vertical)

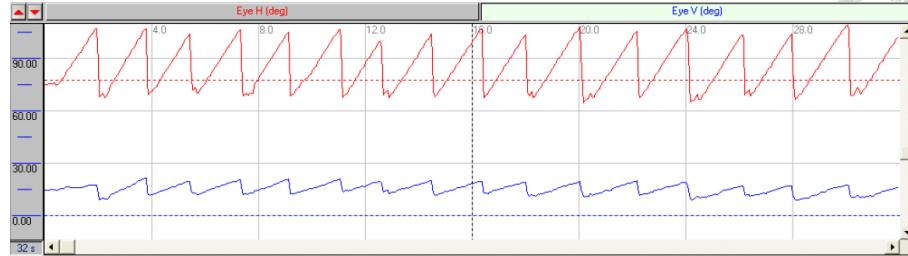


(c) Saccadic Eye Movements

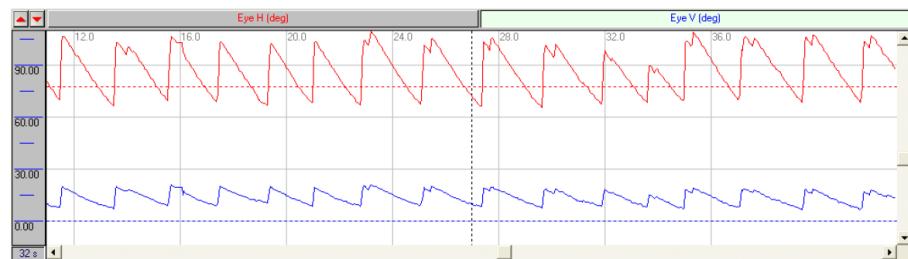


(d) Smooth Pursuit

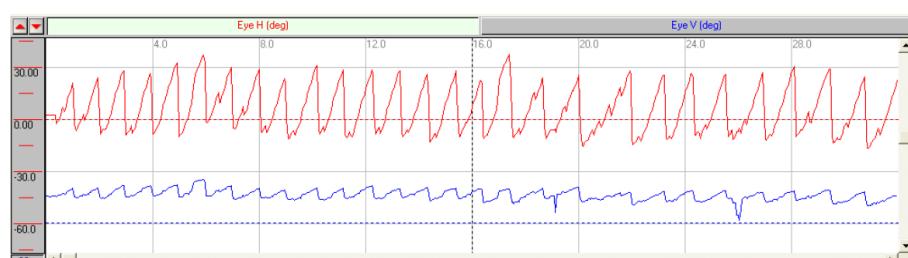
Figure 5.2: Result of VOMS test in HoloLens2TM



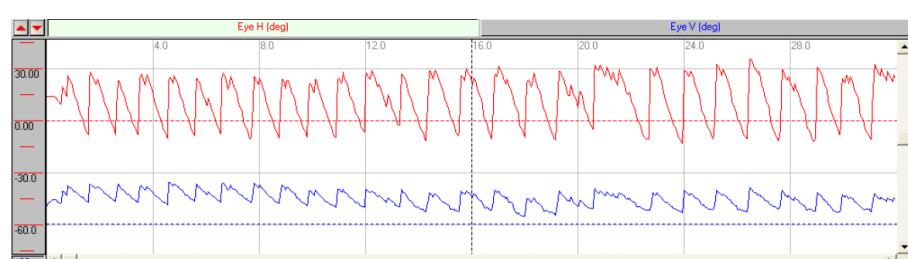
(a) OKN-Slow-Toward Left



(b) OKN-Slow-Toward Right

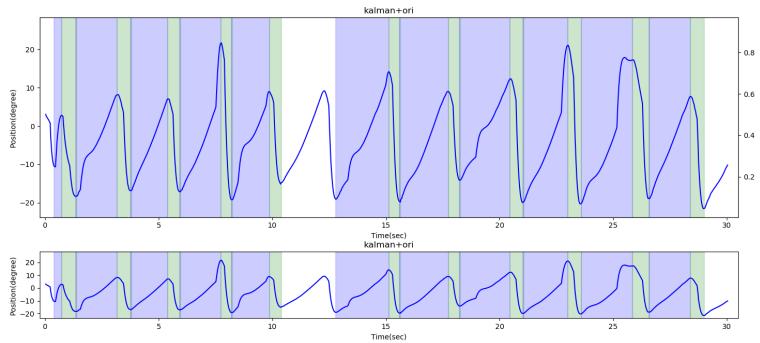


(c) OKN-Fast-Toward Left

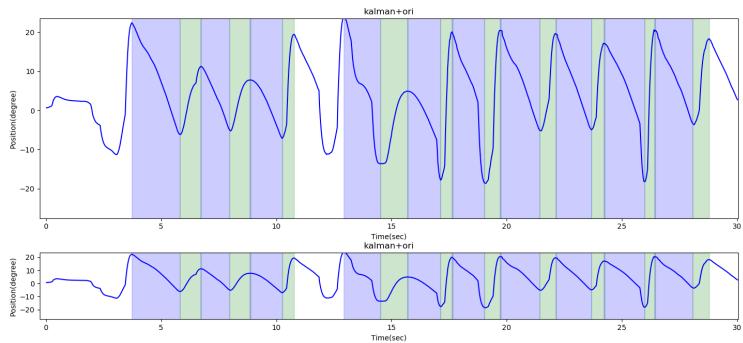


(d) OKN-Fast-Toward Right

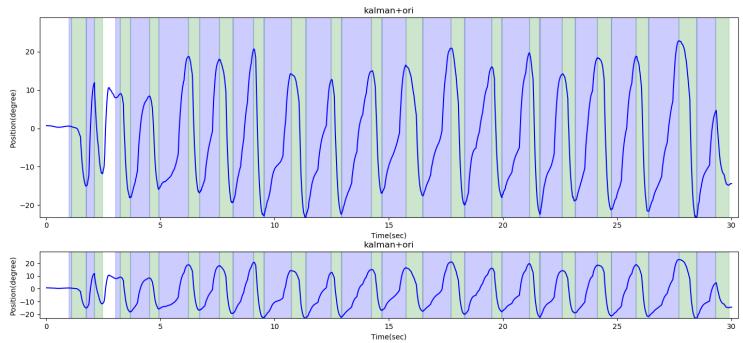
Figure 5.3: Results of OKN test in the VNG device.



