Application of computational methods as an adjunct to upper airway assessment

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Declaration of Originality

I declare that the work presented in this thesis is my own, and any work done by others is explicitly attributed.

Louisa Ritchie
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Abstract

This work comprises of an investigation into the application of virtual geometric reconstruction and computational fluid dynamics to the upper respiratory tract, to investigate how their anatomical form affects airflow and to examine the potential of 3D modelling of the airway as a potential surgical adjunct. For the latter purpose, the technology would need to have the ability to produce clinically relevant flow information in a timely, cost-effective fashion. Furthermore, it would need to ensure accurate model reproducibility, with specified limits to inter-user variability; thereby reducing costly post-processing in order for computational simulations to be performed.

In this work, computational analysis of airway flow is subjected to critical assessment, examining each stage in the process of model building, testing and validation. The first stage is that of translating clinical scan data (usually CT or MRI) into a virtual 3D model for geometric analysis and flow simulation. In defining the airway geometry, key issues are variations in the quality of scan data, together with variations in the procedures used for image analysis and segmentation. Either may compromise the accuracy and the reproducibility of results and some of the results to be presented will indicate that there is a need for systematic research into threshold choices used for image segmentation of both normal and pathological geometries. A further issue is dynamic airway movement: most current scan data does not capture such data, but examples are shown to indicate the scale of such neglected effects.

Having obtained a virtual anatomy, in the following stage computational fluid dynamics simulations can be performed to assess flow dynamics. Even though 3D virtual modelling is already used clinically by cardiothoracic and maxillofacial surgeons, knowledge of specificity and sensitivity of measures applied to geometries as complex as the nasal airway as indicators of physiological performance or markers of pathology is still unknown (Rao and Menon, 2015, Saad et al., 2013). In particular, uncertainties in determining the original geometry affect the predictions of flow, which is an issue as yet scarcely addressed. Here, results of a pilot study detailing a methodology to investigate the scale of such effects in computational prediction of nasal airway flows will be described.
Whilst completing the two stages, namely model building and computational simulation provide the required output of air flow prediction, a third stage necessary for developing the technology is validation. In this work, an experimental procedure based on rapid prototype manufacture of replica airways, introduced as part of an investigation of the effects of glottis aperture on pressure loss in the trachea, provides a means for validating the computational methodology. Indeed, such replica models may offer an alternative to computational methodologies for more complex problems.

Finally, the processes by which models are created and simulations performed are discussed in the context of requirements for validation and streamlining of the process for clinical acceptability.
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Chapter 1: Introduction

Motivation and aims of the study

Most medical therapies have an objective measurement by which to determine the outcome. By contrast, surgical therapy applied to the airways is, in many areas, limited by the paucity of objective quality outcome measures. Although the purpose of much airway surgical intervention can be clearly stated as ‘improving airflow’, determining the degree of improvement, or even how best to achieve this can prove elusive. Detailed measurement of airflow distribution in the airways is not possible, given their small size and complex shape; those measurements that are possible are typically limited to overall pressure loss and flow rate, as is the case for rhinomanometry for the nose. Unfortunately, however those measurements that are feasible often do not provide sufficient information to fully inform clinical evaluation and decision making.

The use of image-based computational modelling is an emerging tool that is hoped will address the problem. In engineering, computational simulations have become an established tool to model and anticipate how modifications to a device will affect performance, with computational fluid dynamics now accepted as a standard tool in aerospace, formula 1 and other areas. Translating these tools to the field of medicine and surgery is the objective of much current research, principally for application to the cardiovascular system, but more recently also to the respiratory system (Remuzzi and Manini, 2014, Rao and Menon, 2015). Patient-specific CFD models could be an ideal technique to assist surgeons in clinical decision making when assessing upper airway dysfunction, by providing objective data to correlate with subjective symptoms and reduce surgeon subjectivity and therefore variability; it might also allow surgical simulation and the success of surgery to be quantified.

Before computational modelling can play a significant role in airway medicine and surgery, key aspects of the technology however require assessment, testing and refinement within the relevant contexts, rather than relying on experience in related areas, such as cardiovascular mechanics. Several particular features of large airway respiratory mechanics need to be considered. Firstly, the dynamics of airflow
in the large airways exhibits greater susceptibility to turbulence than in the large arteries, a consequence of the mostly higher Reynolds numbers as described later.

Secondly, the issue of anatomical variability needs to be considered: a single scan merely provides a single snapshot in time of the large airways. Not only is airway geometry highly complex, particularly in the nose, but it is dynamic, responding to changes in environment, posture and autonomic stimuli. In the nose particularly, airway geometry differs significantly between individuals, challenging the applicability of population-based generalisations.

**Aims of this study**

The presentation of the work is organised as follows:

**Chapter 2** briefly reviews the pertinent features of upper airway anatomy clinical assessment and then considers in sequence:

- procedures for virtual model creation and airflow analysis;
- definition of models and segmentation;
- the stages in moving from segmentation to virtual airway models, illustrated for the nose;
- essential mechanics of flow, introducing Reynolds number and pressure losses;
- and finally provides an overview of geometry features and airflow in the upper airways from the nose to the carina.

**Chapter 3** examines the effect of inter-user variability in segmentation within the nose and trachea as well as the impact of different imaging modalities for the airway.

**Chapter 4** discussed the literature related to computational fluid dynamics of the airways, followed by an investigation into the consequences of geometric variability on nasal airflow distribution.
Chapter 5 comprises of a summary of the methods by which the glottis can be evaluated and considers in sequence;

- the dynamic assessment of glottic function through the use of endoscopes;
- manual and semi-automatic glottic segmentation from endoscopic film;
- methods for automatic glottic segmentation;
- dynamic imaging of the glottis.

Chapter 6 presents a literature related to experimental and computer assisted design of tracheal models. And considers in sequence;

- the design of a modular replica experimental model of the upper airways;
- the design of an idealised model of the upper airways;
- experimental results comparing pressure loss distribution between a replica and idealised model.
Chapter 2: Review of Clinical Context and the Image to Computational Model Technique

2.1 Upper Airway Anatomy and Clinical Assessment

2.1.1 Nasal anatomy and function

There is significant variation in both internal and external nasal anatomy, which can be secondary to ethnic and to eco-graphical distribution to iatrogenic causes. Nasal anatomy has evolved to give equivalent function regardless of the environment in which a person lives. With this innate variation in mind, it seems fundamental that studies pertaining to nasal health accommodate that variation. As a consequence research targeted at providing patient specific treatment for nasal disease needs to take into account the subtle anatomical differences and how this can affect a patient’s physiology (Snow, 2003, Churchill et al., 2004).

Figure 1 Bony and cartilaginous anatomy for the nose (MSK-anatomy, 2012)
Anatomically the nose is subdivided into the external and internal nose. The structure of the external nose comprises skin overlying a cartilaginous-bony structure (Figure 1), the profile of which is dependent on the position of the nasal bones and the midline septum which divides the two nasal cavities. External trauma can often result in displacement of the septum or nasal bones resulting in a distortion of one of the nasal cavities which may compromise nasal function.

Entering the nostrils, in the area known as the ‘vestibule’ there is a continuation and thickening of the facial skin which is hair bearing stratified keratinizing squamous epithelium. Adjacent to the septum after 5mm the skin transitions to ciliated columnar epithelium, like that of the lower respiratory tract, however more superiorly in the vestibule squamous epithelium continues to the lower border of the upper lateral cartilage. The nasal cavity extends directly backwards and is continuous with the lower airways; tasked with three functions which it is anatomically evolved to perform. Primarily the nose promotes heat and moisture exchange to condition the air prior to entering the lungs: in vivo studies have recorded air temperature of between 31°C and 34°C in the nasopharynx with a relative humidity of 90-95% indicating the nose performs the bulk of this task. This will vary depending on the outside ambient room temperature and the respiratory rate and studies are still subject to inter-user variability in probe measurements of 0.5°C and 3% humidity (Keck et al., 2000, Wolf et al., 2004). Additionally, approximately 100,000 seromucous cells exist within the nasal mucosa creating between 1.5 to 2 litres of mucus a day, which humidifies the inspired air and traps harmful particles (Ugwoke et al., 2005). This mucous is then swept in a continual mucociliary transit towards the posterior nose and ingested.

The nose can filter particles of a size greater than 10 μm, its filtering efficiency dropping off to almost zero for particles as small 1 -μm, then increases again where about 80% of 1 -nm particles will be absorbed at flow rates of 15 l/min. The larger the particle the greater chance it will be deposited in the anterior nose, thus aerosolised medications must be of small particle size to minimise early deposition (Garcia et al., 2009).

The nose also has the protective role of olfaction through the 1st cranial nerve, the Olfactory Nerve. The nerve enters the superior nasal cavity through the cribriform plate supplying the mucosa in the roof of the cavity, superior turbinate and septum with multiple sensory nerve endings (Elad et al., 2008).
nerve endings come in contact with volatile olfactants in the area of the olfactory slit. Hahn et al estimated only 10% of the nasal airflow passes through this superior portion of the nose, where the flow velocity is reduced presumably to allow enhanced olfactory receptor binding (Hahn et al., 1993).

Various projections and narrowings of the nose such as the internal nasal valve, nasal rim and turbinates, have been suggested to enhance turbulence or increase mucosal exposure to the air. Inspired air passes from the nasal vestibule to the nasal cavity through the internal nasal valve, the small cross-sectional area of the valve when compared with the cavity results in a jet, which is predisposed to breakdown and turbulence at higher flow rates. The nasal rim on the entrance to the nose projects above the floor of the cavity. The turbinates or chonchae are curled bones projecting from the supero-lateral nasal walls which have a thick mucosal covering with erectile qualities, these projections divide the cavity into clefts, each called a meatus (Churchill et al., 2004). By partitioning the flow between the various meatuses, the turbinates greatly increase surface area; directing the flow through narrow passages also tends to reduce flow disturbances. There are 3 turbinates, inferior, middle and superior, although the superior can be absent in up to 80% of the population (Naftali et al., 2005). The septum divides the two nasal cavities and similar to the turbinates has erectile mucosa, allowing the airflow to each cavity to be modified by autonomic feedback or in response to environmental, infectious or immunological triggers.

The paranasal sinuses, of which there are four, are air filled cavities, which have a close relationship to the nose. Despite the nasal lining being continuous with that of the sinuses, they have little role in air conditioning, their role in fact being rather uncertain. The sinuses may provide a buffering support in facial injury, they make the skull lighter and have a role in acoustics during phonation. The detailed anatomy of each of them is beyond the scope of this report and in most models used for comparative studies the sinuses are excluded.

2.1.2 Nasal Pathologies

Nasal symptoms cause a significant reduction in quality of life and associated financial burden to society (Fokkens et al., 2007, Shedden, 2005). The main symptoms are nasal obstruction, excessive mucous production, crusting and bleeding, and through careful history taking, these are attributed to disorders
of the nasal mucosa, structural deformities of the nose or both. Mouth breathing leads to rapid drying of the saliva on the oral mucosa and teeth, leading to halitosis and dental caries; this is a common complaint of patients who suffer with nocturnal nasal obstruction.

Though the nasal resistance is higher than that of the oral airway, most healthy people breathe preferentially through their nose. However, during periods of high oxygen consumption such as exercise, there is a switch to mouth breathing. This typically occurs when minute volume goes above 35 l/min, average minute ventilation during light activity such as driving a car is 11-12 l/min whilst at rest or sleep it is lower, at between 5-6 l/min (Niinimaa et al., 1980, Zuurbier et al., 2009). End tidal pCO2 is lower in mouth breathing than nasal breathing suggesting that nasal breathing results in more efficient gas exchange; the absence of which may be related to nocturnal apnoeic episodes (Tanaka et al., 1988). For the following studies it should be noted that all models derived from CT or MRI scans will reflect patients in the supine or sleeping position with average minute volumes of 5-6 l/min (Stradling et al., 1985).

Inflammatory conditions of the nose such as Rhinosinusitis are prevalent with an incidence between 5-15% (Fokkens et al., 2012). Rhinosinusitis can be linked to allergy and atopy with strong connections to asthma and aspirin sensitivity; it can also be linked to disorder of ciliary dysfunction and immunosuppression. Patients with this condition have swelling of the nasal mucosa, increase in mucous production and sometimes nasal polyps; all of which cause varying degrees of physical obstruction. Other systemic inflammatory diseases such as Lupus, Sarcoidosis and Granulomatosis with polyangitis, can also present with nasal symptoms such as obstruction, crusting and bleeding, the chronic mucosal damage can even result in de-vascularisation of the septum and subsequent perforations. Chronic atrophic rhinitis is specific to the nose and can present with similar symptoms to chronic rhinosinusitis (inflammation), however the presiding complaint is that of nasal dryness.

Structural deformities of the nose secondary to nasal trauma for example can result in distortion of the bony nasal airway and damage to the neurovascular anatomy of the nose, which can produce a combination of airflow obstruction and reduction in airflow sensation. Neurovascular compromise can
occur in outdated techniques such as turbinate excision, where reduction in mucosal sensory neurones leads to a subjective sensation of nasal blockage despite a seemly patent airway.

2.1.3 Laryngeal anatomy and function

The Larynx is made up of a complex cartilaginous framework surrounded by intrinsic and extrinsic muscles. It is mostly lined with columnar ciliated epithelium except for the epiglottis, superior portion of the aryepiglottic folds and the free edges of the vocal folds which are covered with squamous epithelium. Ciliated epithelium, similar to the nose, creates a mucociliary transit containing inhaled particles towards the oesophagus.

The vocal folds are responsible for phonation and lie between the posteriorly-based arytenoid cartilages and the anterior commissure- the most anterior meeting point of the two vocal folds. Abduction and adduction of the vocal folds modulates airflow across the glottis controlling lower airway pressures and creating sound. Rotation of the pyramidal arytenoid cartilages results in the stretching of the vocal cords to vary the tone of phonation when air is passed through the adducted cords (Figure 3).

The larynx is a tri-function organ modulating airflow into the lungs, protecting the lower airways from ingested foods and allowing voice production. Rostral movement of the larynx during the swallow reflex results in the epiglottic base being compressed against the tongue base to fold over the laryngeal inlet. It also results in a steepening of the angle of the piriform recess down towards the oesophageal inlet, facilitating the passage of food.

Eckel (1994) performed a comprehensive evaluation of 53 post mortem human larynxes, the average diameter of the glottis from anterior to posterior was 13.8 mm in men and 10.7 mm in women and the average diameter between the cords post-mortem was 6.2 mm in men and 4.9 mm in women. This morphometric data is helpful when making flow assumptions from computational models to ensure that they are representative of normal anatomy (Eckel et al., 1994).
2.1.4 Laryngeal pathologies

From an anatomical perspective it is useful to split the larynx into three sections (Figure 2), dictated by their lymphatic drainage and range of disorders. The supraglottis is the area from the tip of the epiglottis, down to and including the aryepiglottic folds to the false cords. Below this is the glottis, defined as the space between the vocal cords, below which is the subglottis all the way to the first tracheal ring. The glottis will be further described in Chapter 4.

![Figure 2 A coronal view through the larynx showing the divisions of the supraglottis, glottis and subglottis (Gerber, 2016)](image)

The supraglottis can be affected by laryngomalacia in childhood, where the aryepiglottic folds are excessively taut resulting in the curling of the epiglottis. Excess supraglottic soft tissue and co-existing neuromuscular disorders also exacerbate the obstruction of the glottis and may result in stridor. In adults the supraglottis can be affected by infection, malignancy or trauma. Neuromuscular disorders such as Parkinson’s and Huntingtons impact both the motor and sensory function of the larynx impairing speech and swallowing progressively.

Neurovascular damage to the recurrent laryngeal nerves can result in vocal cord paresis where patients are unable to fully adduct one or both vocal cords. This results in air escape through the inadequately adducted cords, breathy speech and sometimes shortness of breath. The recurrent laryngeal nerve also effects sensation of the glottis, therefore these patients can complain of swallowing difficulties as they are unable to accurately perceive food boluses passing down towards the oesophagus.
Any dysfunction of the glottis whether functional or an obstructing lesion can lead to airway compromise. Emergency surgical treatment for airway obstruction is usually in the form of a tracheostomy where a breathing tube is placed directly through the neck into the trachea. A recognised late complication of a tracheostomy is subglottic stenosis, which can also occur secondary to inflammatory disease or prolonged intubation. Tracheal stenosis predominantly results from mucosal trauma and scarring but can also occur from extra luminal compression such as a goitre. The luminal cross-sectional airway can be sufficiently narrowed resulting in severe and progressive shortness of breath for patients.

High level athletes can suffer with exercise-induced inspiratory symptoms (EIIS) which is a form of laryngeal dysfunction which exhibits similar symptoms to that of exercise-induced asthma, on that spectrum can also occur exercise induced laryngeal obstruction (EILO) (Røksund et al., 2015). These laryngeal pathologies result in a decompensation either at peak exercise or after exercise. To differentiate these pathologies from asthma, a novel technique of cardiopulmonary exercise testing with continuous laryngoscopy is used. This testing requires visualisation of larynx during the dysfunction and a visual estimate of the extent of laryngeal narrowing. In COPD (Chronic Obstructive Pulmonary Disease) sufferers, using the same method of evaluation, there is evidence to show that laryngeal narrowing plays a role in the control of intrathoracic positive pressure. To quantify the larynx’s role in modulating pressure, image stills were taken at different exertional levels and the glottic area manually measured (Baz et al., 2015). One group created a scoring system designed to allow single image stills to be scored independently by two physicians. Whilst providing more objectivity to the process, it is still laborious, requiring two physicians and lacks complete objectivity and reproducibility (Maat et al., 2009). In conditions such as Paradoxical Vocal Fold Motion Disorder (PVFMD), the glottic aperture can narrow rapidly resulting in dyspnoea and stridor; the benefit of dynamic assessment is to demonstrate the trend of glottic narrowing; thus, still-screen shots may be less valuable than serial measurements. Furthermore, being able to compare trends before and after treatment would surely be a stronger marker of outcome (Matrka, 2014).
2.1.5  Tracheal anatomy and functions

The trachea is the conduit of air from the larynx to the bronchi and is formed of both cartilaginous rings, fibromuscular membrane and lined with respiratory mucosa. The trachea is typically D-shaped with the flat side located posteriorly where trachealis lies between the two ends of the C-shaped cartilaginous rings. The mean cross-sectional area of the 1st tracheal ring in adult males is quoted as approximately 3.2 cm³ (transverse diameter 1.9 cm), increasing to 3.5 cm³ (transverse diameter 1.8 cm) at the last tracheal ring (Otoch et al., 2013). In adult females the luminal area is slightly smaller, nearer 1.5 cm in transverse diameter, and in children it varies greatly depending on age. Paediatric tracheal lumen size is relevant for anaesthetists when choosing the appropriate size of an endotracheal tube, typically charts are widely available with age and tracheal diameter to aid this choice.