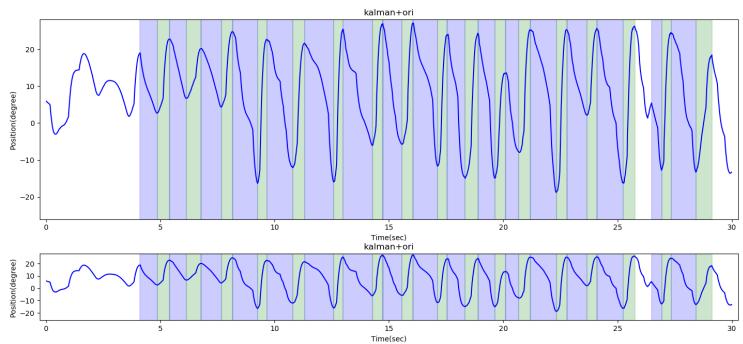
(a) OKN-Slow-Toward Left



(b) OKN-Slow-Toward Right



(c) OKN-Fast-Toward Left



(d) OKN-Fast-Toward Right

Figure 5.4: Results of OKN test, where the green part is fast phase, while the blue one is slow phase.

5.2 OKN Test

The results of OKN test are shown in figure 5.3 and 5.4. The nystagmus detection algorithm is applied on the signal of HoloLens2TM. Several conclusions can be made :

1. Overall, the waves of filtered signal look similar as the typical vestibular nystagmus. However, some of them are not, probably due to lost of eye tracking by the fast speed of OKN test, or that the device performs worse when tracking fast eye movement.
2. The slow phase velocity (SPV) simulated in the OKN test by HoloLens2TM is similar to that of VNG device and quite match the original setting. The average SPV in slow OKN test is about $23.21^{\circ}/s$, while the fast OKN is about $31.83^{\circ}/s$.
3. The nystagmus detection algorithm works fine: The typical waves of nystagmus in slow and fast OKN are perfectly detected by our algorithm, and the effectiveness of the algorithm is further approved by the similarity of waveform generated by HoloLens2TM and VNG.
4. Comparison of both devices: The result is listed in table 5.2.
 - (a) We notice that the result of VNG device is not very close to the target velocity in all sub-tests, while that of HoloLens2TM is closer to original setting of the target in the slow OKN test, but not in the fast OKN test.
 - (b) Both the devices have similar results of OKN test of the same speed but opposite direction, e.g., in slow sub-test, when the target velocity is $20^{\circ}/s$, the result of HoloLens2TM is about $20.42^{\circ}/s$ (left to right) and $20.54^{\circ}/s$ (right to left). Individual difference was observed. A participant may perform better with one direction but worse with the other.
 - (c) The result recorded by the HoloLens2TM is generally faster than that by VNG device, especially in the result of the slow sub-test ($20^{\circ}/s$). The results recorded by VNG device are about 0.73 times less than that of HoloLens2TM. Weighted correction is possible if we multiply 0.73 to the data of HoloLens2TM for normalization. The fast OKN test ($40^{\circ}/s$) recorded by both devices, on the contrary, are quite similar. Weighted correction may not be necessary.

(d) The standard deviation of results recorded by the HoloLens2TM is generally larger than that by the VNG device. The reason may be the difference of calculation methods. In the results recorded by the HoloLens2TM, we count every possible slow phase for average, even those suboptimal or poor waves. On the other hand, the result of the VNG device is calculated from a range of waves selected by the examiner usually more stable with good reproducibility. HoloLens2TM.

(e) Note that the gain of OKN is both inferior to the original target speed in the high speed test ($40^\circ/s$), meaning the speed exceeds certain population's capacity.

Table 5.2

The average result^a of OKN test in Experiment 1 by different device, and its setting.

OKN Type	Device		Setting
	HoloLens2 TM	VNG Ulmer from ©Synapsys	
Left to Right, Slow	$20.42 \pm 5.63^\circ/sec$	$14.78 \pm 2.42^\circ/sec$	$20^\circ/sec$
Right to Left, Slow	$20.54 \pm 7.79^\circ/sec$	$14.63 \pm 1.91^\circ/sec$	$20^\circ/sec$
Left to Right, Fast	$29.43 \pm 9.6^\circ/sec$	$27.53 \pm 4.93^\circ/sec$	$40^\circ/sec$
Right to Left, Fast ^b	$29.16 \pm 7.79^\circ/sec$	$28.92 \pm 3.24^\circ/sec$	$40^\circ/sec$

^a The result of the HoloLens2TM and VNG device is the absolute value of the slow phase velocity (SPV). The result of one subject in HoloLens2TM is invalid, which is excluded from both device group.

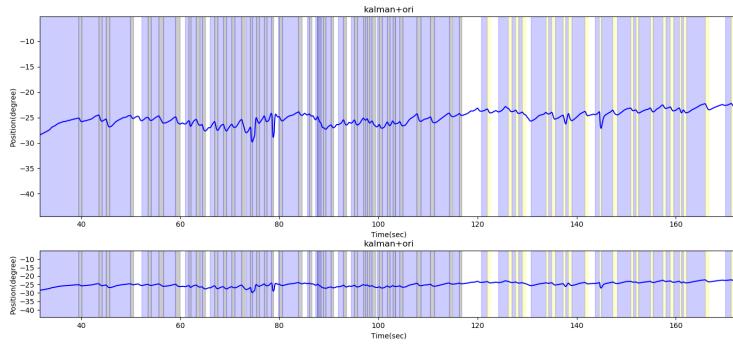
^b There is a mechanical problem when five subjects are testing this sub-test, therefore the result is the average of the remaining data.

Note. This table shows the result of HoloLens2TM, VNG Ulmer from ©Synapsys, and the target of the test. The result is the average of the data collected from the subjects.

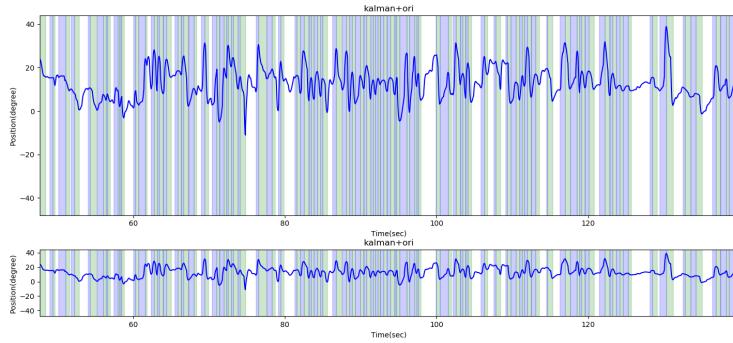
5.3 Caloric Tests

Several results of caloric test are shown in figure 5.5, note that in practice, the horizontal nystagmus is the main focus, thus the result of y axis is ignored:

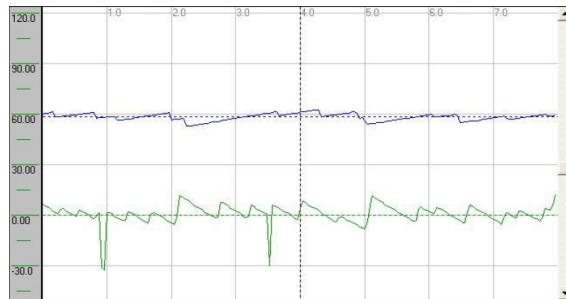
1. The waves of HoloLens2TM are not as ideal as that of the VNG device when the eye movement is too fast. The waves of the caloric test with HoloLens2TM are not always typical as nystagmus, as there are many oscillations, large and small shifts staggered. In other words, the result from the HoloLens2TM is “not



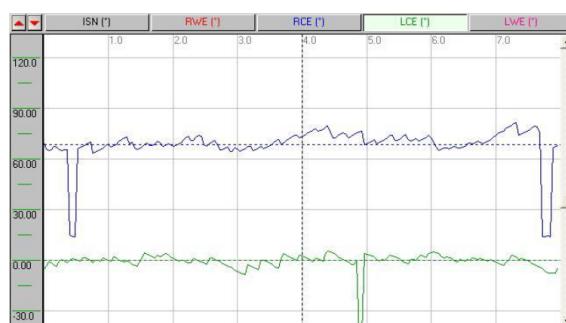
(a) A moderate result of HoloLens2TM. The nystagmus patterns are typical in such results.



(b) A intense result of HoloLens2TM. The nystagmus patterns are atypical in such results.



(c) A moderate result of VNG device.



(d) A intense result of VNG device.

Figure 5.5: Result of Caloric Test in VNG device and HoloLens2TM. We use “moderate” and “intense” to describe the waves with different amplitudes and frequencies.

very saw-tooth-like”, which is the typical shape of the nystagmus. We think it is because that the nystagmus in caloric test tends to be very fast and intense, thus the HoloLens2TM may not track it very well. Moreover, the low sampling rate of it may also contribute. Note that there are typical nystagmus patterns found in some results, but only when the wave is moderate in amplitude and frequency. Here we use the term “moderate” and “intense” to describe the waves with different amplitudes and frequencies through the whole data.

2. Though not typical, the wave still serves for clinical use: Though the result wave may not as typical as the definition of nystagmus, it still shows the nystagmus features, which includes quick and slow phase. We can still find the quick phase and the corresponding slow phase by the algorithm, but the lines which comprise two phases may not be very straight and smooth as expected in typical nystagmus. Due to the intense nature, the nystagmus may have similar value of the fast and slow phase velocity. However, the continuity and pattern of nystagmus are still obvious when recorded by HoloLens2TM, and the data is comparable interaurally in the same person.
3. Nystagmus detection: The results of the nystagmus detection are also shown in figure 5.5. We label the possible nystagmus region of it, with slow phase painted blue and quick phase painted with three other colors. We can get the average SPV of $10.98^{\circ}/s$, while the average SPV of VNG device is about $18.26^{\circ}/s$. The slower result is because that our algorithm looks for peaks in the whole test, while VNG device finds it in a selected range. The nystagmus may differ in magnitude and duration during the whole test process for a subject. In our result, the number of small nystagmus is slightly greater than the big one. On the other hand, the result of VNG device is calculated in the range where the largest (or fastest) nystagmus appears. This makes the result of VNG device faster than ours.
4. Comparison of different devices: The result of the comparison between two device is listed in table 5.3:
 - (a) The standard deviation of both device are large, unlike that of the OKN tests. This is because the caloric test is a test that examines evoked nystagmus by intense physical stimulation, unlike OKN, a test mimicking nystagmus production. Variation and unpredictability is more expected in caloric test.
 - (b) The average and standard deviation of the HoloLens2TM is generally

smaller than that of the VNG device. Difference of tracking technology may contribute to this variation.