The cervical portion of the trachea is intimately related to the thyroid anteriorly, the oesophagus posteriorly and the great vessels of the neck laterally. Any disorders of these structures where enlargement may encroach on the trachea may affect the diameter of the internal lumen. As the trachea descends through the mediastinum it runs posteriorly to the aortic arch and medially to both lungs. In the groove between the oesophagus and trachea runs the recurrent laryngeal nerves responsible for supplying the larynx (Williams, 1995).
The function of the trachea is to act as a low resistance conduit to the lower airway and contribute to pulmonary toileting through mucociliary clearance. Any change in shape of the trachea will influence how air flows through it and any changes to the structure, number or co-ordination of the cilia will impact its ability to clear mucous from the airways. The mucous film itself has numerous roles including trapping of particulate matter, antioxidant properties and acting as a barrier to prevent microorganisms crossing into the respiratory mucosa (Wanner et al., 1996).

Passage of air through the glottis results in the laryngeal jet which hits the posterior wall of the trachea, with areas of recirculation or backflow; changes in the glottic shape influence the pattern and direction of this flow as well as the degree of resistance afforded to the passage of flow. Changes in the shape of the trachea may result in a similar disruption of the mucociliary pathway to that of the nose, where it is known that nasal septal perforations cause a discontinuity of the mucosal surface and a disturbance to laminar flow, resulting drying of the mucosa and crusting of mucous (Lanier et al., 2007). The potential for adverse tracheal geometry to disrupt mucociliary clearance may explain many patients depend on humidification when suffering with tracheal disorders.
2.1.6 Tracheal pathologies

Disorders of the trachea can broadly be separated into structural conditions affecting the shape and therefore the aerodynamics and conditions related to impaired of the mucociliary clearance (Al-Qadi et al., 2013).

Tracheal stenosis is characterised by a narrowing of the tracheal lumen and can arise from the luminal wall or from extrinsic compression. Albeit rare, primary tumours of the trachea such as squamous cell carcinomas or adenocystic carcinomas occur, presenting 70% of the time with exertional dyspnoea due to narrowing of the tracheal lumen (Nouraei et al., 2014). Cancers of the lung, oesophagus or metastatic deposits in mediastinal or hilar lymph nodes can lead to extraluminal compression and in late stage disease erode into the trachea itself. If caught in the early stages and deemed curable these may undergo tracheal resection and immediate anastomosis. At the anastomotic level there can develop benign stenoses; also seen following periods of prolonged intubation, radiotherapy, infection or in certain granulomatous diseases.

Extraluminal compression of the trachea can occur with a goitre, which typically is a benign enlargement of one or both sides of the thyroid gland. Though the trachea in most people has a slight curvature, as the goitre enlarges it can significantly deviate or compress the trachea, leading to symptoms of dyspnoea. This results in a pressure loss due to increased airway resistance. For example, Brouns computational simulations of tracheal airflow show an increase in pressure loss from 7 Pa in a 50% stenosis, to 46 Pa in an 80% stenosis (Brouns et al., 2007a).

2.2 Clinical assessment techniques

2.1.7 Nasal assessment

Surgical assessment of the nose begins with an examination of the external nose, observing deviation, splaying or depression of the nasal bones, asymmetry and condition of the skin. Commonly this will be followed by an examination of the internal nose with a Thudichum speculum, a term called ‘anterior rhinoscopy’, looking specifically at the aperture of the nasal valves, the size of the inferior turbinates
and the trajectory of the internasal septum. To appreciate the full nasal cavity and upper airway a fibre-optic nasal endoscopic (FNE) can be employed. FNE can be performed in clinic or the bedside with the patient awake, with the optional choice of topical anaesthesia, following which anatomy can be clearly visualised to the larynx. Videos and photographs can be taken for monitoring or teaching purposes and in the case of skilled technicians the upper oesophagus can be entered and examined (Simon and Sidle, 2012). However, examination is ultimately dependent on the experience and technique of the surgeon, as well as the co-operation of the patient; as a result, inter-user variability is significant and can ultimately lead to difference in surgical management (Hardcastle et al., 1985). The view through the FNE, like all endoscopes, is binocular which can distort dimensions and proximity of the pathology to the camera.

Patients with symptoms suggestive of sinus disease or any malignant process may undergo cross-sectional imaging in the form of Computerised Tomography (CT) which uses ionising radiation. CT provides unparalleled multi-plane images of the bony sinuses, skull base and orbits; when viewed in all three planes it allows the extent of any sinonasal disease to be determined as well as delineating variations in bony anatomical landmarks to assist in surgical planning. CT sinus scans can be performed within a few minutes and usually do not require the administration of intravenous contrast. A non-contrast CT sinus is readily available in most hospitals and would cost the NHS £97 per patient including reporting as opposed to £222 for a contrast MRI sinus; the contrast being necessary to provide equivalent radiological information (England, 2013). Whilst MRI does not use any ionising radiation, a typical CT paranasal sinuses results in the radiation exposure of 0.6 mSv, equivalent to 2 months of background radiation exposure (Lin, 2010).

Nasal obstruction is a complex symptom that results from a perceived increase in nasal resistance secondary to true obstruction or sensory deficiency. This perception may be due to changes in the sensation of the nasal cavity, which is mediated by the trigeminal nerve. For example, topical anaesthetics lead to subjective feeling of blockage and trigeminal nerve stimulants lead to a perceived sensation of improved airflow with no change in their airway anatomy (Eccles and Jones, 1983). Patients with a true change in airway calibre secondary to trauma are likely to perceive a nasal
obstruction due to an increase in airflow resistance. However asymptomatic individuals with congenitally altered anatomy may become symptomatic due to a change in the physiology of their nose such as the rhinitis or a change in the pattern of their nasal cycle (Hanif et al., 2000).

Quality of life surveys and symptom scores are frequently used to assess patient subjectivity nasal symptoms. Perception of total nasal obstruction does not correlate with examination or rhinomanometry findings; however, there is slight correlation with each nasal cavity being tested individually (R, 1998, Eccles, 1998). NOSE and SNOT-22 questionnaires are two such validated outcome scores and are used pre and post-operatively to provide qualitative data related to nasal symptoms (Stewart et al., 2004).

2.2.2 Objective rhinometry tests to assess nasal resistance and patency

Acoustic Rhinometry (AR) uses analysis of sound waves rebounded off the walls of the nasal cavity to determine mean cross-sectional area (MCA) and nasal volume (Roithmann et al., 1995). It is less time consuming than other modalities and requires less patient instruction, thereby making it useful in children. However, it does not assess the dynamic function of the nose and requires the use of nozzles at the nasal interface which can be difficult to create a good seal. Although there is evidence to suggest a good correlation between MCA and subjective nasal patency, there is firm evidence demonstrating significant variability between operators and technique which undercuts its clinical application (Clement et al., 2014).

Active anterior rhinomanometry (AAR) provides a more functional measurement of airway measuring nasal pressure and nasal airflow at the nostrils. The pressure probe is taped into the nostril, which results in less distortion than if a nozzle were used and then an airtight mask applied over the nose. This gives a single airflow measurement at the nostril but does not identify causal anatomy.

2.2.3 Laryngeal Assessment

Assessment of laryngeal competence begins with a history from the patient exploring voice quality, respiratory function and swallowing followed by an examination of the neck and a flexible
nasendoscopy. Lung function tests such as peak flow and spirometry give information pertaining to the airway overall but are not clearly able to distinguish laryngeal dysfunction from lung disease. Any abnormalities seen on inspection may prompt a clinician to request cross-sectional imaging, usually in the form of a CT.

In the case of vocal cord paresis, for example, assessment is limited to endoscopy and patient subjectivity. There are no objective tests which can be used to quantify disease or act as quality outcome measures following treatments. Treatment modalities frequently used are non-surgical voice therapy or surgical vocal cord medialisation. Voice therapy aims to maximise any retained function by exercising and augmenting existing muscles. Temporary vocal cord medialisation is performed by injecting a resorbable material into the paraglottic space which pushes the paralysed cord closer to the midline. Permanent vocal cord medialisation is called a Type I Thyroplasty, where a window is made in the thyroid cartilage and non-absorbable prosthesis is placed pushing the cord medially.

### 2.3 Background to virtual model creation and airflow analysis

#### 2.1.8 Imaging

Computerised Tomography (CT) characteristically provides clear bony detail with clear delineation between bone and soft tissue, whereas Magnetic Resonance (MR) images give greater soft tissue detail showing contrast between cartilaginous and soft tissue anatomy. CT is the most commonly used imaging modality to evaluate the airway and is often considered preferable to MR imaging due to its greater patient comfort, shorter scanning duration resulting in less movement artefact and greater cost effectiveness.
CT has been shown to be superior in demonstrating bony detail for planning Endoscopic sinus surgery but equivalent to MR images when assessing for location and extent of sinonasal disease. In patients with metallic dental implants or those likely to require serial imaging, such as those with Inverted Papillomas, Hähnel recommend MRI be used to reduce long term radiation exposure (Hähnel et al., 1999). There is also a relatively high rate of sinus disease picked up incidentally during alternative imaging, with a 46.8% finding of maxillary sinus disease on 164 cone beam CTs as part of dental investigations (Pazera et al., 2011).

A CT is made of multi-segment X-rays taken on an axis around a stationary patient. The X-rays pass in a fixed diameter beam from the X-ray tube to the scintillation detector on the other side where the level of attenuation is measured. The anatomy featured is separated into 3-dimensional units called Voxels, each of which is ascribed a Hounsfield Unit (HU), which are based on how much radiation a voxel of tissue attenuates. Different tissue types typically express specific HUs, for example water = 0 and bone = +1000 (Fenna, 2002). HUs are conveyed through pixel grey-values, which in the standard DICOM image file format range from 0 - 4095, reflecting the density of the tissue. Thus, there are 4096 different shade of grey in these 12-BIT images, when the DICOMs are uploaded to many computer image-viewing systems, the number of Hounsfield Units may be reduced to 0-255, which is an 8-BIT format.

CT images are taken in a spiral format in the axial section and then can be reformatted to show coronal and sagittal planes. The width of the beam and the rate at which the X-rays are taken determines the
resolution of the image (Goldman, 2007). CT images can be subject to metallic streak artefacts particularly from dental amalgam and implants, which can compromise delineation of anatomy when trying to segment images. However, CT images are taken in a single breath hold, reducing movement artefact that can often affect MRI quality.

MRI uses radiofrequency (RF) pulses within a strong magnetic field to stimulate hydrogen nuclei within tissues, provoking changes in alignment of the spin of the protons; after excitation, the proton spins realign to the direction of the magnetic field releasing energy which is detected by the scanner. Based on the amount of energy and the speed with which it is released the MRI can determine the characteristics of tissue and ascribe a grey-value to it (Singh and Neutze, 2012).

MR and CT images are compared (different subjects) in figure 5. Note the excellent tissue contrast in MR imaging. However, note also that in MR imaging, bony areas as well as airspaces correspond to zones of signal loss, whilst in CT imaging, bony areas strongly absorb and appear bright. Lack of MR signal from bone is due to the much lower water content and the very fast rate of signal decay in solids. For information about CT and MRI risks see appendix 1.1.

2.3.2 Image settings

Radiographers, tasked with acquiring scans, program a CT scanner to run a protocol designed to provide maximal anatomical detail to meet the clinical question, using the least radiation possible. Our local protocol for a ‘CT paranasal sinuses’ has a field of view from the frontal sinus to the hard palate with 1.5 mm thickness and matrix acquisition of 128x0.6mm.

MR image quality is dependent on the fixed field strength (1.5 Tesla or 3.0 Tesla) of the machine and the protocol used to capture the image. The MRI can be programmed to capture images in two formats: T1 weighted or T2 weighted. Instead of determining the hydrogen content of tissue, the T-weighting looks at direction of movement of the hydrogen atoms; T1 looks at longitudinal movement and T2 transverse movement. The clinical comparison of T1 and T2 is helpful to identify pathology, for
example tissue with high fat content appearing bright with T1 weighting, and regions with higher water content (for disease or oedema) bright in T2 weighting.

MR image resolution is dependent on multiple parameters: field of view, slice thickness and matrix size. Field of view (FOV) is the 3D area captured in mm², the smaller the FOV the smaller the voxel size and therefore the higher resolution. Thick slices result in large voxel size, where the return radiofrequency (RF) signal is a mean of the signals of the tissues within it. If the anatomical contents of a voxel have dramatically different RF signals they will be combined and the resulting image will lack definition and the anatomy will appear blurred, which is known as a partial volume effect (Westbrook et al., 2011). Matrix size is the number of frequency encoding steps in one plane by the number of phase encoding steps in another plane. The frequency encoding is the number of times the signal is sampled by the computer; this does not increase scanning time. However, increasing the number of phase encoding steps will proportionally increase the scan time. The MR images used in this study have a matrix of 512 x 512 and an acquisition matrix of 3,203,200 data samples in both frequency and phase directions. The choice of image acquisition protocol and settings represents a compromise between nominal resolution, signal-to-noise and contrast-to-noise as well as scan time. Pixel size can be determined using the equation below indicating the resolution of the image.

\[
\text{In plane resolution} = \frac{\text{FOV}}{\text{Pixel size}} = \frac{180 \text{ mm}}{512 \text{ pixels}} = 0.351 \text{ mm/pixel} \quad (2.1)
\]

Due to long scanning times MR images can be subject to movement artefact resulting in image degradation. Blumenthal et al. studied the effect of movement artefact on automated brain morphometry in MRI. Their results showed a significant decrease in estimate grey-matter volume proportional to the degree of movement artefact, indicating that movement artefact may also change volume measurements in airway geometry (Blumenthal et al., 2002).

In order to bridge the gap between clinical medicine and research in this area, CFD simulations need to run making use of routinely used clinical scan protocols. Currently a typical NHS clinical scan does not provide sufficient detail to model the nasal cavity due to large slice increment and poor resolution, however MR imaging is becoming increasingly cost effective and therefore accessible to our National
Health Service. The effect of differing imaging techniques on the definition of the airspace is still an unresolved issue, so there is an inherent uncertainty regarding the proper geometry on which to base CFD simulations. Chen et al. compared the airflow dynamics surrounding a septal deviation derived from a CT scan against a normal subject’s MR images and whilst a difference between the two subjects was shown the effects of scan type of intranasal geometry was not evaluated. Although one study has shown that MRI and CT images result in statistically comparable 3D models with a low margin for error, this was in long bones which are anatomically less complex than the upper airways and therefore less subject to partial volume effects (Chen et al., 2009, Rathnayaka et al., 2012).

2.4 Models and Segmentation

Creating representative models of anatomy is dependent on the complexity and detail of the specific area combined with the accuracy of the modelling process. Historically anatomical modelling has largely been reliant on in-vivo specimens, either moulded or plastinated, or casts. There are pros and cons to all methods. Cadaveric and plastinated models preserve detailed anatomy. However, during the tissue preserving process, so popularised by Gunther Von Hagen, the tissue undergoes fixation, dehydration, forced impregnation and polymerization which can lead to a 10% tissue decrease of tissue volume. This variability in volume loss is hard to quantify and therefore cannot be accounted for (Croce et al., 2006, von Hagens et al., 1987, Caenen et al., 2005).

More recently, advances in imaging quality combined with more powerful computing technology has allowed creation of computational models from real patient scans. Computational modelling used the process of segmentation to produce a 3D image constructed from 2D multi-slice MRI or CT data. In our studies, both MRI and CT images were segmented using the image processing software ‘Mimics™’, Materialise Interactive Medical Image Control System software (Mimics, Materialise, Ann Arbor, Michigan), with post-processing done in the 3-Matics design platform.
The basic starting point for segmentation relies on thresholding; the method by which grey-scale images are separated into subsections based on the image intensity of individual voxels. The grey-scale value ascribed to any pixel reflects a mean density of the tissue surrounding that area in a CT image, whereas in MRI, grey values are associated not only with the proton density but the chemical environment of the protons, which also affects the signal. In either case, finite resolution means there is a stepped progression of grey-values as opposed to a linear progression. In areas of detailed anatomy if the resolution of the image is too low, the voxel size will be too large to allow clear discrimination between the boundaries of two tissues. This is fundamental, as if there is insufficient difference between grey-values of the opposing tissues, anatomy may not be included in the model. More information on thresholding is given in appendix 1.2.

As an illustration of the process, Figure 6 shows a close-up of the left inferior turbinate with the airway coloured in purple. A tangent through the turbinate has been drawn and the grey-values of each pixel plotted on the histogram in Figure 7. The black line shows the threshold for the segmentation, any pixels with a lower value are coloured in purple corresponding to the segmented area above.
When considering the future clinical applicability of patient specific modelling it is fundamental to acknowledge the high operator time-cost to manually segment an airway, a CT taking several hours and an MRI even longer (Quadrio et al., 2015). The eventual model, whether computational or physical, should be a realistic reflection of the anatomy not only in terms of features but also volume, despite any shortcomings in the quality of the scan. Repeatability and reproducibility should be possible irrespective of operator and on occasion judicious interpolation may be needed if the quality of the model is not to be compromised. Most segmentation software now comes with automated segmentation modules, these have been widely trialled in segmentation of the brain for assessing brain volume. Whilst there is no exact comparison available for Mimics™ software used in our study, some studies looking at comparability in brain imaging have shown a favourable correlation between manual and automated segmentation when assessing brain volume; however, the results were increasingly less comparable with increasing age of the patient. As patients get older, brain volume decreased, thus during segmentation there is a small target volume resulting in a higher ratio of mistakes to volume (Wenger et al., 2014). Information regarding accuracy of segmentation can be seen in appendix 1.3.

![Figure 7 Histogram demonstrating grey-values along an axis. Areas which have been captured during segmentation shown in purple, all falling below the chosen threshold marked by a black line.](image)
2.4.1 Errors in Segmentation

In order to use the model in vivo, or computationally, the model has to be free of slice-continuity or artefactual errors. Errors occur when pixels adjacent to each other from slice to slice are not selected, leading to missing pixels or irregular inaccurate surfaces. Types of error include missing pixels, corner to corner pixels and overspill (see figure 98 in the appendix 1.4). In figure 4, where the inferior segment has corner to corner pixels, the segmented area will eventually be thinned during the smoothing process and may close sufficiently to be perceived as blocked. Errors such as this must be identified and repaired during the segmentation, requiring an operator who has anatomical knowledge. The engineers are able to perform post-processing in order to create an accurate boundary for CFD, but it can be time consuming and anatomically inaccurate. See appendix 1.5 for further details.

2.5 From Segmentation to airway models: the nose

Prior to segmentation the majority of models were experimental. For example, the geometry used for Hahn et al. model was taken from a 2 mm slice CT scan of the right nasal cavity which was upscaled by 20x and traced onto Styrofoam blocks. The airway silhouette was then cut out and the Styrofoam blocks stuck together, lined and painted to create a smoothed cavity into which 85 pressure taps were drilled. The drilling of taps into a model can lead to irregularities in the internal surface of the nose. For comparison in our experimental model described later, advances in manufacture enabled this problem to be avoided by incorporating taps into the geometry prior to printing. Additionally, the smoothing module available in the software prevented any possible steps caused by subtle differences in geometry between slices which may have been a pitfall of their modelling technique.

This is one of the few models which provides cross-sectional areas with which to compare to our study. Of the 5 planes, only 3 roughly correspond (see appendix 1.6). The measurements from our geometry demonstrate a smaller patent airspace except in the post nasal space. The difference may be caused by the poor quality of their scan, performed 17 years prior to ours. Additionally it is clear from their Figure 1B they have chosen the more patent side of the nose, whereas many of our studies are based on a
congested nasal cavity (Hahn et al., 1993). The still image of a coronal slice of a CT nose published by Olson et al. shows a grainy image with an absence of sharp contours between anatomy. Compared with the detailed CT derived image used by Wen et al 25 years later, the detail of individual geometric representation is clear (Wen et al., 2008).

To appreciate anatomical variation 10 healthy volunteers had an MRI nose, which were segmented by a single user. As all noses had different geometries, to standardise measurements two planes were created and the scans reformatted to assess the dimensions of the region around the anatomical ‘internal nasal valve’. One plane was a tangent taken 1 slice anterior to the head of the inferior turbinate (1mm slice MRI) at 90° to a line level with the bony nasal dorsum (dorsum line). The second plane was a tangent taken 1 slice anterior to the head of the inferior turbinate at 90° to a line level with the bony hard palate (palate line). The planes used correlate with the methodology used Bloom et al. to describe the internal nasal valve radiologically.(Bloom et al., 2012) The areas were segmented using the same threshold and the 2D mask area extracted for each side to determine the effect of decongestion on the cross-sectional area.

Figure 8 Lateral wall of the nasal cavity showing methodology used to extract anterior cross-sectional area data at reproducible locations in the nose. Planes in red are drawn parallel to the palate and the dorsum respectively. Planes in orange are constructed to be perpendicular to each red plane as shown and used to slice the geometry to extract the airway cross-sectional area.
Figure 9 A subject shown in two reformatted planes showing the Palate line and the Dorsum line in red with the 90 degree tangent in orange.

Figure 10 A chart showing the effect of decongestant on a cross-sectional plane at a 90 degree tangent to the bony nasal dorsum through the internal nasal valve.
The results show that both cross-sectional areas taken through the region describing the internal nasal valve get larger with the application of nasal decongestant. This is largely active both on the inferior turbinate, the geometry of which is not captured within this plane, and the nasal mucosa of the septum and lateral nasal wall.

2.6 Mechanics of Flow: Reynolds number and Pressure Loss

2.6.1 Reynolds number

Low speed flow within a conduit, such as a blood vessel or an airway, can be idealised as a laminar flow Newtonian flow provided the Reynolds number is sufficiently low. A Newtonian fluid is one where the coefficient of viscosity remains constant irrespective of the shear rate i.e. the rate at which layers of the fluid slide past each other. Blood is not Newtonian, since it has a much higher viscosity at very low flow rates, but air is effectively Newtonian at any flow rate which greatly simplifies the modelling of

![Graph showing the effect of decongestant on cross-sectional area.](image_url)

*Figure 11: A chart showing the effect of decongestant on a cross-sectional plane at a 90 degree tangent to the palate through the internal nasal valve.*
airflow. Interestingly, Poiseuille was a medical physician who has given his name to one of the most famous results in fluid mechanics.

\[ \text{Re} = \frac{(\rho V D_H)}{\mu} \] (2.2)

The nature of a flow can be characterised most basically by the Reynolds Number (Re), which is a dimensionless number that reflects a ratio between inertia forces and viscous forces within a fluid.

Typically, low values of Reynolds numbers reflect laminar flow and high Reynolds numbers turbulent flow (Massey and Ward-Smith, 2005). Laminar flow reflects orderly movement of particles. High viscosity fluids tend to exhibit flow natures which are laminar as the Reynolds number is directly proportional to velocity and inversely proportional to viscosity.

In the case of a simple pipe, the distribution of flow velocities across the lumen reduces to a simple form, known as Poiseuille flow. Specifically, Poiseuille’s law predicts a linear relation between flow rate in a pipe, Q, and the pressure drop \( \Delta P \) over a length \( L \) of a pipe of radius \( r \) where \( \mu \) is viscosity.

\[ \Delta P = \frac{8 \mu L Q}{\pi r^4} \] (2.3)

This law can be applied to flow in any straight tube such as a hypodermic needle. However, as the upper airways are not single diameter tubes, Poiseuille’s law does not provide an accurate description of the flow. One obvious failing is that flow rate in the airways is not directly proportional to the pressure drop, which would be implied by Poiseuille’s law. This is both a consequence of the complex geometry...
and of the transitional nature of the flow. However one factor highlighted by the above relation is the exquisite sensitivity (fourth power law) of pressure drop to the pipe radius. Pressure drop is an important measure, since it translates into the effort required to drive flow to the lungs.

Typically within a pipe, laminar flow will change to turbulent flow at a threshold of between $2000 \leq \text{Re} \leq 4000$. Anatomical flow conduits are far from simple pipes: for a complex conduit, in place of a diameter, the hydraulic diameter is commonly used, defined as 4 times the area divided by the perimeter (see Figure 12).

Transition to disturbed flow in anatomical conduits often occurs at much lower Reynolds numbers than for a simple pipe, typically due to the presence of constrictions which cause jets, separations, bends and bifurcations further complicate the flow in airways and the vasculature.

In engineering, it is possible to perform experiments on simple configurations, such as bends and T-junctions and to derive empirical correlations relating quantities such as pressure drop to the flow, whether flow is laminar or turbulent. Airway geometry is unfortunately far too complex to allow a direct translation of flow data obtained in engineered conduits to provide accurate predictions. This is where CFD offers a valuable role.

### 2.7 Airflow in the Upper Airways: Nose to Carina

#### 2.7.1 Nasal geometry and airflow

Respiratory rate lies between 12-20 breaths/min (7-8 L/min) at rest and will rise during exertion, illness or in patients with underlying respiratory disease (Physicians, 2012). This thesis is not concerned with oral airflow but the common characteristics of nasal airflow and its relation to geometry.

During inspiration, air enters the external nose in a ‘sink-type’ flow, meaning that air is drawn from a wide surrounding volume and accelerates rapidly at the entrance to the nostrils or nares (Figure 13).
Air passing into the internal nose through either nostril typically accelerates through the nasal valve (nv) and is partitioned into parallel paths by the intruding turbinates (middle turbinate (mt) and inferior turbinate (it) marked in the figure 14a below). Regions of high speed correspond to elevated wall shear stress and from figure 14b it appears that most of the airflow bypasses the uppermost regions of the nasal cavity.

Figure 13 Path lines of flow approaching the nose and corresponding external velocity field during inspiration showing little mixing. Air flowing off the face enters the lower airways at speed, whilst air from the tip of the nose travels at a lower velocity towards the olfactory cleft (Doorly et al., 2008a)

Figure 14 View of one side of the internal nose with the septum removed, illustrating flow path lines and wall shear stress distribution (Doorly et al., 2008a)

Measuring nasal airflow in vivo and modelling it computationally is challenged by the dynamic nature of nasal physiology, marked by changes in airway calibre and the nature of the surface, compounded
by the effect of atmospheric variables on both of these. The asymmetric, convoluted anatomy of the nasal airway make it difficult to achieve a universal impression of flow from sporadic probe measurements which require interpolation of flow between measurement points. The very act of taking probe measurements may have an impact upon results secondary to the observer effect, where the act of measuring within the nose would likely alter nasal physiology and nasal airflow (Doorly et al., 2008b).

2.7.2 Laryngeal geometry and airflow

The larynx, in contrast to the rest of the airway, has the ability to markedly change its diameter not only during restful breathing, but to a greater extent during vocalisation. As laryngeal airflow is so
fundamental to our understanding of the physiology of respiratory disease and particle delivery systems, accurate modelling of geometry and airflow becomes an essential tool to increase our understanding (Schlesinger and Lippmann, 1976). Figure 15 shows a clinical endoscopic view of a normal male larynx during restful breathing (left) and during phonation (right). The same anatomy is then shown in Figures 16 & 17 as a 2D image of a CT with a segmented glottis and the resultant 3D model. The anterior commissure, the narrowest point of the glottis, is labelled with a black arrow and is visualised in all pictures except in the computationally simulated nasendoscope image where the epiglottis obscures it. The adduction of the arytenoid cartilages, to which the vocal folds are attached, are observed between the left and right photographs marked with yellow rings.

The flow within the larynx is characteristically turbulent, the glottis acting in some respects like a simple orifice plate. An orifice plate, used for measuring pressure within pipes with a well-developed flow-profile, is a thin metal plate with a central sharp edged hole with pressure tappings inferior and superior to the plate. The narrowed glottis, like the orifice plate, causes an increase in supra-glottic pressure; and then an increase in trans-glottic airflow velocity to form a jet (Corcoran and Chigier, 2000).

Figure 16 Axial section of the glottis within Mimics. The glottic area is shaded in green, the arytenoids circled in yellow and the anterior commissure shown with an arrow

Figure 17 Computational endoscopic view in 3-matics with a partial view of the glottis. The anterior commissure is obstructed by the epiglottis
The laryngeal jet is typically turbulent, the intensity of which can change considerably depending on the speed of flow and the local anatomy. Lin et al. suggest that certain geometrical features increase turbulence, thereby increasing tracheal wall shear-stress and making patients more prone to certain types of diseases such as idiopathic subglottic stenosis, similar patterns of which have been seen in blood vessels (Birchall et al., 2006, Lin et al., 2007). Additionally, laryngo-tracheal airflow studies with no oropharynx required the inlet boundary conditions to be fixed in terms of velocity and whether the flow is assumed to be laminar or turbulent. The specific features of the flow travelling from the oro- or nasopharynx will not be incorporated, which could potentially distort results (Lin et al., 2007).

2.7.3 Tracheal geometry and airflow

Unravelling the complexities of tracheal airflow remains a high priority for medical researchers, influencing the programming of ventilators to delivery of pharmaceutical inhalants and the scope for surgical prediction and outcome measures.

Since the trachea is a conduit and does not take part in any gas exchange, air needs to reach the alveoli as quickly as possible whilst expending the least energy. Consequently, maintaining an adequate tracheal diameter and avoiding unnecessary flow losses is fundamentally important for effective ventilation.

In the normal anatomy, the major source of inspiratory energy losses in the trachea are accounted for by the dissipation of the laryngeal jet. In simulations the laryngeal jet is found to be highly variable depending on the shape of the glottis. Simulations comparing triangular, circular and elliptical glottis shapes resulted in a range of jet speeds, pattern of vortices and peak velocity decay in the upper section of the trachea (Brouns et al., 2007b). Whilst in the nose, at ventilation rates laminar breathing presides, the flow pattern in the trachea can transition between laminar and turbulent relative to the amount of exertion (Brouns et al., 2007a). However previous investigations have largely concerned idealised tracheal geometries and the extent to which results from these studies may be applied to realistic tracheal
geometries is unclear. In view of its importance, a particular focus of this work will be devoted towards investigating the effect of glottis aperture on trans-tracheal pressure drop and flow energy losses.
Chapter 3

3.1 Summary

This chapter examines the effect of inter-user variability with regards to segmentation of the nose and trachea. Current imaging modalities for the airway are examined to determine how well they capture geometry and how each modality can affect the way anatomy is perceived. A study to compare segmentation abilities in different groups using Magnetic Resonance Imaging (MRI) of the nasal cavity and Computed Tomography (CT) images of the trachea is performed and the results compared.

3.2 Inter-user variability

Manual segmentation is a time-consuming process, which requires contour tracing through multiple slices of image data. Although image recognition is used widely and successfully in industries and in areas of medicine such as Radiation Oncology, automated anatomic recognition remains complex, not only due to the huge variation in size, position and composition of organs, but due to imaging limitations. Indeed, image data can vary so much in resolution and image quality that there is an inevitable and undesirable risk of variability when isolating specific anatomy. The risk of variability is further complicated by user subjectivity in the interpretation of anatomical feature boundaries.

3.2.1 Impact of image data on variability

Image data affects the ease with which an area of anatomy can be segmented, usually due to the homogeneity of the image and clear boundaries between it and structures around it. For example, Figure 18 shows a clear definition between bony and soft tissue anatomy of the femoral head; however Figure 19 clearly indicates how soft tissue definition can alter depending on the imaging modality and protocol utilised. (Sims et al., 2009b)
Whilst CT images show excellent contrast between bones and soft tissue, different soft tissues, for example fat and muscle, can exhibit very similar Hounsfield units (a quantitative scale for describing radiodensity). Additionally, as the anatomy becomes more detailed, the resulting contrast between organs can become blurred. (see Clinical example of contours and partial volume effect in appendix 2.1) If the contour of an organ cannot be consistently defined, the eventual volume is likely to be inaccurate, which can have huge clinical consequences when planning Radiotherapy fields for example. The quality of the contour is equally relevant to studies delineating the airway, as this will eventually form the boundary definition for the computational domain in CFD; spurious irregularity of the boundary as well as inaccurate boundary location could result in significant changes to the results.

One of the greatest impacts on MRI resolution is the partial volume artefact; whereby different tissues represented within the same voxel have an average of their signal leading to a lack of definition between them. To avoid missing fine anatomical detail the slice thickness can be reduced to make the voxel size
smaller, however in so doing, the signal-to-noise ratio (SNR) is affected. To understand the impact of the SNR on image quality, the fundamentals of MR need to be discussed.

Image noise, which is essentially unwanted signal, can be created by the electronics of the machine or physiologic noise; the amount of which is usually considered to be a constant. The main image signal detected by the MR comes from protons in hydrogen nuclei and the degree to which they can be magnetised. Different tissues are known to have different numbers of protons and therefore the difference between them is clear based on the amount of signal they emit. To improve definition between the tissues the ‘field of view’ FOV can be reduced, resulting in smaller voxel size. This however, will result in fewer protons being included within a voxel, thus reducing the overall signal from that voxel, thereby make the ratio of signal to the background noise smaller. This results in the noise dominating the image which is demonstrated through the image appearing granular, but with better spatial resolution between tissues. Conversely increasing the voxel size leads to an improvement in the smoothness of an image but identifying a clear contour between tissues is harder. Slice thickness is the other dimension of the voxel and by reducing slice thickness spatial resolution can also be improved. Image matrix size equally changes voxel size and alters the ratio signal to noise.

The importance of signal to noise ratio is that by varying different parameters within an MR protocol one can change the resulting image. However, this is a constant trade-off between resolution and the smoothness of an image. One of the only ways to maintain high resolution without succumbing to noise is to create an average of signals. By taking further full sets of scan data and taking the average of the signals across multiple data sets, the resolution improves with the number taken. The downside is that with each successive set taken, the scan time is increased and thereby the cost of the acquisition. If partial volume loss leads to small anatomical details being missed, for example small anterior septal spurs, then conceivably this could affect the eventual outcome of the CFD. Equally, if in an attempt to improve resolution the voxel size is decreased this may worsen the signal to noise ratio leading to a lack of definition between tissues and more difficulty determining the boundary of the anatomical area.
3.3 Methods of segmentation

Segmentation, like many slow processes, has been a subject of interest for semi or total-automation. To reduce the time-cost in manually tracing contours, one of the earliest automatic contouring algorithms were known as ‘snakes’ which lock onto nearby edges or contours in an image. Subsequently, the snake tool runs through sequential slices automatically identifying the same contour. The accuracy of these ‘snakes’ is dependent on an initial boundary drawn by a user as well as the settings of multiple parameters; both of which are equally prone to variability, (Kass et al., 1988). Similar contouring tools are still readily available in most segmentation software including the Mimics™ package and can be useful for determining 2D surface area of a mask.

To make clinical interpretations from CFD studies, the accuracy of the anatomical model must be quantified. During the initial stages of using Mimics™ for segmentation, it was noted that users varied in what they included or excluded. This resulted in inter- and intra-user variation between models and we wanted to quantify this difference and determine the margin of error in segmentation. Further details related to semi and fully automatic segmentation systems can be found in appendix 2.2.

3.3.1 Review of studies on inter-user variability in segmentation

Literature related to this topic uses terms such as observer-variability and user-variability interchangeably. Many of the papers investigating user variability are comparing manual segmentation methods against semi or fully automated methods. A table summarising recent inter-user variability papers can be found in appendix 2.3. The main driving factor behind automatic segmentation is time and money, particularly in the field of radiotherapy planning times when identifying Organs At Risk (OAR) and deciding on treatment fields. Identifying these structures requires skilled personnel trained in segmentation and anatomy but the process of choosing organ boundaries runs the risk of variability between observers, culminating in the real risk that in one person’s radiation field planning may be better or worse than their colleague. Whilst all patients are different anatomically; a patient with active cancer does not wish to be a target of subjectivity and its sequela.
Sims (2009) and Tinglehoff (2007) are two authors who have evaluated user-variability with relation to head and neck anatomy (Sims et al., 2009b, Tinglehoff et al., 2007). Sims, like most authors investigating automation of segmentation, was motivated to find a faster, more accurate way of delineating OARs, whilst Tinglehoff focussed on the variability that comes with manual segmentation of the sinus and nasal cavity. Sims’s study compared automatic and manual segmentation techniques of the parotid, mandible and brain-stem (OARs) from a CT. They found the segmentation volume from the automatic tool to be within 1+SD of the manual volume, except for in the parotid and brainstem which was over and under estimated respectively. The impact of this is whilst automatic methods are time saving, some contours must be reviewed and edited prior to finalising treatment plans. Similar to our study, they found that some areas of anatomy are particularly prone to variability.

Tinglehoff also studied the nasal cavity and some of their methodology compares closely with ours, however they compared users against each other whilst our gold standard was an average of two segmentations from expert users, both surgeons with experience using segmentation software. Their conclusion was that it would be inaccurate to use a single manually segmented study as a gold-standard as the inter and intra-user variability is too great to make it reliable. Whilst there are similarities with the methods applied in this work, their studies extracted volumetric data, whereas this study was applied to 2D data for the purposes of time costs, consequently results are not easily comparable.

Radiotherapy is one of the foremost treatments from prostate cancer and therefore a driving factor for streamlining of automation. Fiorino (1998) had concerns that inter-user variability in prostate contouring may be greater than previously published leading to unnecessary radiation exposure (Fiorino et al., 1998). They contoured OARs in 35 scans and found there was inter-user variability of 5% (range 1.5-9%) but this was significantly different from one patient to another. Whilst some patient images were easier to segment, they found variation usually located in same anatomical regions- typically where organ interfaces were unclear i.e. between the prostate and bladder. Their conclusion was that the variability should be included in the planning radiation fields to ensure that all the prostate is adequately included. The clinical implication of inter or intra-user variability in RT planning is significant; from under-treating a malignancy to irradiating and irreversibly damaging healthy organs.
Contouring, essentially drawing a line around an area of anatomy, is one method of segmentation. Another tool widely available in segmenting software is ‘region growing’ where a ‘seed’ pixel is chosen, and all pixels of a certain pre-selected threshold in contact with that seed are then automatically selected to form a ‘mask’. A study was run to establish the difference in time, accuracy and inter- and intra-user variability of a region-growing tools versus manual segmentation for prostate cancer (Mazonakis et al., 2001). In addition to demonstrating region-growing resulted in more consistent results, it was also shown to be a 1/3rd faster than conventional manual contouring. Reassuringly there was good correspondence in volume results between manual and region-growing techniques. In agreement with our study they found that manual corrections did need to be applied to some areas—typically where leakage of the mask occurred into surrounding structures that had similar Hounsfield units to the target organ; this was reduced with the application of contrast media within the bladder, which would not be an option in the nasal cavity. The greatest problem with region-growing is the need for a user to place a ‘seed pixel’, which opens it to immediate variability. Haas et al. sought to validate a fully automatic segmentation software, removing choice from the equation (Haas et al., 2008). Their algorithm, based on pre-segmentation, anatomic orientation and structure segmentation aimed to segment out bones and organs irrespective of the sex or anatomical orientation of the patient. It was tested on 52 CTs of the pelvis and thorax which were then reviewed by five radio-oncologists and rated from 1-4 based on accuracy of the contours and requirement to make corrections, a score of ≤3 would equate to time saved. In the pelvis 68% of cases had a score of ≤3 (mean 2.6) and in the thorax 91% had a score ≤3 (mean=1.9). This would indicate that particularly in the thorax, automated software would lead to considerable time saving even if some of the images required manual alterations of the contours. The main outcome of this study is the benefit of semi-automation in speeding up the segmentation process with little increase required in hardware.