(c) The VNG device still generates a better waveform than HoloLens2TM, possibly due to different tracking technology or filter used.



Table 5.3

The average result^a of caloric test in Experiment 1 with different devices.

Caloric Type ^b	Device	
	HoloLens2 TM	VNG Ulmer from ©Synapsys
Left Ear	$8.97 \pm 5.97^\circ/\text{sec}$	$17.49 \pm 9.19^\circ/\text{sec}$
Right Ear	$12.98 \pm 9.29^\circ/\text{sec}$	$19.04 \pm 11.45^\circ/\text{sec}$

^a The result of the HoloLens2TM and VNG device is the absolute value of the slow phase velocity of caloric nystagmus.

^b The stimulation is water in room temperature.

Note. This table shows the result of HoloLens2TM and VNG Ulmer from ©Synapsys when performing caloric test. The result is the average of the data collected from our subjects.

5.4 Results of Questionnaire

We collected 16 responses after their experience of the whole procedure from the participants. The following lists the result of each question.



1. The difficulty to operate the application during the test:

- Easy: 8
- Normal: 8
- Hard: 0

2. Is there any problem when operating the application:

- Yes: 3
- No: 13

3. Your opinion on the process of test, application, and the device(HoloLens2TM) itself? (This question is free to answer): Only 12 of them replied to this question. Here we only list some of the whole results, with them translated to English.

- The new device(HoloLens2TM) is convenient, but the eyes need to adapt to it. Moreover, it may make user feel dizzy or generate rejection reaction.
- Can't successfully touch the panel during the experiment.
- Hope that the field of view can be wider (or it will make the touch fail), and the angle of the water pouring be more accurate.
- Hope there is a different way to conduct the test, either preparing a chair which can support the neck more or coming out with a better posture so that the participant won't feel uncomfortable during the test.

Based on the first two question, we can assume that the operation is not very difficult for users, and even if there is a problem during the test, the participants are able to manage with the help of staff.

Generally, the user's comments focus on the operation of the device and the application. Because the calibration of eyes is a necessary process before the test and is the system process of the device, it's difficult to have a better way to improve this problem. On the other hands, we can improve the application

and the process of the test with these responses. Overall, the use of the device to conduct the test is convenient and easy to operate.





Chapter 6

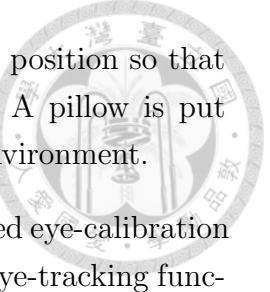
Experiment 2

The purpose of the second experiment is to validate the use of HoloLens2TM practically in the clinic. Standard examination of nystagmus is designed and installed in the device. It is the combination of several test, including Gaze Nystagmus, Positioning Nystagmus, Dix-Hallpike Nystagmus, and Positional Nystagmus tests, with some modification in order to perform the test comfortably with the HoloLens2TM. Currently, the tests are performed through Frenzel Glasses (see section 2.1.3), with an experienced examiner (usually a doctor) directly monitors the patient's eyes through the lenses. During the examination, the examiner has to turn the patient's head to trigger nystagmus. Our device is automated. The patient was guided to perform all tests by themselves by following the pre-recorded audio instructions and visual instructions. The examiner gave instruction from aside if necessary. For a healthy person, absence of nystagmus is regarded normal.

6.1 Test Flow

The main test process is shown as figure 6.1, which are Gaze Nystagmus (GN), Dix-Hallpike Nystagmus (DN), and Positional Nystagmus respectively (PN). These tests correspond to gaze nystagmus, the combination of positioning nystagmus and Dix-Hallpike nystagmus, and positional nystagmus respectively. Each category is composed of several sub-tests, which last for 15 seconds in Gaze Nystagmus and Positional Nystagmus, and 20 seconds in Dix-Hallpike Nystagmus. The whole test flow is listed as follow:

1. The experiment-staff notifies the propose and process of the experiment to participant. The experiment is conducted only when the participant fully notified and agrees to conduct it. An informed consent form in duplicate is then signed by the participant before the test.



2. The experiment-staff helps the participant adjust their body position so that the participant can comfortably lie down with the device. A pillow is put under the participant's neck to provide a comfortable test environment.
3. The participant is asked to go through the automatically started eye-calibration program of HoloLens2TM, which ensures the accuracy of the eye-tracking function of it. If calibration is not completed, the output data are deemed invalid.
4. The application of nystagmus program is activated by the experiment-staff.
5. The program automatically proceeds, with auditory and visual instructions given to the participant so that he/she can successfully follow the whole procedure. The experiment-staff will help the participant with problems during the whole procedure.
6. There is time break between each subset of test.
7. GN: In GN test, the participant is asked to gaze at the specific direction. The direction are: front, left, right, up, and down, with the head stay still.
8. DN: In DN test, the participant is asked to perform several position and posture changes. The participant is asked to turn their head toward left/right, lie down with head fixed toward the direction, and keep looking straightly. After that, the participant then asked to sit up, with head still facing left/right, and keep looking straight.
9. PN: In PN test, the participant is asked to sit tight, with head toward specific direction (front, left, and right) and look straight. After the first three sub-tests, the participant is asked to lie down. In the next three sub-tests, the participant is asked to turn his/her head toward specific direction (front, left, and right) when lying, and keeps looking straight.
10. After all tests finish, the participant is guaranteed with proper rest before they are fully recovered from the tests.

This study is approved by National University Hospital Institutional Review Board. The participants are patients of NTUH ENT clinic, all well informed with the test process, and the potential symptoms (such as vertigo induced by the maneuvers). The participants of the test are selected by an experienced ENT doctor, with detailed medical history and the physical exams done in the clinic. The participant can quit the test whenever he/she think they can't proceed for any reason (the data collected is then discarded). The data collected during the test is de-identified and will be

deleted after the project finishes. The experiment is performed with examiners supervising, including an otolaryngologist.