It seems widely accepted that manual segmentation in radiotherapy planning takes longer and is more susceptible to inter- and intra-user variability. Sharp noted that CTs for planning radiotherapy may be high resolution but subsequent ‘Dose Grid’ CT’s may be lower resolution leading to differences in contours; but fundamentally small millimetric differences in contours may not impact on radiation dose
This point is critical as finer resolution scans may result in better definition between structures, but the extent to which that changes the clinical outcome whether it be radiation dose or CFD results must be weighed up against the relative risk of radiation to that patient.

Manual segmentation will likely become obsolete as segmentation algorithms improve, however during the search for increasing accuracy groups will have to determine how individual patients or image data can challenge automation. A study to assess the impact of image type on segmentation of the prostate was run looking at Kilo-voltage CT versus (KVCT) Mega-voltage CT (MVCT) (pertaining to the voltage applied to the X-ray tube and subsequent energy of the X-ray photon). Their contouring study clearly showed a consistent over-estimation of volume of the prostate and seminal vesicles in MVCT in comparison to KVCT with a ratio of 1.1 and 1.2 respectively (Song et al., 2006). The role of such studies is important in determining gold standard imaging for clinicians; ensuring that image data not only captures pathology but also interacts maximally with systems designed to interpret them.

Some specialities are assessing the use of segmentation for monitoring disease progression or tumour growth. Ultrasound (US) Doppler is commonly used to assess the size of the carotid artery and atheromatous plaques within them; the presence of which can increase stroke risk. One early study looked at the role of deformable models in semi-automatic segmentation of 3D Doppler ultrasounds which could allow screening and subsequent monitoring for disease risk. They noted a fundamental flaw in determining accuracy of segmentation which is the lack of gold standard to compare it to. Like other authors they used a mean of multiple manual segmentations as the gold standard. This group compared manual segmentation to their semi-automatic model and again found more variability in manual segmentation (Gill et al., 2000). However, the concept of using 3D models for disease monitoring is novel and may be of relevance to monitoring tracheal compression and displacement in retrosternal goitre management. A comparison between two inter-user variability studies is found in appendix 2.4.
3.4 Mask Formation and Thresholding

The method of segmentation can impact upon surface area and volume and this was explored using the tools in Mimics™. These include automatic ‘mask expansion’ tools, details of which can be found in appendix 2.5.

3.4.1 The effect of thresholding on error rate in segmentation

Five anonymised segments of a 3-Tesla MRI of the nasal cavity were selected at equal increments from each other demonstrating distinct parts of anatomy of the nasal cavity. Slice 1 is at the post nasal space and 5 most anterior.

Figure 20 Five coronal slices of Subject D’s MRI segmented by the non-medics and medics. 1 is the post-nasal space and 5 is the most anterior slice
The 5 slices of subject D’s nose were segmented by a single user using the same technique but varying the initial threshold. Prior to manual modification, the number of errors were counted and corrected before extracting 2D mask area to compare against error rate. Figure 20 shows the effect of threshold choice on mask 2D area and error rate for a segmentation of an MRI nasal cavity. Whilst increasing the threshold leads to an exponential increase in the mask area and subsequently the model volume, the error rate varies. There appears to be an idealised threshold (320-340) where the errors are minimised and thus time taken to correct these is reduced.

![Effect of threshold change on mask area and rate of errors when segmenting the nasal cavity from MRI](image)

Figure 21 A graph showing the gradual increase in mask area as the threshold increases plotted against the number of errors (Y axis right). The post nasal space has a much greater mask area in comparison to more anterior segments of the nose.

Figure 21 uses the same data as Figure 20 but to demonstrate the % area increase which appears proportional to the threshold increase. As the post nasal space is the largest area it doesn’t significantly increase in size, whilst slice 3 is in the narrowest part of the nasal cavity and increases by almost 40% by increasing the threshold by 100. Narrower airways will be prone to more resistance and if one cavity increases by only 10% and the other by 40% with the same threshold change, the effect on the accuracy of that CFD could be significant.
3.5 Methodology

In this inter-user variability study two forms of imaging modality were evaluated: MRI of the nasal cavity and CT trachea. The acquisition data is in the appendix 2.6.

The aims of the following studies are to establish whether different users could reproduce useable masks which correlated with our ‘gold standard’ defined as a mean of two masks created by two experienced users. We also evaluated time to segment and presence or absence of ‘mask errors’ which will result in a poor-quality model.

3.5.1 Assessing Inter-User Variability in Nasal Airway Segmentation

A 15-step protocol was developed to standardise the segmentation method. Steps 13-15 instructed error correction (see appendix 2.7). A 10-minute instructional screen-shot video with written annotations was shown to each user to familiarise them with the software, with an experienced user explaining the function of the tools available. 20 users took part in the study. 10 ENT trainee surgeons and 10 non-medics.

The data collected included:
• The effect of thresholding, incidence of error and seniority therefore experience
• Variability in segmentation through the nose to determine if some anatomical areas are more prone to error
• The consequences of geometric variability on airflow using CFD
• Inter-user variability when segmenting the trachea

The specifics of the methodology and how the data was extracted is in appendix 2.8. Figure 23 demonstrates the planes of comparison for the inter-user variability study and Figure 24 the anatomically derived landmarks for analysing subsections of the nose.

Figure 23 Sagittal section of the nose showing five slices (green) used for the inter-user variability study plotted against the anatomical lines (red) used for dividing the levels of the nose.
3.6 Results

3.6.1 Assessing Inter-User Variability in Nasal Airway Segmentation - Results

To investigate the inter- and intra-user variability in segmenting between non-medically trained and medically trained users; two groups of equal non-medics to medics with 10 participants in each group segmented 5 anatomically different slices of Subject D’s MRI nose following a strict 15 step protocol. The data collected was threshold choice, mean mask area for each slice, time to segment and error rate.

3.6.2 The impact of thresholding on mask area and volume

The average threshold choice was higher in the non-medic group, with a greater variance between individuals. Higher threshold choices correlated with a higher mask area, which correlates with a single user study by Quadrio (Quadrio et al., 2015).

Figure 24 A sagittal slice of an MRI nose with a grid (blue) created within a box made of 4 lines (red) placed around anatomical landmarks. PS= posterior septum NS= nasal septum PL= palatal line TOP=parallel to PL from the posterior wall of sphenoid sinus.
<table>
<thead>
<tr>
<th></th>
<th>Non-medics n=10</th>
<th>Medics n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean threshold</td>
<td>406</td>
<td>316</td>
</tr>
<tr>
<td>Mean mask area (mean mm² ± Standard Deviation)</td>
<td>1542.2 ±99.9</td>
<td>1419.7 ±31.0</td>
</tr>
<tr>
<td>Mean error rate (mean ± Standard Deviation)</td>
<td>4.8 ±4.2</td>
<td>8.5 ±3.4</td>
</tr>
<tr>
<td>Time to segment (mins)</td>
<td>38.7 ±6.5</td>
<td>21.1 ±6.3</td>
</tr>
</tbody>
</table>

Table 1 Mean threshold choice, mean mask area, error rates and time to segment for non-medics and medics.
The difference between total mask area measurements was calculated using an independent t-test for inequality of variance within which the data showed no outliers and a normal distribution.

The mean surface area was greater in the non-medics (M=1542.3±102.3) with a greater variance than the medics (M=1419.7±31.1). The non-medics mask area was 122.5 mm² (95%CI, 47.8 to 197.2) larger than the medics. The t-test showed that there was a statistically significant difference in the mean mask area between medics and non-medics (p-value=0.004).

Figure 26 Boxplot showing the distributions of area measurements depending on speciality removed, illustrating flow path lines and wall shear stress distribution (Doorly et al., 2008a)

Figure 27 Non-medics 2D mask area mm² across 5 slices of subject D’s nasal MRI
The greatest variance occurred in slices 2 and 3, particularly amongst the non-medics. This occurred for two reasons: 1. There is a lack of boundary between the superior nasal cavity and ethmoid sinuses which leads users to stray into the sinus cavities; medics with anatomical knowledge had less chance of doing this. 2. The narrow airway calibre in these sections leads some users to choose a higher threshold to ensure the airway is continuous to avoid errors.

![](image)

**Figure 28** Medics 2D mask area mm² across 5 slices of subject D’s nasal MRI

### 3.6.3 Impact of threshold choice on error rate

In comparison to the standard geometry measurements, medics tend to under-represent the size of the nasal airway, this is also reflected in the number of errors made. (appendix 2.9)

Both errors and time to segment were analysed using an independent t-test. The data had no outliers, normal distribution and homogeneity of variance for both groups. The time taken to segment was greater amongst non-medics (M=38.6±6.5) compared to medics (M=21.2±6.4). The non-medic time to segment was 17.6 minutes slower than the medics time to segment (95% CI, 11.5 to 23.7). There were statistically different timings between the groups p<0.0005. The non-medic mean error rate was 3.7
errors (95% CI, -7.29 to -0.11) lower than the medics error rate. There was a statistically significant difference between the error rates between the two groups p=0.04.

Error rate decreases with time taken to segment with non-medics taking an average of 00.38.59 mins and medics taking an average of 00.21.09 mins.

![Figure 29 Box and whisker graph showing error rate for non-medics and medics, error rate was significantly greater in the medical group, but this corresponded much shorter segmentation time](image-url)

3.6.4 The effect of seniority on mask area and volume

A Fisher test, which is useful for smaller numbers, was used to test the difference in variances between an expert group and a junior doctor group in delineating the mask area to study the effect of seniority. The p value=0.892>0.05 showing that there was no sufficient statistical significance to reject the null hypothesis of equality of variances, however this may be secondary to our small sample size.
Figure 30 shows the distribution for different groups based on seniority, Slice 1 has been omitted from this chart to enable a fairer comparison of Slice 2 and 4 which both hold outliers. Slice 1 had no outliers and little variance between expert and junior groups and therefore is the least interesting from a comparative perspective. Whilst there is more variance in the junior group, one outlier is found in expert group in slice 2. This is secondary to their initial threshold choice which was the highest in the medics group thereby resulting in the greatest area measurements for their model. In contrast the other outlier in the Junior group chose the lowest threshold of the medics group overall, and thus resulting in the smallest overall model.

Figure 30 Boxplot showing the distribution of expert users and junior users in mask area
Variability in segmentation throughout the nose

To determine the difference in segmenting between the upper, middle and lower nasal cavity, medics were compared against non-medics in each sub-divided region to determine if a certain area of the nose is more prone to inter-user variability.

Table 2 Comparisons of area means between medics and non-medics for superior, middle and inferior nose. There was a statistically significant difference
Independent t-tests were run to determine the difference between non-medics and medics in segmenting the superior, middle and inferior nasal cavity. For the superior and middle cavity, no outliers in the data were identified on inspection of a boxplot. However, two outliers were identified in the inferior cavity medics group which were included in the t-test. All data was equally distributed, however there was inequality of variance.

In all areas of the nose, the non-medics masks were shown to be statistically significantly larger through the independent t-test. In the superior nasal cavity, the non-medics masks were 30.9 mm² (mean±SD=246.9±29.6) larger than the medics (mean±SD=216.0±8.7) (CI 95% range 9.4 to 52.4 and p value=0.009).

In the middle nasal cavity non-medics masks were 23.9 mm² (M=421.0±24.9) larger than the medics (mean±SD = 397.0±9.9) (CI 95% range 5.5 to 42.4 and a p value=0.015).

In the inferior nasal cavity, the non-medics masks were 27.6 mm² (M=620.1±28.2) larger than the medics (M=592.5±10.3) (CI 95% range 6.8 to 48.4 and a p value=0.014).

The greatest difference inter-group difference between mask area lay within the superior cavity, where the boundary between the nasal cavity and sinuses was unclear. However, the greatest intra-group range was in the superior cavity for non-medics where anatomical knowledge was key to excluding irrelevant anatomy, but the inferior cavity for medics where the threshold choice has a greater impact on anatomy inclusion.

In conclusion, threshold choice is a fundamental step in segmenting and has a direct impact on the ability to accurately represent geometry. Low thresholds successfully pick up anatomy of narrow calibre. Therefore, as demonstrated by Quadrio et al. anatomy such as the maxillary sinuses may be excluded; however, this has little impact on eventual flow fields (Quadrio et al., 2014). The next step is to evaluate the role of threshold choice in MRI on CFD outcomes, to determine whether there is a threshold at which geometry is best represented with the most accurate CFD results.
3.6.6 Assessing inter-user variability in segmentation of the trachea

Previous investigations by this group observed the effect of extrinsic compression on the trachea on airflow distribution and pressure loss. In comparison to the nose, the tracheal geometry is far simpler and whilst this would suggest segmentation would be less prone to error, our aim was to quantify inter-user variability. An idealised model was created by a single expert user and compared with models created by 37 users from different clinical backgrounds. A thresholding test was performed whereby the threshold was compared against model volume, above the threshold of 441 (known as the low threshold line) the boundary between the tracheal wall and hilum of the lung is breached leading to inclusion of the lung and 6-fold increase model volume (Figure 32).

Figure 32 An anterior view of the tracheal model. Green model (left) has a threshold of 441 (volume 66 cm³), Orange model (right) has a threshold of 442 (volume 442 cm³), reflecting the threshold boundary at which the apex of the lung is included resulting in a 6-fold increase in volume

Figure 33 Blue model (left) with a threshold 806 (Volume 506 cm³) and lilac model (right) with a threshold of 807 (volume 30157 cm³) reflecting the threshold at which soft tissue is breached to include all air outside the body in the CT scanner resulting in a 60-fold increase in volume
At a threshold of >806 (the high-threshold line) there is a further breach across a soft tissue boundary into both lungs and air surrounding patient in the CT scanner- this results in an unusable model (Figure 33).

It was noted that 86% of users chose a higher threshold in the axial section than the sagittal section, resulting in a greater number breaching the high threshold line leading to spilling of the mask into the outer scanner airspace. A One-way ANOVA test was used to determine if there was a significant difference in threshold choice between groups of different profession when segmenting in different planes. Participants fell into four groups: Medics (n=10), Surgeons (n=7), Radiologists (n=10) and Non-medics (n=10). All data was normally distributed and there was homogeneity of variances in both planes. A single outlier was identified in the data for the sagittal plane in the ‘Surgeon’ group and left in for analysis. Mean threshold was 583±132 (Range 415-856) with no statistical difference found between the different group’s threshold choices in the sagittal section (p=0.464). Similarly, there was no statistical difference in threshold choice chosen in the axial plane p=0.466, mean 405±258 (range 0-1024). Multiple linear regression analysis showed no impact of profession factor on threshold choice but showed a strong association between threshold and volume choice. As a group, radiologists had the least variation in their threshold choice but largely chose higher thresholds to ensure all anatomy was captured. (More detail in appendix 2.10)

Figure 34 A graph showing threshold choice in the trachea for different professions against model volume and cross-sectional area
The threshold chosen by a surgeon with prior experience with segmenting multiple tracheas had a value of 583, which corresponded with the mean threshold chosen by all users in the sagittal section. Threshold choices for segmenting in the axial plane were uniformly lower across all users with a mean value of 405 resulting in large volumes. Translating the range of threshold values to corresponding tracheal volumes yields $56000 \text{ mm}^3$ (threshold value 415) and $42000 \text{ mm}^3$ (threshold value of 856).

Given that tracheal length is fixed, these figures can be interpreted as a mean cross-sectional area range of $56000/42000$ or 1.333, or a cross-sectional diameter variation of $\sqrt{1.333}$ i.e. 15%. Although Figure 34 suggests model area remains static, in fact area and volume scale proportionally and the apparently larger excursions in volume are due to the different choices of axis origin for the plots (volume being offset).

### 3.7 Conclusions

Accuracy in geometric representation is fundamental to ensuring reproducible, reliable computational flow dynamic results. Whilst mis-interpretation of the calibre of the nasal airway will have few serious clinical effects, by contrast in modelling the trachea, small geometry changes in regions of constriction are known to have significant impact on function (Bates et al., 2016). The relation between flow and area is considered further in Chapter 5 regarding trans-glottic airflow.

This study demonstrates firstly that there is a significant difference in apparent nasal airway calibre derived from MR images between non-medics and medics (refer for example to the clear difference in nasal surface area as evaluated by medics, mean $M=1419.7\pm31.1$ vs that by the non-medics $M=1542.3\pm102.3$). Secondly there is found to be a considerable range in tracheal lumen determination between medics and non-medics, and moreover there is a greater consistency in lumen determination between radiologists compared with that of other users, including medics (figure 34). In both cases the primary difference can be traced to a single step in the modelling process: threshold selection. Although this pilot study has small sample numbers it raises some important questions.

Regarding the nose, firstly, it is evident that current imaging, particularly MRI, is not sufficient in facilitating the automated creation of virtual nasal geometries. Secondly the difference in geometric
metrics indicates that if manual segmentation was to be the gold standard for applications of CFD to airway flows, then the cost involved would be increased if it were to require a medically trained professional in order to segment more anatomically accurate models and models may still require extensive pre-processing to correct any errors. Despite there being a number of studies pertaining to the use of CFD in evaluating nasal airflow, none of them comment in-depth on the quality of their model and how they have made steps to validate the accuracy of it—specifically with regards to inter-user variability. This makes it difficult to quantify the accuracy of individual CFD methodology from study to study.

For models derived from CT imaging of the trachea, inter-user variability showed no significant variation between professional groups when choosing a threshold in the axial or sagittal plane (p value =<0.05). However, there was clear association between threshold and volume choice (coefficient of the threshold being significant p-value = <0.05), large volume jumps indicating the presence of ideal high and low thresholds. Whilst there is no statistical difference in threshold choice between segmentations in the axial or sagittal plane between groups, it is fundamental that users can more easily delineate any overspill when segmenting in the sagittal plane over the axial plane, which directly correlates to volume. This re-affirms the importance of visualising the model in 2D and 3D simultaneously to ensure the threshold choice is appropriate.

Quadrio’s group have made steps towards showing the sensitivity of current CT resolution in achieving usable airflow results; however, this has yet to be applied to MRI. In addition, they have shown a linear correlation between threshold choice and flow rate, which is explained by higher thresholds resulting in greater airway diameter and therefore less airway resistance. (Quadrio et al., 2015)

As image quality improves and computing power is more readily available; automated segmentation tools will become faster and more accurate. Each tool will need to be validated and a clear margin of error published. In the interim we suggest that manual segmentation of the human airways follow a set protocol designed to guide individual users through reducing errors which may compromise the reliability of results long term. Whilst it is recognised that the nasal geometry is significantly more
complex than tracheal anatomy, the criticality of accuracy with respects to CFD is yet to be examined and this will be explored further in Chapter 4 and 6.