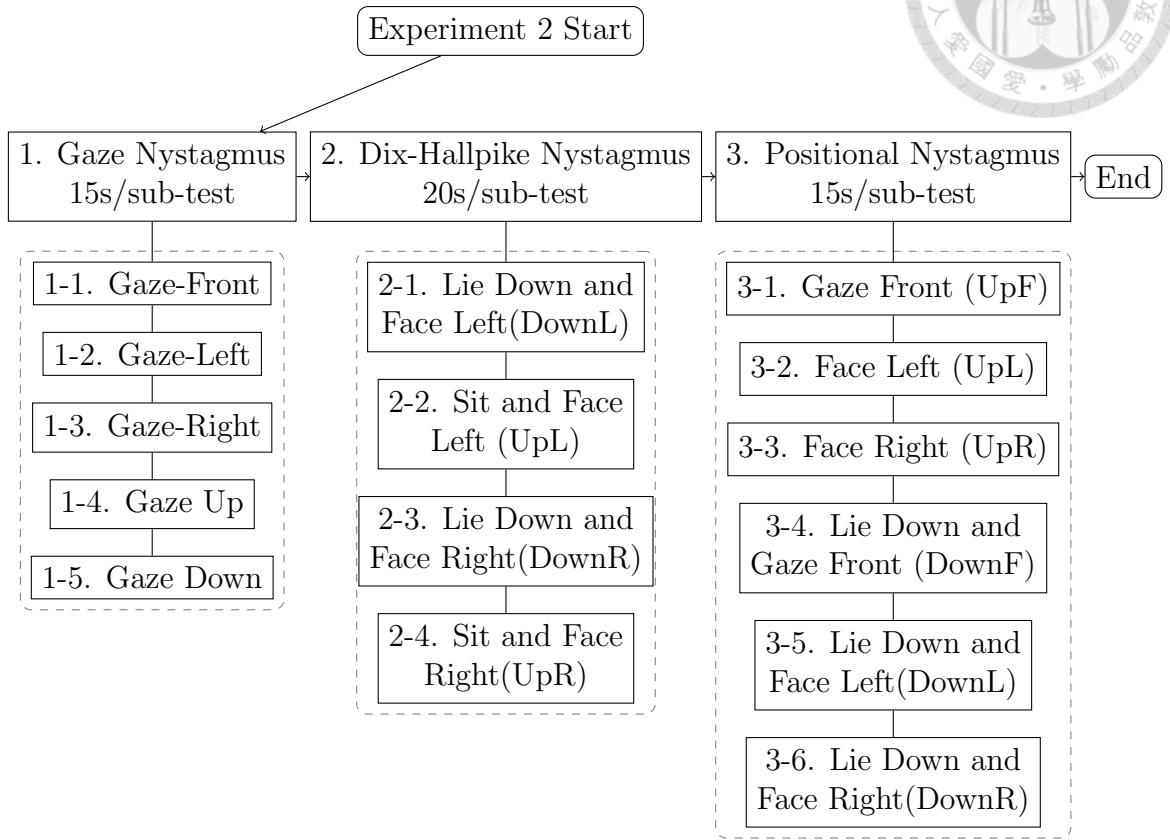


Figure 6.1: The flow of experiment 2, consist of the modification version of Gaze nystagmus, Dix-Hallpike Nystagmus, and the Positional Nystagmus.

6.2 Design of Test Application

The screenshot of the application is as figure 6.2. The panel in the middle shows the category of the test, the number of the next sub-test, and a count-down timer shows the remaining time before the next test starts. The button on the right is the start button. By clicking it, the test will automatically starts, and the whole test is then automatically proceeded with pre-recorded auditory and visual instruction. After all sub-tests of a category finish, it will automatically switch to the next category. The examinee can rest for a while before they press the start button to start next test. The 1, 2, and 3 button represents the Gaze Nystagmus, Dix-Hallpike Nystagmus, and Positional Nystagmus respectively. One can also select certain category to perform the individual test needed. The exit button is the one at the upper-left, with home icon attached on it. Other details are the same as the details of application mentioned in section 3.4.2.

Based on the feedback of the experiment 1, we optimized the user interface of the application. The size of start button is magnified, and is positioned at a handy place for right-handed people. Other buttons not frequently used, such as category choosing buttons and exit button, are thus be placed at the rim of the control panel. This optimized design is more user friendly, and even older people (over 60 years old) can easily operate the application by themselves during the experiment.



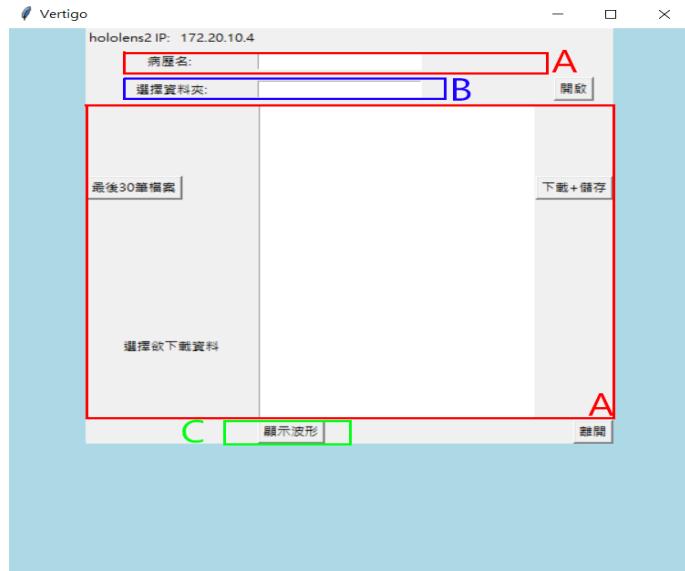
Figure 6.2: The application of the experiment 2 in HoloLens2TM. It is built with Unity3D (Unity[®]), using the Mixed Reality Toolkit developed by Microsoft[®].