In the future, like many treatments, patient-specific modelling will be fundamental to determining the effect of airway structure on air flow dynamics and further correlating this with individual patient’s complaints; this would enable tailor made treatment plans which are objective and where the outcome is quantifiable (Churchill et al., 2004).
Chapter 4

4.1 Computational Fluid Dynamics

Computational fluid dynamic (CFD) experiments can predict the behaviour of a flow, given precise specification of geometry and boundary conditions, by using algebraic equations which describe the discretised form of the conservation laws of momentum, mass and energy. Mathematically, CFD corresponds to numerical solution of the Navier-Stokes equations that govern the motion of fluids. The methodology can be applied to the flow of fluid or air in environmental, meteorological and mechanical phenomena; however, in this case specifically the flow of interest is that of air within the respiratory tract. The process of running a CFD is explained in further detail in Appendix 3.1.

There are many reasons for employing CFD. Firstly, it allows experiments to be performed that would otherwise be impossible for reasons of ethics, cost or safety. Secondly, it is used where no techniques exist that are capable of directly measuring a particular quantity of interest. Thirdly, it provides a convenient means to isolate the effects of different parameters, for example the effect on a specific part of the airway, where different degrees of narrowing can be simulated by altering the geometry specification used by the CFD computation.

The accuracy of CFD relies both on the levels of uncertainty in the model and the care exercised in performing the computation. Airflow within a tube can be laminar, transitional or turbulent depending on multiple factors including the geometry, degree of any restrictions and the flow rate. In the case of nasal airflow, the nature of the flow is determined by the geometry of the airway and the flow rate, with factors such as temperature (influencing buoyancy) of secondary importance. Typically, nasal airflow rates are between 5-6 l/min in an adult at rest, this can increase to 12-40 l/min during exertion above which necessitates a degree of oral breathing (Wen et al., 2008, Stradling et al., 1985). To run a CFD simulation, the geometry and flow rate are usually assumed constant. Uncertainty in the specification of model parameters such as geometry is an important factor to be considered as described in more detail later. In the airways, as in the wider biomedical field, numerous other factors have the potential to compromise the validity of CFD modelling, including the non-rigidity of anatomical conduits (effects
such as congestion/decongestion for the nose or dynamic airway motion in the trachea), the variability of flow patterns (e.g. in breathing), and the general need to truncate the region over which the simulation is performed. Available computing power is also a fundamental limiting factor in the range of problems to which CFD can be applied, since computations as yet remain both time and hardware expensive. Although problems such as the modelling of airflow in a rigid geometry at relatively low speeds can be solved to a high degree of accuracy using CFD, the computational cost is still too large for routine use and so assumptions need to be made. Typically, the number of mesh elements is limited as is the time step (i.e. the frequency with which the flow prediction is updated). This in turn means that the smallest scales of motion are not resolved and tracking the flow features is only approximated. For this reason, validation of computational modelling is still generally required.

Experimental measurements on replica models are the preferred means for model validation. Conversely, experimental measurements of flow are limited by scale and the number of measurements that can be made at any point during a given instance – for example, in the model used to study glottis aperture effects, measurements were taken from 37 taps. In contrast, CFD can sample the flow at an unlimited number of locations; CFD can also produce outputs for variables that are difficult or impossible to measure and lastly CFD does not rely on physical probes that can alter the flow.

In the laboratory setting, CFD is allowing research into basic physiology that has previously been too complex to model; for example, microvasculature disease and atherosclerotic deposition. Larger multi-scale studies which combine multiple patient’s data, running models for different lengths of time and using different anatomical examples, show considerable potential as aids for patient prediction and risk stratification. Both patient-specific CFD and multi-scale studies should allow us to understand why blood, air or fluid flows the way it does in the body; specifically, it could allow us to make predictions about how a disease process may incite flow change or how medical intervention to slow or reverse a process (Morris et al., 2016).

However, due to a combination of time constraints, cost limitations and shortage of validated examples, CFD’s role in medicine is still relatively limited. Of all specialties cardiac medicine has possibly seen most benefit through the use of CFD in the development of cardiac stents and prosthetic valves, however
the bridge between laboratory studies and day-to-day clinical impact is yet to be built despite potential. Vascular simulation is now being translated into clinical tools to allow non-invasive modelling of patient-specific blood flow, for example the approval by the UK National Institute for Health and Care Excellence (NICE) of the HeartFlow FFRCT analysis package for estimating fractional flow reserve from coronary CT angiography (Hlatky et al., 2015, Morris et al., 2016).

In the nose and upper airways, CFD has been used to establish airflow dynamics and its effects on patterns of moisture & heat exchange as well as for particle deposition (both for inhalational medicine delivery and for environmental exposure studies). Prior to the development of CFD, attempts to map airflow in the airways relied on experiments, using a number of techniques including hot wire measurements, smoke streams in air or dye streams in water (see Figure 35) and laser Doppler anemometry. More recently, particle image velocimetry, which tracks the motion of microscopic particles illuminated by a laser light sheet has been used to produce detailed maps of airway flows (Doorly et al., 2008b). Although CFD has been applied to the upper airways, the complex unsteady nature of the flow regime means that quite restrictive assumptions about the turbulent flow behaviour are generally employed. Computing upper airway flow without recourse to such assumptions, i.e. performing what are referred to as ‘direct numerical simulation’ or DNS studies cannot be achieved without enormous supercomputer resources. Consequently, there is a degree of uncertainty regarding predictions, and experiments continue to serve a role as a means to check the accuracy of airway CFD.

Figure 35 A sagittal slice of an MRI nose with a grid (blue) created within a box made of 4 lines (red) placed around anatomical landmarks. PS= posterior septum NS= nasal septum PL= palatal line TOP=parallel to PL from the posterior wall of sphenoid sinus
4.2 CFD in the literature

An overview of CFD studies in nasal airflow is given in Rhinology (Bailie et al., 2006). In the following we consider merely a few significant studies with regard to the critical issues of defining the geometry, the flow boundary conditions and the modelling assumptions used.

Recently, fully automated segmentation of the nasal cavity has been trialled through a software platform which segments, runs a CFD and exports the analysis (Burgos et al., 2017, Doorly et al., 2008b, Gambaruto et al., 2009, Wolpoff, 1968). The novelty of this program is that the outcome of the CFD is made available in a simplified format for clinical use, including a 3D endoscopic reformat with a fluid dynamic data. This is available in a format orientated towards clinical interpretation which is a step towards developing software applicable to the clinical environment. This software has been reportedly run accurately on over 100 different geometries; as in Doorly (2008) and Gambaruto (2009), the CFD assumes laminar flow conditions, with flows of less than 15 l/min during the inspiratory phase. Regrettably specific data is not available in the paper by Burgos et al. nor is any detail pertaining to evaluation of accuracy or variability in the geometry acquisition. Currently therefore, the tools available to support clinical decision making with regards to the airway considerably lag in comparison to those available to cardiology.

As stated, airway flows are more complex. The work of Zhao (2004) was primarily concerned with olfaction and particle deposition; this work claimed to have developed a method whereby a CFD can be run on a modifiable model of the nose within a few days. A single CT scan of a congested nose with 1mm slice thickness was segmented by a radiologist using the software package AMIRA™, within which the model was corrected and smoothed. The resulting model was imported into the CFD package ICEM™ and a mesh of 1.7 million hybrid elements created. A CFD simulation with double the number of nodes was also run, and no significant difference was found, thus the original number was deemed sufficient. The authors then blocked or expanded the olfactory slit and nasal valve by virtual geometry manipulation to observe the effects. They found, unsurprisingly, the size of the cavity was proportional to flow rate; as in Doorly (2008) the greatest volume of flow was observed to be directed along the floor of the nose and middle meatus close to the septum. Only 2-8% of inspiratory air flow was observed to
travel through the olfactory slit; flow to this region is largely unaffected by its volume (within range considered), but very sensitive to the anterior nasal valve geometry. A 1.5% decrease in local airway volume at one nasal valve resulting in an 18.7% decrease in global airflow through the corresponding nostril and equating to an 76.9% reduction in air directed to the olfactory slit in the specific example considered. This confirms that the nasal valve is largely responsible for the rate of airflow entering globally and locally in the nose.

Wen (2008) used a single CT sinus of an adult male to evaluate airflow between the left and right nostrils (Wen et al., 2008). The model was segmented automatically, with the mesh quality determined by producing 4 models containing varying numbers of tetrahedral cells ranging from 82,000 to 1.44 million cells. They found that the average wall shear stress and velocity converged at around 950,000 elements and thus this value was used as a compromise to reduce the computational costs whilst maintaining accuracy. This is less than Zhao’s 1.7 million elements and far less than Doorly’s 15.5 million elements; which whilst relevant in their individual study, they concede is not necessary to adequately resolve pressure loss, velocity and wall shear stress (Doorly et al., 2008a).

The flow rates considered, these vary between studies. Scans are largely acquired with the patient supine in a resting position which will correlate with ventilation rates of between 5-6 l/min (Stradling et al., 1985). Additionally, left and right nasal cavity are not symmetrical in terms of airflow, as typically one is in a state of congestion whilst the other is decongested. In high flow rates the difference between the two nasal cavities becomes more distinct as do the local differences in each cavity. Wen (2008) used flows between 7.5-15 l/min whereas Zhao (2004) used 15 l/min which are assumed to be laminar (Wen et al., 2008, Zhao et al., 2004). However, 6 l/min has previously been shown by Doorly (2008) to provide laminar flow, whereas moving towards 7 l/min the flow in the nose begins to display the onset of transition to turbulence. Wen (2008) found that up to half of the upper airway resistance was found in the first 2-3 cm of the nasal cavity. Certainly, the highest shear stress is seen on the anterior face of the inferior turbinate and the nasal wall adjacent to the inferior turbinate, the cause of which is local drying and vascular damage which can lead to epistaxis (See figure 14). Low flows within the meati contradicts the suggestion that the sole role of the turbinates is to increase the surface area for air
conditioning. They suggest turbinates have a fundamental role in changing the dynamics of the airflow, to circulate low flows to the olfactory region and re-direct flow to increase particle deposition early in the nose to prevent inhalation (Wen et al., 2008). This is corroborated by Horschler (2003) who noted a twisting of the streamlines running through the channels of the nose particularly on inspiration, resulting in the air having prolonged contact time with tissues. By comparison this effect was not seen on expiration which is contrary to previous studies suggesting inhalation and exhalation are similar (Hörschler et al., 2003, Wolf et al., 2004).

Unlike other papers, Naftali (2005) used an unsteady flow computation in their CFD and found maximal flow of 3.8 m/s at the nasal valve, compared with 2.4 m/s in previous experimental studies and CFDs using steady state algorithms. They repeated the study with a steady flow of 7.5 l/min and found the nasal valve directed flow towards the middle meatus increasing the air-conditioning capacity by 3%.

It is well recognised that the turbinates contribute towards heating and humidifying air, with the septum and lateral walls being responsible for 60-70% of air conditioning. Computational simulations suggest removal of the inferior or middle turbinate results in an approximate reduction in heat and water vapour flux in the nasal cavity of 16% and 12% respectively (Naftali et al., 2005). Although it should be noted that a limitation of any computational model is the assumption that the nasal lining can heat and moisten unlimited amounts of air, whereas it is understood that changing air conditions can lead to dryness, crusting and bleeding.

Several studies have considered the effects of variations in geometry on nasal airflows, but few have considered the effect of different observer segmentations. In the work of (Doorly et al., 2008b), the geometries of three unilateral patient noses were analysed. Moreover, three different models of Subject 1 were made, comprising one by ENT surgeon, one by an engineer and a third comprising a simplified geometry. All cases showed broadly similar patterns of pressure loss and overall flow characteristics, but large differences in both the level of trans-nasal inspiratory pressure loss and the appearance of transitional flow. Specifically, largest pressure loss was found to occur in the interior nose to the anterior head of the middle turbinate – a region characterised by high shear stress in comparison to the posterior and superior regions of the meati. Unsurprisingly, the geometry corresponding to a decongested nose
displayed much larger passage cross-sectional area, resulting in low trans-nasal pressure loss. An interesting observation was that averaging geometries inevitable regularised. For example, variations in the curvature of the septal wall are averaged out, resulting in a clear path for the flow; the danger is thus that the ‘average’ nasal model is too regular to correspond to that of any real subject.

The concept of simplification and idealisation was then further investigated using Fourier descriptors with relation to nasal geometry (Gambaruto et al., 2009). Fourier descriptors are a means to define the boundary of a 2D image in compact form, where every (x, y) point on a boundary is mapped to a fourier number and the boundary can be recovered from the inverse Fourier transform. The full 3D volume is derived as before by interpolating a surface over the stack of 2D boundaries – the difference being that boundaries are no longer defined in terms of individual pixels but by fewer (up to 20) coefficients. Whilst Fourier descriptors offer a means to combine geometries, they were also studied to evaluate their use as a means to characterise the shapes of nasal contours. Shape characterisation allows the identification of common geometric traits, in different airway geometries. For example, in terms of ethnicity, it has long been suggested that leptorhines (tall, narrow noses) exhibit different features to that of platyrrhines (short, broad noses) depending on the climate conditions of their ethnic origin (Wolpoff, 1968). Studies from different countries often use a narrow spectrum of nasal shapes and thus inter-study comparisons can be hindered. Given the adaptability of humans, possible variations in upper airway geometry that might be linked to ancestral geographical origin are likely to be less significant than those associated with different pathological conditions. The main thrust for studies on shape characterisation form the clinical standpoint is to determine whether different modes of geometric variation are linked to different pathological functioning of the airways. Unfortunately, it was noted that the Fourier descriptor approach did not produce a sufficiently compact shape representation to facilitate its use.
In summary, previous studies have indicated that:

- the geometry of the anterior nasal valve not only contributes significantly to trans-nasal resistance, but plays an important role in determining the direction of airflow through the nasal cavity (Zhao (2004);

- studies of nasal airflow have been performed primarily for ventilation rates between 6-15 l/min;

- experiments using rigid in-vitro models indicate airflow in the normal nose to be laminar at low flow rates (steady flow of 12 l/min corresponding to a ventilation rate of 6 l/min, but transitional at higher flow rates.

- idealised models derived by averaging geometries have the effect of straightening the septum and smoothing features (Doorly 2008), lowering trans-nasal pressure loss and may produce results at variance with those in real geometries.

- there is a need for better shape characterisation tools to test the extent to which different geometric traits are associated with physiological performance, in order to inform clinical decision making.

4.3 Methods: Consequences of geometric variability on nasal airflow distribution

The level of uncertainty associated with CFD predictions of nasal or indeed upper airway airflow has not been comprehensively studied. Of the many potential contributors to uncertainty, possibly the most basic is simply that of the geometry. In the previous chapter, uncertainty in airway definition given CT scan data was considered. In this section we consider the generation of models from MRI. This is more challenging, since the spatial resolution of MRI scans is often less and more susceptible to patient movement. We also extend the previous work by investigating how geometric uncertainty for models derived from MRI affects the ensuing level of uncertainty in CFD flow predictions.
In this pilot study, a single MRI was segmented by two ENT surgeons with experience in segmentation using Mimics™. Subject D is a healthy male with no nasal symptoms or history of nasal surgery. Two MRIs were taken in a state of congestion and decongestion. Both models were exported from the segmentation software in STL format, translated to a virtual model and a CFD simulation performed by a single aeronautical engineer (Qiwei Xiao), as per the stages outlined in figure 36. The simulations in this study were run using STAR-CCM+™ software.

![Figure 36 Comparison between CFD and experimental data for 20 l/min in a 10 degree and 53-degree glottis showing excellent correlation between results](image)

After the STL geometry file is exported, the model undergoes pre-processing where the engineer selects the boundary conditions, decides on the mesh continuum and physical continuum. Timestep and flow solvers also need to be selected. Multiple simulations need to be run in order to determine the ideal mesh and timestep; the choice of these parameters will determine how long each simulation takes. It is important to note that the complete inspiratory-expiratory cycle of breathing is not simulated, as this would require far too large computational resources to do so without flow model approximations. Consequently, only constant inspiratory flow is simulated. It is generally accepted
that for purposes of mean flow distribution and trans-nasal resistance estimation, steady flow simulations suffice. In physical terms, the justification is that whereas the inspiratory part of a breathing cycle typically lasts 1 - 2 seconds, flow transits the entire nasal cavity in a time of order 1/10 of a second.

A complication is that whereas the flowrate is steady, the flow shows some spontaneous disturbances even at such low flow rates. Consequently, a fully unsteady flow is simulated with averaging applied over a time that is much shorter than a full breath cycle as the simulation only needs to run to the point that the flow becomes steady. In these studies, simulation ran for 0.3 seconds which was long enough to achieve this.

The simulation can be run using laminar or turbulent flow - if choosing turbulent flow there are multiple subtypes of codes that can be used. However, the simulations for this study have not used turbulence modelling in the flow solution because the flow within nose has been demonstrated in previous models to be steady and laminar (Kelly et al., 2000). Unsteady laminar modelling can arguably better cope with the separated flow features in the trachea than simple turbulence models. The main aim of the CFD is to solve the Navier-Stokes equation, after which the data required can be extracted during the post-processing.

These studies simulations took approximately 3 days to run in a 16 core CPU work station. Once the engineer has decided on the boundary conditions and completed all the pre-processing, running variations of the same model simply requires the mesh to be created and repaired. The anatomical complexity of the nasal cavity and trachea makes the mesh significantly more complex and thus repairing it can be a time-consuming process.

4.4 Effect of geometric variability on nasal airflow distribution

The MRI scans obtained for Subject D, where their nose was respectively in a state of congestion and decongestion, was segmented by two experienced users (User R and User L). Computational flow dynamics studies were then performed for the respective virtual geometries for comparison. As an illustration of the scale of differences in the assumed geometries, and the effect on the derived flow fields, Figures 38 and 39 compare maps of the flow velocities at the same sagittal section.
The three vertical lines shown on the two flow models below are called 1V (most anterior), 2V (middle) and 3V (most posterior). The difference between the respective user’s mass flow rate distribution was generally observed to be negligible, except for the top left region in the decongested cavity where there was an area of recirculation around the plane of 1V resulting in back flow. This region is 100x smaller than the other sections within the nose thus the difference between the mass flow rates looks greater than it is. The difference in pressure drop between users is significant, however pressure drop overall is poor predictor of nasal health and only in cases of severe obstruction does pressure drop become more relevant.