6.3 Design of Viewing Program 2

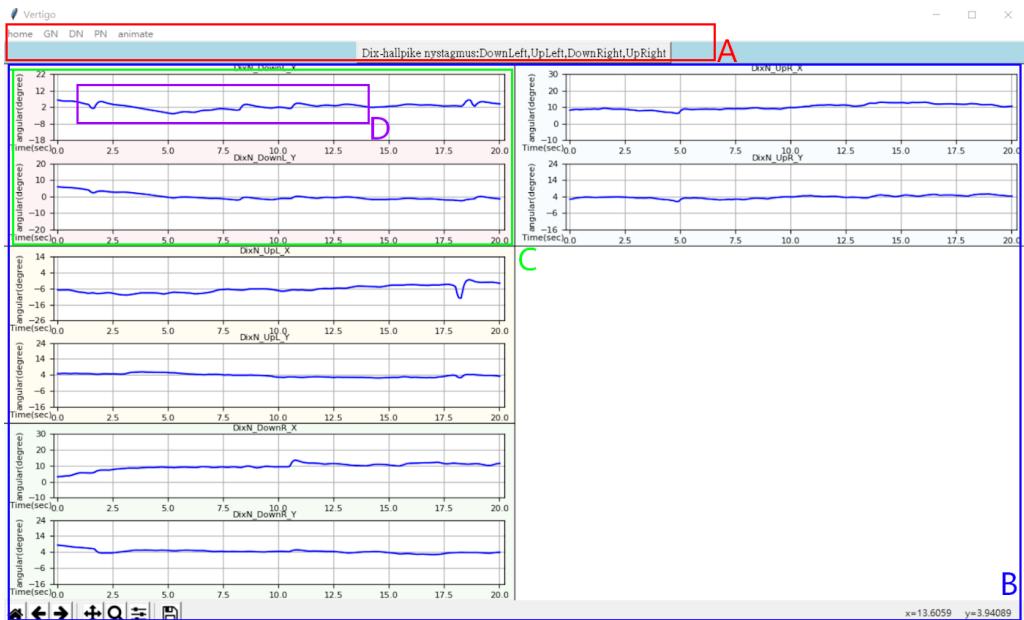
We designed a viewing program optimized for experiment 2. The program is also based on *Tkinter*[Lundh, 1999] and *Matplotlib*[Hunter, 2007] with *Python*. The demonstration of data is the same as that mentioned in 3.3.

The program is divided into two part. The first part is the file selection and download. The file selection function is for data examination and analysis, while the data download is for clinical use. When a test finishes, the data is stored in HoloLens2TM. By downloading it through Windows Device Portal, which is built on REST-API, with WiFi connection, we can get the data easily and can immediately check the results of the test on a computer.

The second part is the data viewing. As the figure 6.3 shows, the waveforms of all sub-tests of each category are demonstrated simultaneously on the screen. To get a clearer view, the results can also be viewed in the application 1.



(a) First part of viewing program 2. Region labeled A is for data downloading from HoloLens2™. B is for local data examination. Click button C to switch to data viewing.



(b) Second part of viewing program 2. Region labeled A is composed of category switching buttons. B is the data viewing window. The data is shown as C, with X and Y axis data shown up and down respectively. D shows one example of nystagmus wave should be seen in the experiment 2.

Figure 6.3: The viewing program 2



Chapter 7

Result of Experiment2

7.1 Expected Nystagmus In the Clinical Test and the Limitations

We first address the nystagmus should be seen clinically. As mentioned in section 2.1.7, BPPV is the most common disease in our clinical experience. Therefore, the nystagmus, if occurred, should be firstly assumed to be those related to it, which is listed in table 2.2. Note that there is no guarantee that the nystagmus should appear even for those who feel severe dizziness during the test. The limitations and problems may be as follow:

1. The period between vertigo attack and clinic visit is too long, and the nystagmus may have already alleviated.
2. It may take a while for the nystagmus to take place after triggered by the maneuver (long latency) before the examiner already finishes the test.
3. The nystagmus may be a slow one, whose slow phase is very long and travels for a large degree, and small one, which only lasts for few seconds and travels for a small degree. Such nystagmus may be ignored by the examiner.
4. The type of vertigo does not always induce characteristic nystagmus, and the trigger maneuver may not always induce nystagmus due to individual or environmental conditions.
5. Certain nystagmus be triggered in a healthy patient, e.g. end-point nystagmus.

We hope the use of HoloLens2TM in the examination can help us fix the second and the third problem, and still result in the same result of doctor's examination.