Proportional mass flow rate was calculated by the following equation:

\[
\text{Proportional mass flow rate}(m) = \frac{\text{nasal subsection}}{\text{Sum of Left or Right sections/Total m}}
\] (4.1)

![Sagittal section through the Congested nose of subject D comparing inspiratory airflow rate predications of the same subject anatomy by different users (User R). 1V, 2V and 3V represent planes (see figure 22)](image)
An independent t-test was performed to determine if there was statistical significance between the mass flow rate distribution between the two congested models created by different users. Left and right nasal cavity mass flow rates were combined to give total mass flow rate in upper, middle and lower zones of the nose in three separate planes 1V, 2V and 3V. The p value=0.276 >0.05, showing that there was no significant statistical difference between the mass flow rate for combined left and right nasal cavity in Bottom, Middle and Top zones.
Figure 40 Proportional Volume in the left and right side of a Congested nose from a geometry segmented by two different users

Figure 41 Proportional Volume in the left and right side of a Decongested nose from a geometry segmented by two different users
USER R: Proportional Mass flow
Congested LEFT nasal cavity

USER R: Proportional Mass flow
Congested RIGHT nasal cavity

USER L: Proportional Mass flow
Congested LEFT nasal cavity

USER L: Proportional Mass flow
Congested RIGHT nasal cavity

Figure 42 Proportional mass flow rate in the left and right side of a Congested nose from a geometry segmented by two different users

USER R: Proportional mass flow
decongested Left cavity

USER R: Proportional mass flow
decongested Right cavity

USER L: Proportional mass flow
decongested Left cavity

USER L: Proportional mass flow
decongested Right cavity

Figure 43 Proportional mass flow rate in the left and right side of a Decongested nose from a geometry segmented by two different users
To ensure assumptions from the t-test were precise and valid, a single one sample t-test was performed on the log of the ratio of User R/User L. This enabled a fairer comparison between the two models as it avoids inconsistent measures of the error due to scaling problems from the units used. Again, the left and right sides were combined for each section and the Top, Middle and Bottom zones were compared in each plane. The test showed a p-value= 0.463 confirming no statistical difference between the two-model’s mass flow rate.

![Figure 44](image)

**Figure 44** A comparison between % mass flow rate at 30L between Lower, middle and upper sections of the nose in plane 1V in a congested nasal cavity. Equivalent plots for levels 2V and 3V can be found in appendix 3.2.

Similar to the congested models, an independent t-test was performed to determine if there was a difference between the decongested models. The p value was, p=0.648>0.05, showing that there was no sufficient statistical significance to reject the null hypothesis of difference in mass flow rate between two the segmentations.
Further CFD were performed on 3 versions of User R’s model, based on adaptations at the external nose and nostrils, with the same internal cavity geometry. Model R1 is the original segmentation, model R2 is a new more accurate nose attached to the old internal geometry and the model R3 is further smoothed version of the new nose attached to the old internal geometry. This attachment is anterior to the internal nasal valve thus the cross-section of this sensitive area should not change.

An independent T-test was performed to compare the mass flow rate distribution of the full nasal cavity between the 3 models, looking at flow through the inferior, middle and superior nasal cavity. No statistical significance was found comparing Model R1 versus R2 p-value=0.842, Model R1 versus R3 p-value=0.879 and there was even less difference between R2 and R3 p-value=0.967.
Despite the mass flow rate distribution remaining unaffected the pressure loss is changed by the adaption to the external nose. The pressure loss is measured from a theoretical 0.5m sphere around the nostrils to the larynx. The pressure loss is increased from R1 to R2 by 28% and from R1 to R3 by 27%.

**4.5 Conclusions**

With no statistical difference found between the mass flow rate distribution between User L and User R’s models, this would confirm that in this case the models are less sensitive to small geometric changes than previously thought. Whilst slight changes to the shape of the external nostril can affect pressure loss quite significantly. In this study the degree of congestion does not impact on the difference in mass flow rate distribution between the two models.

This would suggest that some areas, even the external nose, are more sensitive to change and can have a significant impact on pressure. This has implications on surgery such as cosmetic rhinoplasty, which
is seemingly a change to the external nose but may have a more profound effect on airflow than previously suspected.

A larger comparison study would be beneficial to quantify the effect of different geometric changes on airflow dynamics. Future studies should validate their choice of laminar or turbulent flow as well as flow rate and number of cells used for their mesh to ensure comparability across studies.
Chapter 5

5.1 Overview

In this chapter the geometry of the larynx and in particular that of the glottis is considered, since the glottis plays a major role in determining tracheal airflow, particularly during inspiration. The degree to which the glottic aperture varies is clearly of prime importance from the flow perspective. Until recently it was not possible to capture data which simultaneously links glottis aperture and flow, and this remains a challenging task.

The geometry of the glottis is first described along with earlier works that recognise its significance in terms of flow modulation. Results of earlier static measurements on glottis aperture are tabulated. Since the glottis aperture varies dynamically, procedures to quantify glottis aperture from nasendoscopic images are then outlined. A pilot study undertaken to determine the relation between glottic area and the clinical measure of anterior commissure angle is reported. Finally, given the labour-intensive nature of manual segmentation and interrogation of laryngoscopic images, a semi-automated procedure to extract anterior-commissure angle measurements is tested to investigate clinical feasibility.

5.2 Geometry of the glottis and the laryngeal jet

The glottis is normally the narrowest point of the airway and is charged with modulating airflow, phonation and airway protection. It consists of two folds, the false cords or ventricular folds (larger and superior) and the true cords/folds. The whole larynx is a dynamic organ, which can lengthen and narrow, particularly at the level of the true cords, where adduction of the cords leads to total airway closure. The glottic aperture changes not only to vocalise, but during breathing and swallowing.
The narrow aperture of the glottis compared to the superior and inferior airways is the origin of the laryngeal jet. The glottis is responsible for a certain amount of airflow modulation and this can change the characteristics of the jet and has been a source of interest to groups investigating particle deposition. Investigators have focussed both on the dynamics of flow as well as the manner in which different particles engage with that flow. Given that one of the main roles of the extra-thoracic airway is to filter potentially harmful small particles from inspired air, designers of aerosolised respiratory medications have this innate disadvantage to overcome (Heenan et al., 2003, Stapleton et al., 2000).

Corcoran et al have shown that individual geometry can influence direction, velocity and dynamics of flow which can result in the formation of reverse or rotational flow known as eddies (Corcoran and Chigier, 2000). Whilst the present studies do not specifically concern particle deposition, many studies,
such as the preceding that concern deposition are relevant through contributing to the understanding of flow fields in the trans-glottal airway geometry.

Glottic dimensions vary constantly throughout respiration, but many geometric measurements from the literature are extracted from a snapshot in time. In the work of Eckel et al (1994), morphometric measurements were extracted from 53 post mortem larynxes from equal gender groups. Mean AP diameter was 13.9±2.9 mm in Males and 10.7±1.6 mm in Females (Figure 48). The following year the same group (Eckel and Sittel, 1995) extended their project to include 20 fresh frozen larynxes, reporting values of glottic area for Males as 85.4±38.4 mm² and for females as 53.2±15.9 mm². Brancatisano (1983) also provided glottic area measurements in live adults using a bronchoscope, reporting a mean of 126±8 mm² during inspiration and 70±7 mm² in expiration (Brancatisano et al., 1983). Whilst Eckel’s measurements will be subject to a slight post-mortem reduction in tissue volume and those of Brancatisano to scaling inaccuracy, these results provide a benchmark against which to compare geometries used in the present study. Only one study (Scheinherr et al., 2015) used endoscopic images and provided a solution to the problem of scaling; resulting in a mean glottic area of 196±42 mm² for males and 177±27 mm² for females. In the work reported here, 3D segmentation is applied to the laryngotracheal airway from a single CT from an adult male, and do not reflect a mean across a population. The CT was acquired in a supine position as supposed to sitting which additionally may affect the size of the glottis. The AP diameter of the glottis stays largely constant during breathing in

Figure 48 Photographic image showing the human larynx in 3 different degrees of closure. The left image showing full opening at inspiration with the glottic area marked, middle image partial closure with the antero-posterior (AP) diameter and the right-hand image an almost closed with the epiglottis obstructing the view of the anterior commissure.
comparison to the aperture area, as the cartilages which suspend the larynx do not move antero-posteriorly. The arytenoids are able to abduct and adduct, which this results in large area changes but small variations in AP diameter. The AP diameter in the adult male in our study was 25 mm which we have used as a constant in order to scale the photographic images.

<table>
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<tr>
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<th>Mean inspiratory males mm²</th>
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<th>Mean inspiratory females mm²</th>
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<tr>
<td>Eckel and Sittel, 1995</td>
<td></td>
<td></td>
<td>85.4±38.4</td>
<td></td>
<td>53.2±15.9</td>
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<tr>
<td>Brancatisano et al., 1983</td>
<td>126±8</td>
<td>70±7</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Scheinherr et al., 2015</td>
<td>217±54</td>
<td>178±35</td>
<td>196±42</td>
<td>189±32</td>
<td>168±31</td>
<td>177±27</td>
<td></td>
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<tr>
<td>Derived area measurements from glottic videos</td>
<td>212.7</td>
<td>106.8</td>
<td>163.4</td>
<td></td>
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Table 3 Cross-sectional area measurements from various studies. Whilst our patients mean inspiratory area is equivalent to Scheinherr’s results, our expiratory area is much smaller. The % increase in area is more equivalent to that of Brancatisano’s results.

Glottic aperture is currently assessed visually using a flexible nasendoscope in awake patients or rigid laryngoscopy in anesthetised patients. To take geometric measurements, the glottic aperture must be approximated visually or image stills printed, and measurements taken by hand. Both are time consuming and inaccurate, whilst neither approach facilitates the understanding of trends, nor allows quantification to demonstrate efficacy of medical intervention. This is of particular relevance when treating vocal cord palsies, where the inability to adduct one or both cords leads to symptoms of dysphonia, dysphagia and breathlessness. Where there is insufficient closure of the vocal cords, surgical therapies can be applied to reduce the glottic aperture or resulting ‘phonatory gap’. This has to be done by eye and with follow up visits frequently to different doctors, objective assessment is lacking. The ability to perform objective measurements of glottic aperture would circumvent possible clinician subjectivity in assessment of laryngeal function pre and post-operatively and facilitate comparisons.
5.3 Dynamic assessment of glottic function

The two studies described in the following were performed in collaboration with the Royal Brompton Hospital. They were conducted in order to investigate the role of segmentation in quantifying real-time glottic aperture measurements as part of respiratory function testing. The first study is of Continuous Laryngoscopy during Exercise (CLE test), whilst the second is an investigation of glottis motion in a single subject using continuous laryngoscopy under Continuous Positive Airway Pressure (CPAP) conditions with oesophageal pressure and air flow recorded.

**Study 1.** For patients experiencing stridor during exercise, Tertiary Respiratory medicine facilities can perform Continuous Laryngoscopy during Exercise (CLE test), which allows physicians to evaluate the dynamics of the larynx during exercise. The procedure is performed on a treadmill or a resistance bicycle where the patient wears a helmet onto which is mounted a flexible nasendoscope. This is passed through the nose and taped in place to be suspended above the larynx, thereby minimising the caudal/rostral movements of the camera which will affect scaling.

The nasendoscope is linked to an endoscopic video stack which films at 25 frames/second or captures stills during the experiment along with other biotelemetry data. This data includes heart rate, volume of oxygen consumed (VO2), respiratory quotient (RQ), maximal minute ventilation (MMV) and forced vital capacity (FVC). Specific limiting factors related to capturing images is covered in appendix 4.1.
Currently this test is performed on patients with Chronic Obstructive Pulmonary Disease (COPD) as well as those complaining of symptoms of Exercise Induced Inspiratory Symptoms (EIIS). The latter is frequently mistaken for asthma or COPD as the symptoms are similar, however continuous laryngoscopy during exercise testing allows the paradoxical vocal movements, the hallmark of EIIS to be identified, and unnecessary pharmaceutical agents to be discontinued if not required.

**Study 2.** In CPAP, air is supplied via a mask at an elevated constant pressure of a set value (typically 5 - 11 cm H₂O, but in some cases, even higher levels) which reduces the work of breathing by ‘splinting open the airways’ (i.e. increasing alveolar volume thus reducing effort to inflate). However, the user has to initiate and regulate their own breathing. Patients with advanced COPD or sleep apnoea may use CPAP machines during rest or whilst sleeping. Whilst primarily used in patients with severe respiratory disorders, it can additionally be used in pre-term infants to support them without intubation.
5.3.1 Experiment 1

Six patients undergoing diagnostic respiratory testing underwent a ‘Continuous Laryngoscopy during Exercise’ (CLE test) on exercise bicycles. Anonymised clinical videos of the flexible nasendoscopy taken at initiation of exercise and during moderate exercise were identified by the lead respiratory physician. One patient was excluded from this study as the video quality was poor, with the glottis being repeatedly obscured due to swallowing. Patients 4, 20, 23, 32 and 34 were included. Videos were cropped and converted to DICOM images for segmentation in Mimics.

![Figure 50 Still images from CLE of Subject 20 (left) and subject 34 (right)](image)

5.3.2 Experiment 2

A single healthy subject underwent continuous laryngoscopy at rest with simultaneous intra-oesophageal and intra-gastric balloons pressure measurements to compare against mouth pressure with a CPAP mask. CPAP settings were modified, and the subsequent pressure changes compared whilst the subject was supine and sitting during quiet breathing. The flexible nasendoscope was fixed via a head mount and travelled through a custom hole made on the anterior surface of the facemask. The following measurements were captured: CPAP setting, mouth pressure, mid-expiration oesophageal pressure and end-expiratory oesophageal pressure. The start time on the video and pneumotachograph were recorded.
to synchronise the data. The aim of this study was to compare the movement of the vocal cords and the angle of the anterior commissure against the pressure recorded.

The team responsible for collecting the data were using a prototype mask where there was a significant leak at the point of FNE entry at higher pressures, meaning the CPAP settings may not perfectly equate to the actual pressures measured by the mouth pressure manometer. Subsequently, modifications have been made to this mask to prevent this.

In total 24 videos of a single healthy subject were captured, taken during an initial experiment to capture the above data. Of these, 5 were chosen from both the supine and sitting sets and analysed. The videos were cropped and converted to grey-scale using the Matlab script and imported into Mimics, segmented and glottic areas extracted. Glottic angles were manually drawn on each DICOM image, using an angle tool. Oesophageal and mouth pressures were manually extracted from screen stills taken during the video. DICOM stills after being converted to grey-scale with the telemetry on the right-hand side of the image (see appendix 4.2).
5.4 Glottic aperture segmentation results

5.4.1 Experiment 1: Results

To determine the efficacy of segmentation in identifying glottic area, five patient videos from continuous laryngoscopy during exercise were imported into Mimics™ as grey-scale DICOM files. A threshold was chosen by a single user to capture as much of the glottic area as possible and the 2D mask area was plotted against slide number to give an arbitrary view of glottic closure. The 2D area measurement does not have a fixed unit as there are no comparative measurements available on the video to quantify it. For example, the closer the camera gets to the glottis the more it occupies the screen and the larger the glottic area would appear.

The subjects with the longest unobstructed view of the glottis were Patients 32 and 34. Figure 52 shows Patient 32 with a broad range in glottic aperture with short periods of total glottic closure during swallowing (at slides 295 and 358), whereas figure 53 shows Patient 34 with minimal change in glottic aperture, showing the glottis is open most of the time.

![Patient 32](image)

*Figure 52 Case 32 with Chronic Obstructive Pulmonary Disease*
Whilst the pattern of respiration can be appreciated within a single study, it is not possible for one to be directly compared against another, due to the arbitrary values of area. Therefore, a ratio of glottic change to mean glottic area was calculated. Ratio of glottic area may be a simple way of discriminating between cases where there is no scale available.

Whilst percentage change can be useful, because there are instances of glottic closure that can become confusing thus Figures 54 and 55 were calculated by
The video from Subject 34 has been cropped down to <20 seconds to equal the number of slides in that acquired for subject 32. Subject 32, who has COPD, has a much more variable and greater % change in area compared with Subject 34 (no respiratory disease), with 40% area changes during restful breathing compared to 12% respectively.

For further charts related to the flow modulation at the glottis see appendix 4.3.

5.4.2 Experiment 2 Results

A total of 5 videos were chosen for a normal subject undergoing continuous laryngoscopy during CPAP. Below are the features of the different videos taken. It is important to note that due to magnification, it is challenging to directly compare the glottic area as the scope may move between studies. Some further limitations of comparability include varying numbers of breath cycles between videos and higher leak rates in the CPAP mask at high pressures.
The mouth pressure manometer gives smooth readings which inversely correlate with the glottic area. However, the oesophageal pressure measurements seem to vary more during maximal inspiration dropping to near 0 mmHg as the glottic area is maximal at the end of inspiration. The angle of the glottis correlates closely with the glottic area. Observing how glottic area interacts with mouth and oesophageal pressures, it can be seen that CPAP settings increase the overall pressures recorded by the manometers. However, this does change based on the position of the patient, oesophageal pressure

![Figure 56 Video D Supine patient (CPAP=15)- Glottic area against oesophageal & mouth pressure showing that when lying down the oesophageal pressure is greater than that of the mouth pressure](image-url)
becomes lower than mouth pressure when the patient is sitting up. This is a likely a causative factor in gastro-oesophageal reflux which is worse when supine.

To understand the influence of CPAP pressures on glottic area, a linear regression analysis was used to compare the glottic angle and mouth pressure in videos D and T, showing a strong negative correlation between mouth pressure and glottic angle in both videos (Video D correlation co-efficient -0.828, \( p=3\times10^{-18} \), Spearman rank correlation coefficient \( r=-0.788 \), \( p<0.01 \). Video T correlation co-efficient -0.862 \( p=8.9\times10^{-27} \), Spearman rank correlation coefficient \( r=-0.779 \), \( p=5.3\times10^{-15} \) ) (Using Corr function Matlab).

When the pressure increases, glottic angle decreases, specifically in Video T (CPAP 3) increasing the pressure by 1 mmHg, the glottic angle reduced by a factor of 6.8. Comparing the data from the highest and lowest CPAP settings there is an inverse correlation which becomes stronger the lower the CPAP setting. For a constant CPAP setting the mouth pressure would be expected to be lowest on inspiration which would correlate with a larger glottic area, whereas during expiration the mouth pressure will increase and glottic area decrease.

![Figure 57 A scatterplot with a linear regression fitted line of Video T (CPAP 3) showing mouth pressure against glottic angle](image-url)
To understand the role of the glottis in regulating pressure the area measurements from the videos were scaled using the AP diameter as a constant of 25mm derived from a CT of an adult male (see Figure 48). The mean cross-sectional glottic area across all videos was 163mm² (range 151.4 to 171.3 mm²) which is keeping with the study by Scheinherr et al., 2015. Average maximal glottic area 212.7 mm² and average minimal glottic area 106.8 mm² with a mean of 163.4 mm².

To determine if there is an association between glottic area and glottic angle (figure 60) a linear regression analysis was performed. As the area has no unit due to issues of scale when the images were obtained, the data has been normalised by subtracting the mean area (μ) from each value (labelled x) divided by the standard deviation (σ)

\[ z = \frac{x - \mu}{\sigma} \]

At the lowest CPAP setting of 3 the average % change in glottic area is 70% (glottic angle range is 32-50 degrees). When compared to a CPAP setting of 13 in the same position, the % change is reduced to 39% (glottic angle range is wider at 22-51). High pressures result in the glottis opening to the same
aperture on expiration but narrowing to a greater degree on inspiration. The area change is largely due to the arytenoids remaining medialised, obscuring the posterior commissure and it may be that the supraglottis has a greater role in limiting airflow. From the limited data set we have it is difficult to make clear statements about the effect of position on glottic airflow regulation. Results pertaining to oesophageal pressure are in appendix 4.5.