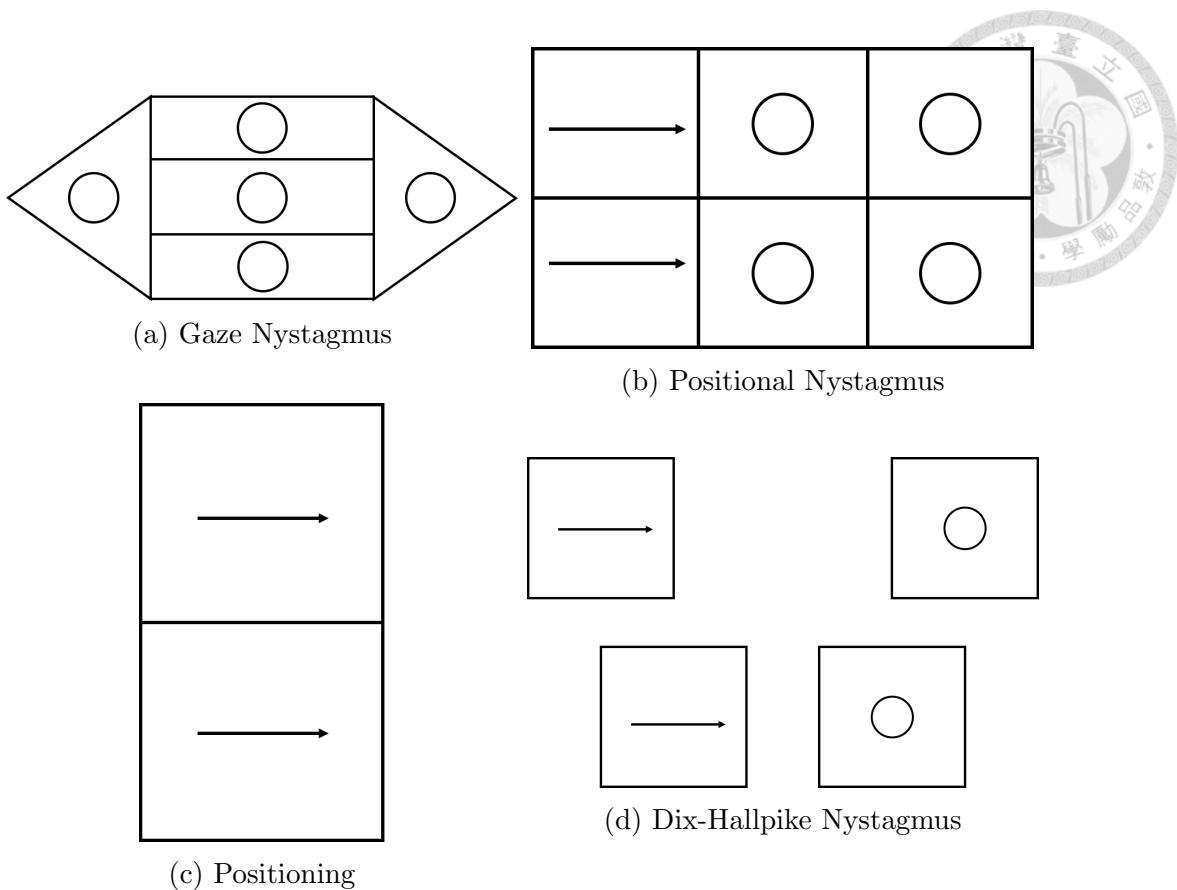


Figure 7.1: One example of clinical nystagmus examination. The direction of the figure indicates what the examiner actually sees. For example, the left triangle in figure 7.1a means “the subject looks to his/her right”. Similarly, the upper right square in 7.1b means “the subject lie down with head turning to the left and looks straight”, while the lower right means “the subject sit up with head turning to the left”. The mark works the same as the figure. The circle means “no nystagmus”, and the arrow’s direction indicates what the examiner see in the subject’s eye. The right-oriented arrow in the figure means left nystagmus. Note that Positioning test is similar to Dix-Hallpike test.

7.2 The Diagnosis of The Doctor (Specialist)

Figure 7.1 shows an example of nystagmus observation via Frenzel goggles recorded by the clinician. It is composed of Gaze Nystagmus, Positioning Nystagmus, Positional Nystagmus, and Dix-Hallpike Nystagmus.

When nystagmus is absent, a circle will be marked in the column corresponding the test; while nystagmus occurs, an arrow is drawn in the column indicating the direction and intensity of the nystagmus. Note that the direction of the arrow indicates what the examiner sees in his/her own eye; i.e., the direction is opposite to the examinee’s orientation. For example, the upper left square in the Dix-Hallpike and

Positional Nystagmus means subject lying down and turning head toward right; the arrow toward left stands for right nystagmus. In other words, it is a record of what the examiner see. The clinician will then make diagnosis according to the results. In this project, 10 out of 56 patients had nystagmus detected by Frenzel glasses.

7.3 The Results of HoloLens2TM

The results of HoloLens2TM are examined by a specialist in vertigo. The results are shown according to their category in the program we design. The doctor then chooses the candidate result to be shown in the program of experiment 1 if can't see clearly. With the support of the nystagmus detection algorithm, we can judge whether the nystagmus exists more easily. When there is a conflict result with that from the Frenzel glasses,

1. Most of the waveforms are straight line with several small jerks. The straight line indicates no nystagmus expected in a healthy person. The small, independent jerk occurs frequently in many participants. We assume such jerks are from random eye movements.
2. Artifacts may occur in the beginning of the test, probably because the subject may still adjust their posture. Nystagmus usually does not occur that soon.
3. The result of Gaze Nystagmus is mostly nystagmus-free, as the participants may already undergo central vestibular compensation.
4. There is invalid data in some participants, which may be attributed to poor eye tracking. Sometimes when the subject turn his/her head, the HoloLens2TM may be loosened, and thus causes failure of the eye tracking.
5. There are 21 out of 56 patients' results are judged as nystagmus by the same algorithm. Nystagmus in two cases are not definitely clear. Gaze nystagmus only appeared in one case.

7.4 Comparison of Nystagmus Detected by Frenzel Glasses and HoloLens2TM

We compare the nystagmus detected by Frenzel Glasses and HoloLens2TM and analyze their differences.

Table 7.1

Detection of nystagmus by HoloLens2TM and Frenzel Glasses^a in standard clinical tests of nystagmus.



Result	Result Type	
Number of Positive: Negative	HoloLens2 TM	Frenzel Glasses
Gaze Nystagmus(GN)	1 : 55 ^b	0 : 56
Dix-Hallpike Nystagmus(DN)	18 : 38	9 : 47
Positional Nystagmus(PN)	9 : 47	6 : 50
Vestibular Nystagmus in tests	20 : 36	10 : 46

^a Positing Nystagmus in clinical test is regarded the same as Dix-Hallpike Nystagmus in this study.

^b The only one positive GN case is not counted here because it is diagnosed as end-point nystagmus, which is a normal physiological phenomenon.

1. Except for one case, the results of Gaze Nystagmus are all negative. As expected, the Gaze Nystagmus is mostly absent in the outpatients due to central vestibular compensation. The only positive one may be the end-point nystagmus, which happens when eye looking at the extreme left/right. Such nystagmus is regarded as a normal physiological phenomenon, not associated with abnormality[[Eggers et al., 2019](#)]. Therefore, this case is not discussed in the following content.
2. Dix-Hallpike nystagmus is most frequent detected. As expected, BPPV is most common in the outpatient.
3. The positive cases (10 cases in total) in the Frenzel glasses group are also positive in the group of HoloLens2TM, with only one case not definitely conclusive. “Positive” indicates at least one nystagmus appearing in tests, and negative indicates none in tests. Positive nystagmus in the two groups are not necessarily in the same sub-test category.
4. There are 10 cases of positive nystagmus in the group of HoloLens2TM but not in that of Frenzel glasses. The reasons can be the following: false-positive detection of nystagmus by HoloLens2TM, nystagmus of very small magnitude ignored by Frenzel glasses, and inconsistent presence of nystagmus in the recovery stage of vertigo. These conflict results are further analyzed by taking other clinical information into account.

5. Clinical information of the 10 conflict cases were analyzed to make primary impressions.

- (a) 5 out of 10 cases are diagnosed as BPPV, and positioning nystagmus is reasonably to occur. Results from HoloLens2TM do meet the expectation (listed in section 7.1). These nystagmus may be too small to be detected via Frenzel glasses.
- (b) The other 5 cases have diagnosis other than BPPV, such as idiopathic vertigo, vertebrobasilar artery insufficiency and vestibular migraine. These diseases are not diagnosed with characteristic nystagmus. It is not possible to explain the origin of nystagmus waveform recorded by HoloLens2TM with the clinical information at hand.

Analyzing conflict data proves that HoloLens2TM is able to detect minor nystagmus not identified by Frenzel glasses. In conclusion, our system of nystagmus detection in HoloLens2TM is more sensitive than the Frenzel glasses.



Chapter 8

Discussion

8.1 Performing VNG Items Independently in HoloLens2TM Without A Projection Screen

In addition to the two experiments mentioned before, we had performed a preliminary research to perform the VOMS test with target items completely generated by the HoloLens2TM itself without the assistance of a projection screen. The project was later postponed because there is no similar paradigm to validate and compare the data. Some problems were encountered; for example, the small field of view of HoloLens2TM limits the traveling width of moving test targets, e.g. pursuit. Furthermore, the display of the target in the device is not very clear with strong light in the environment. In addition, user interface optimization, online analyzing, and a tutorial is necessary for this expanded examination. On the other hand, if problems are solved, this device becomes multi-functional; it detects spontaneous nystagmus like Frenzel glasses, but with better sensitivity and at the same time it can substitute the huge, immobile and expensive VNG device.

8.2 The Use of HoloLens2TM as Diagnosis Device in Emergency Deartment (ED)

Using HoloLens2TM as diagnostic tool in the ED is our important goal, since this wireless automated device may exert its maximal power in ED. Diagnosing vertigo patients is difficult in ED due to patient's poor general condition, insufficient time and resources for comprehensive study of disease, and lack of specialized manpower. Form this view point, an automatic diagnostic device like HoloLens2TM really helps in the very busy environment like ED. Some modification of our device such as

simplified test procedures may be needed to adapt to ED, as the patients with vertigo are usually too weak to follow complicated instructions. Future clinical trial in the ED is currently in design.



8.3 Other Devices

There are other devices of VR and AR with built-in eye tracking function. Before HoloLens2TM, we have installed the nystagmus detection algorithm in another eye tracking device, FOVE (Copyright ©FOVE, Inc), and the results were encouraging and promising. However, FOVE is not universally popular and its functions are limited. We turned into Microsoft®HoloLens2TM for its wireless mobility (a cable required between FOVE and the computer), and capability of functional expansion under Microsoft®'s popularity. Generally speaking, with appropriate modification, our whole process of nystagmus detection, including experiment detail, program designed (application in the device and viewing program), nystagmus detection algorithm, and data validation, can be ported to other suitable device.

8.4 Limitation

There are some limitations of the device.

1. The frame rate (fps) of the data is not stable and is considered to be low compared to other works. Though the fps in our result is about 50, we found out there are a few 30 fps data. As for the low fps, we think it is one of the cause of the jagged waveform in the original wave. It does not affect our result dramatically, but we think several nystagmus in caloric test can not be correctly sampled and thus can not be detected because the fps, or sampling rate, is too low according to sampling theorem[Shannon, 1949].
2. Mounting the HoloLens2TM steadily on the subject's head during testing is important. If not securely placed, the data collected by HoloLens2TM are affected to a certain degree. Therefore, a proper fixing method for the HoloLens2TM should be carefully designed to provide stable results.



Chapter 9

Conclusion

We proposed the use of HoloLens2TM to detect nystagmus in patients with vertigo/dizziness. The accuracy of our device is comparable to benchmark device, VNG. Our system is also proved to be more sensitive and superior to current tool, Frenzel glasses, in the detection of nystagmus in the clinical trial of outpatients. Further work may be required for optimization and expansion of its use, e.g., in the emergency room.



Chapter 10

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