In summary segmentation of the glottis using software such as Mimics is a relatively fast and reproducible way to elicit glottic area in comparison to manual measurements. However, this is highly dependent on the acquisition of high-quality video data of the larynx which is affected by patient tolerance, individual anatomy and camera positioning.

The initial study showed a greater percentage change in glottic area at restful breathing in the patient with Chronic lung disease compared with a healthy patient (40%/12%). Whilst percentage change in aperture can be examined, the inability to apply a scale to the images limits the degree to which results can be compared against their own data and the populations as a whole. The conversion of pixels to

Figure 59 Video D supine patient (CPAP=15)- Glottic area against anterior commissure angle
millimetres would be possible if the distance between the glottis and camera could be measured and one way to elicit that would be using image guidance software. Endoscopes have the ability to be registered with existing cross-sectional image data from individual patients, a technique that is used in complex sinus surgery to identify and avoid vital structures (Lapeer et al., 2008). A group that overcame this problem used APg as a geometrical invariant and testing it on manually printed images of the glottis. Using this method they derived a 10% error rate however this would be a useful tool to ascertain true geometric measurements. (Schein herr et al., 2015) A simpler way of drawing comparisons, which would benefit further analysis, is to compare the area trace throughout the respiratory cycle which in this case showed a distinct difference in morphology between patients with and without respiratory disease.

Studies performed on a healthy candidate investigating the implication of CPAP on the glottis showed a strong negative correlation between glottic angle and mouth pressure, this correlation became weaker the higher the CPAP setting. This may suggest that as the resistance at the mouth becomes greater the
glottis opens to reduces glottic resistance, largely the glottis is narrower on exhalation. The same correlation was not found for oesophageal pressure and glottic angle.

A linear regression analysis found a strong correlation between the glottic angle and glottic area, signifying that the glottic angle may provide a good substitute for area in cases where the glottis is partly obscured by supraglottic structures. The benefit of this may be that future studies looking at looking at glottic shape with reference to respiratory function may be able to interpolate the angle by drawing tangents following along the lines of the vocal cords even when the anterior commissure is obscured, which is frequently the case.

Future studies should explore the dynamics of glottic angle and area in patients with and without lung pathology at different levels of exertion.

5.5 Automated glottis identification
5.5.2 Glottic detection in the literature

Currently the mainstay of assessing the glottis is through the use of endoscopic cameras and the subjective interpretation of quality of function by a medical professional. The glottis is clearly visible as an aperture bordered by the two vocal cords which opens into the trachea below. In order to mitigate the subjectivity of individual interpretation of endoscopic images, research has been focused on creating an automated program capable of glottis area motion detection. Ideally, such a program should be capable of running on NHS standard resolution endoscopic images, with a user-friendly interface and clinically related data output interpretable by a clinician.

Initial studies directed at minimising subjectivity aimed to create a validated scoring system for CLE to overcome inter-user and inter-centre variability. Maat (2009) videoed 100 volunteers (80 patients with exercise induced dyspnoea, 20 healthy volunteers) of which 60 videos of adequate quality were obtained (Maat et al., 2009). Two independent laryngologists scored the videos twice from 0-3 for supraglottic and glottic collapse. There was seen to be a significant difference between CLE scores out of 4 between patients (3.34±1.34) and volunteers (0.65±0.66) with a p-value of <0.001. They also compared the CLE
scores with patient symptom scores and found that glottic adduction at maximal exertion strongly correlated. In terms of inter- and intra-user variability, the variability appeared to be more linked with the degree of glottic closure. In moderate glottic closure there was almost 100% agreement within and between groups, however there could be as little as 70% agreement in other areas, which would be a cause for concern regarding classification reliability. Whilst no gold standard score exists with which to compare results to, spirometry measurements and telemetry obtained before and during the test respectively were used to give an impression of extent of CLE.

Continuous laryngoscopy during exercise has also been used in patients with COPD to understand if the glottis is regulating intra-thoracic pressure. To investigate this Baz (2015) from the collaborating group at the Royal Brompton Hospital explored whether there was a correlation between ratio measurements of the glottis, the ‘Glottic narrowing ratio’ (GNR) and exercise tolerance and hyperinflation.

Glottic narrowing ratio (GNR) is taken at the mid-point between inspiration and expiration. The distance between the cords is measured at the mid-point of their length, at end of inspiration (a) and at the end of expiration (b). Whilst this ratio may be useful in determining a broad overview in glottic pattern it does not demonstrate change over time or identify patterns. Additionally, this measurement is likely to be affected by magnification of the larynx due to scope position. Glottic angle measurements may not be so distorted as the angle is likely to remain consistent irrespective of magnification.

19 patients with stable COPD and 11 healthy volunteers underwent CLE, end-inspiratory and end-expiratory stills were used to measure the Glottic- and Supra-glottic narrowing ratio (GNR/SGNR). GNR was reduced during expiration by a median of 10% in healthy volunteers compared with 50% of COPD sufferers. This was similar at the supraglottis but not to the same extent.
Interestingly the ratios were not related to BMI, sex, age or height, nor was there any change in the ratio during exertion in either group. They were however able to find a proportional link with disease severity when comparing GNR with FEV1 (Baz et al., 2015).

The GNR has advantages, however the technique used to measure it is laborious and prone to variation. Dailey (2005) developed a Matlab script for automating capture of the anterior commission angle (Dailey et al., 2005). To determine maximum abduction and velocity of abduction and adduction, 19 healthy females were recruited and asked to phonate then perform a sharp sniff at 3 subjective rates (slow, medium, fast). The mean abduction angle was shown to be 51° (range 31-77°) which is wider than previously documented results of ranges between 51-77° (Woodson, 1993). The authors suggested this may be secondary to sample size or the angle of tilt on the larynx, which they tried to compensate for in their code. If algorithms such as this could be adapted to have a simple user interface, they would have a strong role clinically in taking objective measurements such as glottic angles. They may even have a role in diagnosis or differentiation between conditions.

Christensen (2010) developed a semi-automated model to investigate glottic aperture in patients with exercise induced laryngeal obstruction (EILO) and it’s two subdivisions of Laryngomalacia and Vocal cord dysfunction to compare against experts’ interpretations of the same data (Christensen et al., 2010). 97 participants between the age of 14-24 were randomly selected with no apparent exclusion criteria and put through the CLE test. The software, ‘EILOMEA’, then requires a user to choose a single frame during maximal inspiration and expiration in the last 20 seconds of the test, which clearly showed all glottic and supraglottic structures. The user then draws lines on the image to orientate the software, which then automatically calculates the glottic area, this is given as a relative number instead of pixel units. Using boxplots, their group defined a numerical threshold above and below which the patient was likely to have a condition or not- named the P-factor (for vocal cord dysfunction) and C-factor (for laryngomalacia). In comparison to expert’s ratings of the videos, they found ELIOMEA had a sensitivity of 0.65 for vocal cord dysfunction and a specificity of 0.96. Its sensitivity and specificity for laryngomalacia was 1.00, suggested to be more accurate because it is simpler to see if there is supraglottic collapse. In cases of possible dual obstruction at both the glottis and supraglottis, it became
more challenging to differentiate between the two disorders which may explain the reduced sensitivity. Whilst a study such as this is promising, it still requires manual lines to be drawn on images, which are subject to variability and the authors noted that the quality of the images was a significant rate limiting step.

To date, most manual or semi-automatic methods of quantifying the movement of the glottis have focussed on subjective scoring of the degree of closure or through the use of area or ratio measurements in selected still images.

Fully automated algorithms for mapping glottic area, broadly speaking use two methods: **region growing**, where an area selected is made of pixels that have been selected based on their grey-values situated around a seed pixel and **contour tracking** which is a type of edge detection where the algorithm makes sense of 2D images by delineating the object outline.

Yan (2006) developed an algorithm based on histograms, where a histogram of the pixels of the first slide would be created and then modelled in Rayleigh distribution. This would lead to an initial area selection, as each successive slide had a threshold chosen, and could act as a seed point for region-growing techniques (Yan et al., 2006). Wittenberg (1997) was more focussed on motion-tracking of vocal fold trajectories, but similarly used region growing algorithm. The seed pixel was based on the threshold minimum for the slide, with the understanding that the glottis usually appears as the darkest part of the image. The seed pixel for each successive slide is then compared against that of the previous image and if it falls outside of a chosen region surrounding the previous seed pixel, the glottis is presumed to be closed. In order to map glottic motion, an axis line was placed in the AP direction, 4 lines were drawn orthogonal to this- the end points of which reached the edge of the glottis. By mapping the change in where the points were they were able to trace the movement of the glottis (Wittenberg et al., 1997).

The active contour algorithms have already been used in vocal fold motion tracking during vocalisation, which is high frequency motion. As the vocal folds have quite clear edges where the central glottis is much darker, this type of algorithm seems ideally suited. In both manual segmentation and active
contour algorithms, the most anterior and posterior parts of the larynx are subject to the most error. This is likely due to the lack of black-white differentiation at those points and can be overcome by manual adaption, or in the case of automated segmentation by the addition of tools such as canny edge detection, stretching energy and edge energy, the effects of which are seen in their Figure 1 and Figure 5 (Marendic et al., 2001).

5.6 Methodology for automated glottic identification

In conjunction with this group’s work, a specific MSc project focussed on creating a Matlab™ code which automated glottic segmentation to be compared against the manual segmentation techniques from Mimics™. Whilst segmentation through Mimics™ is seen to be labour intensive, with a surgeon carefully segmenting, it is likely to be an accurate depiction of the anatomy and an excellent standard against which to determine the accuracy of the Matlab™ tool. The student used shared Matlab™ files from Mathworks™ to develop and compare her code against, using the mimics files to validate accuracy.

Whilst Mimics™ only works in grey-scale, Matlab is not constrained and therefore colour images can be used. The script works by uploading a video into Matlab frame by frame and converted each frame
to an array of numbers, where each number describes the colour. A seed pixel is chosen manually, and
the code searches the surrounding pixels to find a change in colour suggesting the presence of a
boundary. The code takes 15 minutes to get the glottic area of 657 frames and takes approximately 75
minutes to perform glottic area, anterior commissure angle and curve of the cord measurements (further
details on methodology are in appendix 4.6).

5.7 Results

Two cases were compared against Mimics segmentation data- Case 1 and Case 2.

Case 1 has a long period of swallowing at the beginning thus the analysis starts at frame 575 and records
3.5 breath cycles.
There is excellent correlation between the Mimics and Matlab glottic areas. In case 1 it seems Matlab tends to slightly underestimate the area, whereas in Case 2 it over estimates the area. This may be
secondary to the quality of the videos or more likely the superior ability of the human eye to interpret depth. Whilst the glottis is relatively well demonstrated by a 2D image, the edge of the glottis particularly at the posterior commissure, curves downwards towards the trachea resulting in different light effects. This effect can be interpreted by the eye, however not by the code.

5.8 Discussion

Glottic aperture measurements from segmentation of a video is highly dependent on video quality, particularly movement artefact from swallowing or phonation and light intensity. Iatrogenic anomalies such as a time and date watermark on the screen obscured the glottis in some cases, resulting in errors in area calculation. The main limitation of such a technique is the lack of scale, therefore limiting comparability between sequential cases.

Measurements of the angle of the anterior commissure will not change irrespective of distance of the camera from the glottis, however as demonstrated in figure 50, the anterior commissure can be obscured by the epiglottis. The benefits of such studies are that they pose minimal risk to the patient and require no exposure to radiation, whilst the procedure itself is time-consuming and costly in terms of equipment and personnel. If a procedure protocol could be developed that would decrease the variability between testing centres, then this could be used to monitor patients pre- and post-treatment. This code is dramatically faster than any manual segmentation and with further work could become faster and more accurate. The next step for this work would to perform a broader assessment of the tool clinically to determine the limits of accuracy and the role of protocols in video collection.

Patients with Chronic Obstructive Pulmonary Disease (COPD) often exhibit pursed-lip breathing which provides Positive end-expiratory pressure (PEEPi) by giving expired air resistance against which to flow. This long term results in hyperinflation, barrel-chests and loss of inspiratory reserve volume. Whilst pursed-lip breathing is a clear sign of COPD, there is a hypothesis that the glottis may have a similar role in maintaining positive end expiratory pressure, whereas a normal individual can maintain an open glottis with no extra pressure regulating requirements. Certainly, from Baz et al, it seems that
GNR seems to correlate with the severity of disease, but the larynx performs this task equally at rest and during exertion. By creating validated algorithms, objective data can be collected during CLE for disease scoring purposes, monitoring and centre by centre comparison.

In the future artificial neural networks may provide the answer to long term automation. As a form of artificial intelligence with the ability to learn through pattern recognition, they are already prevalent in industry, with research now focussing towards roles in healthcare. Neural networks in their simplest form are used for identifying hand written numbers on cheques and in their more complex forms can beat world champions at Strategy games like Google’s AlphaGo Algorithm. Their use in image processing, like the brain, the more pictures of an object the algorithm analyses the better it gets at identifying that object and understandably can be used to interpret medical imaging or results. They have been shown to be good in roles of classification- answering a question by placing a data set in a group i.e. ‘are there microcalcifications on this scan?’ to which the groups could be Yes or No. Or given a certain number of symptoms whether they can identify whether a person does or does not have a disease (Al-Shayea, 2011). The investigation into neural networking for the purposes of tracking the dynamic glottis and supraglottis would be a valuable next step for this research.
Chapter 6

6 Aims

This chapter describes an investigation of inspiratory flow through the glottis and into the trachea. As described in chapter 5, the variation in glottis aperture during breathing is fundamental to respiratory airflow. To describe and model the full dynamics of the glottis and the consequences for tracheal airflow involves a large number of parameters, not to mention the demands on imaging and computational resources. Consequently, in this work we restrict our study to the effect on inspiratory airflow of a glottis fixed at varying degrees of opening. A novel method of translating in-vivo acquired geometry to a modular replica experimental model is described that allows measurement of tracheal pressure distributions to be performed for varying degrees of glottic aperture. The experimental results demonstrate how pressure loss varies with both glottic aperture and flow rate and provide comparisons between replica and idealised model geometries.

6.1 Trachea models in the literature

6.1.1 In-vivo measurements

Model formation has developed significantly, not only from a CFD perspective but experimentally where previously some novel, yet laborious techniques were employed. Prior to imaging data, all morphometric measurements were taken from human specimens. Olson (1973) created a rubber cast of the whole airway, mouth to bronchi, from a cadaver of a young male; further geometrical adjustments were made based on literature and images of the larynx taken via a laryngeal mirror. The different laryngeal apertures were then hand sculpted to create five different apertures intended to correspond to distinct phases of inspiration. Airflow dynamics in this model were then compared against a theoretical predictions, as this was before the widespread use of CFD (Olson et al., 1973).

Eckel (1995) made morphometric measurements on fresh cadavers at time of autopsy in 20 patients (10 male, 10 female) (Eckel and Sittel, 1995). Eckel’s measurements of mean glottic area for women was determined to be 53.2±15.9 mm² and 85.3±38.6 mm² in men, which is slightly smaller than values quoted by Brancatisano (1983), where at quiet breathing the mean glottic area was stated to be 98 mm²,
with a mean glottic area on inspiration of 126±8 mm² and on expiration 70±7 mm². However, these measurements, based on stills from endoscopic views in 12 living volunteers (10 male, 2 female), are likely to be subject to scaling error (Brancatisano et al., 1983).

The inter-user variability conducted as part of this study is based on CT imaging of the trachea in an adult male with an apparent glottic area of 198 mm². Due to patient positioning however, the long axis of the trachea does not run parallel to the axial (z) direction in image co-ordinates. When the image is re-sliced with the z-axis parallel to the trachea, the glottic area reduces to 145 mm², demonstrating the effect of patient orientation in the scanner or ‘rotation-error’ when extracting minimum cross-sectional area from 2D images. Compared with glottic measurements to the literature, these values seem larger than other studies; given the data source CT of an adult male, the glottic area is expected to be larger than from female subjects. In the absence of specific morphometric measurements from this individual, the height of his vertebral bodies was used as a surrogate marker of normality and was found to be in keeping with those described in the literature compared with a mean of 140 males (Gilad and Nissan, 1985). The measurements provided in Figure 7 are measurements extracted from the STL, where the minimum cross-sectional area is identified by re-slicing the model at varying angles.

6.1.2 Types of Models

In the work of Katz (1997, 2009) a ‘surrogate’ laryngeal model was made based on morphometric measurements and the restrictions from the false and true cords applied to a straight tube. The laryngeal inlet and outlet had a cross-sectional diameter of 1.8 cm (area 2.54 cm²) (Katz et al., 1997, M. and B., 2009). The false cords fashioned as an ellipse had an AP diameter of 1.0 cm and a transverse diameter of 1.8 cm. The glottis, also elliptical, was positioned 2.1 cm below the false cords. In both studies sizes of the glottis were altered to correspond to flow rates of 15, 30 and 60 l/min indicative of the work of breathing- the glottis aperture increasing with flow. The AP diameter remained constant at 1.6 cm, but the transverse diameter changes between 0.7, 1.11 and 1.93 cm (average 1.24) which results in a mean glottic area of 1.5 cm² (Katz et al., 1997, M. and B., 2009), comparable to the glottic area of 1.45 cm²

Several studies have focussed on the effect of varying glottic shape or size on flow dynamics. The earliest study by Choi (1998) investigated the effect of glottic shape on the onset of turbulence within the laryngeal jet, considering an elliptical and triangular glottis. Their model comprised of a simple tube with an orifice plate (0.28 cm thick) fixed in the middle of the tube, designed to be 40% larger than geometric measurements provided by an earlier paper for ease of measurements. The triangular glottis had an area ratio of 0.36 cm². From their measurements we have calculated an equivalent circular glottis would have a diameter of 1.52 cm, (once scaled down by 40% this would result in a glottic area of 1.08 cm²), both based within a tube with an area of 2.54 cm² (scaled down by 40%= tracheal area of 152 mm²). These values correspond to Katz’s inlet and outlet area when scaled appropriately (Choi and Wroblewski, 1998).

Our model has a tracheal area of 3.08 cm² when measured 2 cm below the glottis, whereas the inlet in the pharynx was 5.8 cm² when measured 2 cm above the glottis. This highlights the fact that models representing the laryngeal airway merely as a uniform tube, with a central aperture reflecting the glottis, lack significant features of the supraglottic airway that will affect flow approaching the glottis.

Renotte (2000) used a more realistic glottic aperture which could be varied in size between 66 mm² and 112 mm² in area by opening the cords on a fulcrum, named Y1, placed in the central airway. Whilst their model is geometrically simplistic, the focus is on the variation of the glottic shape with flow and its effect on the jet (Renotte et al., 2000). Their glottic aperture modification is contrary to what is seen on endoscopic images where the cords open uniformly from the anterior commissure, marked on Figure 65 with a green arrow, as supposed to a central fulcrum point.

Figure 65 Representation of the central fulcrum used in Renotte (2000) to adjust the glottic aperture
Gemci and Corcoran, from the same group, used Phase Doppler interferometry to analyse particle deposition and as a result their model had to be transparent (Gemci et al., 2002). Gemci (2002), as in the study of Renotte (2000), used a straight glass tube with a simple orifice plate fashioned in the shape of a glottis, as inferred from endoscopic images. The edges of the glottic aperture plate were rounded but there was no anatomical tapering of the lumen approaching the plate (0.7cm thick) which was fixed in the middle of a pipe of diameter of 3.2 cm, which was said to be twice the human scale, and possessing an area of 8.04 cm². Scaling these measurements to anatomical dimensions would yield a trachea area of 2.01 cm² and a glottic area of approximately 1.2 cm², as the glottic area was said to be 40% of the internal area of the pipe.

Corcoran (2000) used an opaque polyurethane model of a larynx from a cadaveric specimen and then added a glass tube the same diameter as the trachea as the outflow pipe through which to make measurements. The area of the glottis is unclear but the aperture shape is triangular in shape, in keeping with endoscopic views presented in their paper (Corcoran and Chigier, 2000).

Cheng, Xi, Zhang and Kleinstreuer all performed studies on whole airway models to investigate particle deposition. Cheng (1997) made a full airway model from mouth to third-generation bronchi from a rubber cast taken from a cadaver and added an alginate dental impression of a living adult male at 50% jaw opening. The airway dimensions were extracted by dividing the model into 3 mm slices, the smallest area being 87 mm² which is likely to be at the glottis. It is not clear from their description whether slices were taken perpendicular to the central line of the lumen; if not their measurements may be subject to rotation-errors as described in 6.1.1 (Cheng et al., 1997). The papers by Zhang (2002) and Kleinstreuer (2003), from the same group, adopt Cheng’s model but added some small modifications such as a 2 cm mouth inlet and a modified soft palate (Zhang et al., 2002, Kleinstreuer and Zhang, 2003). Whilst a full cadaveric model is more likely to be geometrically accurate than a pipe with morphometrically derived constrictions, change in tissue volume and elasticity post-mortem, particularly that of soft tissue such as the tongue or palate will affect airway geometry, to an uncertain extent.

Oral cavity models are particularly challenging to create from cross-sectional images as they are acquired with the patients supine which will result in a natural migration of soft tissue, such as the
tongue base and palate, posteriorly. Xi and Longest, (2007) adapted Cheng’s model to observe the degree to which particle deposition of aerosolised medications occurs within the oral airway. They joined the cadaveric-derived oral cavity to a lower airway model derived from a CT of a healthy adult and then successively simplified it to create more idealised models. They noted that regional deposition changed significantly based on specific geometrical changes, particularly the average cross-sectional area of the oral airway and the oral airway curvature as well as the shape of the glottis and the angle of the trachea related to that (Xi and Longest, 2007).

Stapleton (2000) used average measurements from the literature as well as 10 CT scans to create a hand carved model made of geometric shapes which was then made into a fibre-glass cast (Stapleton et al., 2000). They felt by averaging CT data they were more likely to get representative morphometric measurements which meant their study could apply to a population, as opposed to using a single cadaveric specimen. In addition, they noted that the smoothed geometries resulting from averaging do not require high surface mesh resolution to capture natural irregularities in the wall boundary. Their eventual model had a tracheal diameter of 1.54 cm resulting in a 1.9 cm² area, which is at the lower end of measurements by similar studies (respective measurements being Katz et al =2.54 cm², our study=3.08 cm²). In the work of Stapleton, the glottis was represented as an ellipse measuring 1.2 cm AP and 1 cm transversely with a glottal area of 95 mm², which is in keeping with Brancatisano’s average of 98 mm², but larger than that of Eckel. (Brancatisano et al., 1983, Eckel and Sittel, 1995) When compared against Katz’s elliptical glottis which has a varying aperture, the area varies between 87 mm² and 238 mm² (Katz et al., 1997). It is known that the glottis is not elliptical in form and that the shape of the aperture is relevant to the fluid dynamics; additionally, when changing the transverse diameter there is a significant increase in the area which is not anatomically accurate. Heenan (2003) used a double scale model of Stapleton's airway in order to investigate flow dynamics with an elliptical glottis, whilst Brouns used a 3D geometry based on Stapleton’s measurements, but with an interchangeable glottis varying from ‘quasi-circular’, elliptical and triangular to investigate the effect of glottic aperture shape on the tracheal flow (Brouns et al., 2007b, Heenan et al., 2003).
Whilst all the above models have varying effectiveness in terms of geometric representation, the tissue pliability remains difficult to accommodate in any model. Rozycki et al. created a biorealistic model of a human airway for testing endotracheal cuff pressures and suction capability (Rozycki et al., 2015). Their idealised 2-piece model, divided at the subglottis, was derived using measurements from Cheng (1997) and Xi (2007) papers and further scaled to match cross sectional measurements from a CT. The model was then printed in a viscoelastic material with particular attention paid to the tracheal geometry, where the thickness of the luminal wall varied to take into account the rigidity of the cartilaginous rings and the pliability of trachealis. Although the authors applied broad geometric measurements taken from literature, the lack of detail and absence of fine anatomical features may impact on the model’s validity. In addition, the material used to print this model was a mix of Tango+ FullCure930, so that whilst its flexibility is superior to that of a hard-plastic based model, there still lacks a robust comparison between printing materials structural features and their similarity to that of human tissue.

In summary there has clearly been an evolution of models as computational methods have advanced. Time-consuming in-vivo models limited the number of geometries which could be assessed, and early CFD analysis required simplified geometries converted into CAD format to enable comparison between experiments and CFD. There was a trend towards isolating the anatomy of interest and running studies on that area alone whilst dictating the parameters of inflow. There is a danger in such an approach however: reducing the model to cover just the area of particular interest neglects the possible bias imparted to the flow by the omitted geometry, as found for example by (Doorly et al., 2008b), who noted that even the external nose and face impacts flow distribution in the nasal cavity.

The variation in geometry size and shape makes it difficult to directly compare previous studies of laryngo-tracheal flow, although consistent themes are evident in both the model geometries and the resulting flow, with the most prominent feature being the existence of the laryngeal jet. Authors quickly acknowledge that general assumptions about flow is limited by single geometry studies, as well as the lack of natural compliance; other factors such as the time varying dynamics of inspiratory flow rate and perhaps even the temperature profiles of in vivo conditions may induce differences between real and model flows. The benefits of studying patient-specific anatomy is that individual factors such as
respiratory function, age, race and sex can be considered as well as the many small unique anatomical variations that exist. It is postulated here that the future of such studies may end up analogously to the results of the Genome project, where a bank of data exists and patients with similar histories or features can be compared against each other.

Clinical images have to weigh up the risk-benefit ratio, with protocols tailored solely to address the pertinent clinical question, using as little radiation as possible. Rahimi-Gorji (2016) ran their CFD on a patient specific model captured from computed tomography in 0.5mm slices with a total of 1023 slices from mouth to G6 (Rahimi-Gorji et al., 2016). By comparison, the anatomical definition employed for this study was captured in a similar field of view but with a 1 mm slice increment and 2 mm slice thickness, resulting in 323 slices for the same distribution. Data for the present scan was acquired in a Siemens’s helical scanner which results in a multiplanar reformatted images; segmentable in coronal, axial and sagittal planes and was acquired as part of this patient’s clinical work-up. Although a 0.5 mm slice increment results in a finer image quality, this results in greater signal noise and therefore the need to increase the radiation dose.

Finally, previous efforts to model glottic flow consist of straight tube models containing a variety of orifice shapes, curved tube models of varying area that attempt to capture more features of the real airway and a few subject-specific airways. Crucially lacking from the preceding studies, particularly from the real airway studies, are details of how the pressure loss (and hence the energy expenditure) required to drive flow varies with glottic area. This lack of understanding motivated the present work.

6.2 An inspiratory and expiratory model
6.2.1 Methodology

An in-vitro upper airway model with no known pathology was created, based on a clinically acquired CT of a 46-year-old male patient, in accordance with ethical approval from the Joint Research Compliance Office Imperial College London: 15SM2566.
The CT neck and thorax with intravenous contrast was performed in a Philips iCT 256 helical scanner with the patient in the supine position. A series of 323 slices 2 mm thickness with a 1 mm slice increment were acquired with a FOV of 430 mm and a pixel size of 0.56 mm.

The DICOM (Digital Imaging and Communication) files were imported into Materialise’s Mimics™ software Version 18.0. The scan was then segmented manually using the steps highlighted in Appendix 4.6. The sinuses were excluded from the nasal model at the level of the ostium as they are anatomically complex to segment, prone to variation and contribute minimally to the airflow dynamics (Rennie et al., 2011). To create models with differing glottic apertures, the model was modified within Mimics by manually including or excluding pixels according to the anterior commissure angles extracted from a 4DCT from Melbourne, Australia (Low et al., 2011). The glottis was then tapered sequentially through the slices, based on images from the 4DCT and checked in 3D to ensure smoothness.

The resulting models were then smoothed using the in-built automatic smoothing tool on a power of 0.4. The Mimics™ module uses first order Laplacian smoothing, where the smoothing factor is based on a % setting of between 0 and 1.0 i.e. from 0% to 100% smoothing strength. The smoothing tool can repeat its task multiple times at the users’ request; in this case 10 iterations were applied to produce a smooth surface without losing significant detail, although it was noted that up to 100 iterations could be employed with < 1% volume loss.

The model was exported in STL format (Standard tessellation language) to Materialise’s 3-Matics module, a 3D modelling and design platform. When importing different variations of the model into 3-Matics it was fundamental to ensure they remained in the same co-ordinates, thus the first step after importing was to align the centreline of the trachea with the Z axis.

An external wall 3mm thick was built around the model to create the internal lumen. Whilst a typical tracheal wall is between 1-3mm thick, a thicker wall was chosen to ensure robustness of the fabricated model (Lawrence et al., 2014). The aim was to build a model which could be disassembled to facilitate the introduction of different geometry in a specific region or regions, while keeping other sections unchanged. For this study, the interest is in the effect of variation in glottic aperture. Whilst the internal
geometry was not altered, multiple prototypes of the models were created to eliminate negative features such as fragility or instability of the model or variability during the experiment.

Five crop planes were established with fixed co-ordinates to allow repeatable cropping of imported models and the subsequent deconstruction of the geometry. The planes were Nasal, Supraglottic, Subglottic, Left Bronchial and Right Bronchial. Bronchial extensions were applied to the model by using a surface extending tool and then using the bronchial crop planes to make those extensions into separate components.

6.2.2 Stages in designing the joints between sections.

Developing the model required multiple iterations focusing on the stability and strength of the joins, the tap diameter and the type of inlet and outlet.

**Torus join:** The first join-type considered was a torus join, created by using a dividing plane to slice the trachea into two segments. Two solid rings were created, the smaller male part was 12mm in diameter with a 1.5mm ring width. The larger female part was 12.15mm total diameter and 1.65mm ring width. The female torus was subtracted from the lower margin and the small torus added to the upper margin. Thus, a smaller ring slotted into the larger divot. The main problem with this construction was instability and rotation, which continued despite a stabilising peg. Additionally, this technique could only be applied to a round lumen and was not suited to the supraglottic join.
Peg-stabilised join: The torus join was deemed unsuitable, so 4 stabilising pegs were placed at the anterior, posterior, left and right margins. The pegs were created as cylindrical objects within 3-Matics and moved into position by changing their orientation and co-ordinates. Once fixed in their respective locations as defined by co-ordinate values, they would be exported and applied to different versions of the model in a repeatable fashion.

Figure 67 Torus join with a stabilising peg printed using a MakerBot

Figure 68 Subglottic join with 4 stabilising pegs which are filleted and smoothed at the base
The female peg-holders were 0.15mm larger than the male pegs which were 2.5mm wide. To prevent parts snapping off during assembly, the join where the taps attached to the main model were smoothed using a ‘fillet’ tool which removes sharp, fragile corners.

Care was taken to ensure that:

1. The pegs did not compromise the position of the pressure taps.

2. When adding or subtracting the pegs from the model, care was needed to ensure that if the diameter of the peg was greater than the wall thickness of the model, the internal lumen was not affected.

Stabilising pegs were particularly useful in the supra-glottic join where the irregular geometry made applying any torus-like structure impossible. See appendix 5.2.

**Slotted peg-stabilised join:** Whilst stabilising pegs prevented rotation, there was concern that the smooth surfaces between the joins would be prone to air leak. Therefore, a slotted system was created to increase the surface area and thereby the contact area of the join.

![Figure 69 Left Subglottic join with stabilising pegs. Right the same join with bolt attachments](image)
To create the supraglottic join, the original STL was imported into 3-matics again and aligned according to the z-axis. An outer wall, 1.5mm thick, was applied to the model and then the model cropped down to create a 5 mm high cylindrical object, at the point of the join. This object could then be added or subtracted from the lower or upper component to create a projecting element or a deficit. To lock the segments into place once assembled, two cylinders with a 5mm hole in were placed above and below the join. In one a brass anchor fastener with screw threads was placed, in the other a screw which held the segments tightly together.

These provided superior stability for the model, however due to tap placement it was only possible to place one screw attachment on the anterior surface at the supra-glottic join and this was sub-optimal, creating a tension down one side of the model.
The pressure taps were placed at 12, 3, 6 and 9 o’clock from 1 cm above the glottis viewed down towards the carina in 1 cm increments. At the level of the glottis, only 2 taps were placed to minimise disruption to the internal surface, furthermore the lumen size of the tap was reduced from 5 mm to 2 mm. The base of the tap was filleted against the model to reduce the chance of one being snapped off during cleaning or assembly.

The model went through multiple generations prior to deciding on the final product. The changes are shown in table 1 (see appendix 5.3) and Figure 72.

Model X-4 used a full face, as supposed to just a nose, the benefit of which was to provide an adjunct to attach external facemasks or positive pressure devices if required, as well as consider the impact of the face on nasal airflow shown in by Doorly (2008). The nasal cavity was split into 2 parts in the coronal section which, whilst making it easier to clean, created a problem in structurally balancing the parts, as the weight of the face would strain the join in the mid-nose making it more complex to disassemble and reassemble when changing the glottis component. In Model Y, the compromise was to use a reduced face to only include the external nose, with the nasal cavity was printed as a single part (Figure 73). A broad peg was added to the superior nose, to facilitate the attachment of a clamp, aiding
The final model Y was made of 6 parts with 37 pressure taps each with a 2 mm lumen.

Figure 73 Model X-4 with full face and 2-part nose, Model Y with reduced face with stabilising peg superiorly

Figure 74 Model Y with taps labelled 1-37. 5 taps would be sealed off at any one time due to limited pressure sensors on the CANdaq
The final mesh was run through the auto-fix program in 3-Matics where ‘bad’ contours and triangles would be identified and repaired. An example of this would be where triangles fail to meet correctly leading to a dip or deficit in the model, this eventually would create a problem with creating a smooth boundary layer for the CFD or a defect in the printed model.

Five versions of Model X were made with 10°, 19°, 33°, 47°, 53° glotti. The second-generation Model Y was reduced to four variances 5°, 10°, 33°, 53° glotti, as a narrower glottis was seen to produce more pronounced pressure drops and there was an opportunity to compare the narrowest glottis to an idealised model. For images relating CAD models to endoscopic views see appendix 5.4.

The models were printed using an Objet Connex 350 3D printer. The initial prototype airway with a 53-degree glottis was printed in digital ABS-like material made of a mix of two sub-types of plastic RGD515 & RGD535. Due to a change in the material type on the printer; the anterior nose and face, as well as the 19, 33, 38 and 47-degree glotti were constructed using RIGUR RGD450. These products use a non-dissolvable wax-based support material; which was removed using a Water-Jet between 20-120 bar of pressure. A sonic-bath was used to soften some areas of material and a flexible nasendoscope was used to scope each part to ensure the internal surface was smooth. Aesthetically the two materials

![Figure 75 Cross-sectional areas of the 4 glottic models in Model Y: 5, 10, 33 and 53 degrees.](image)
have similar qualities- however ABS has higher tensile strength and thermal resistance than RIGUR in areas of small calibre anatomy.

6.3 Experimental set up

Model X was assembled on a fixed board using rigs to support the individual parts. A wooden mount was screwed to the tip of the face model to provide a stable place to mount it in the clamp. To minimise leaks around the joining parts, vacuum grease was applied to the joining sections and heat shrink tubing with a thermoplastic adhesive on the inside was used to seal the join between the trachea and bronchi. Model Y was simpler to assemble as it was in 3 parts and whilst vacuum grease was still used, there was significantly less core instability.

Figure 76 Layout of the airflow experiment

All taps in use were joined to the pressure transducer using flexible silicon tubes of equal length, any taps not in use were blocked using adhesive tape and covered with a silicon cap to prevent air leak. All joins were checked for leaks circumferentially with a hot wire anemometer. For further information about experimental setup see Appendix 5.5.
Silicon tubes, 1 mm larger than the join size were attached to the bronchial extensions and connected by a Y-connector. The single tube travelled 1 m to an orifice plate, then a further tube of >50 cm connected it to a 240V vacuum pump running at variable RPM to mimic inspiration. To calibrate the flow rate, the orifice plate was attached to an alcohol manometer, by which the flow could be determined by the difference in level of the alcohol columns attached to the tappings before and after the orifice plate. Levels were determined by measuring the distance between the top of the meniscus of the two channels. Only 2 channels were used in the alcohol manometer which was filled with alcohol of a density 0.79g/ml. As low flow rates lead to a very small change in the alcohol columns, a 45° tilt from vertical was placed on the manometer to enable more accurate readings for flow rates less than 50 l/min. Above 50 l/min the tilt was 25° from vertical to prevent alcohol leaking from the manometer due to large column differences (for further information about the orifice plate see appendix 5.6).

To see how the experiment is run see appendix 5.7.

6.3.1 Sensitivity of orifice plate measurements

To determine the sensitivity of the orifice plate, trans-airway pressure loss measurements obtained from the Candaq transducer (Model: Candaq ESP-32HD. Uncertainty from calibration certificate is 1.5 Pa) was compared when the flow was determined by firstly the alcohol manometer and secondly by a micromanometer (Model: Furness FCO510. Estimated uncertainty from calibration certificate 0.014% ± 0.03Pa). Figure 77 shows the comparison. From the plot it there is a clear difference between the flow rate determined by the different manometers particularly at high flow rates, corresponding to a mean difference of 8.3% between the micromanometer estimated flow and alcohol manometers estimated flow.

A two-sample independent t-test showed no statistically significant difference between the micromanometer and alcohol manometer at 80 l/min (p-value=0.389) nor at 20 l/min (p-value=0.471), however this may be due to the small sample size. However, we cannot rule out the possibility of a bias in measurement of flow rate, since the trend of the results from Figure 77 suggest an approximate 8.3% difference in trans-airway pressure loss reflecting difference in flowrates. However, as the two pressure
Manometers were not tested simultaneously, this does mean that may be less accurate. Fortunately, a consistent bias does not alter the relative scaling of losses.

Future comparative analysis would benefit from using a t-piece at either end of the orifice plate to simultaneously measure the readings from the Micromanometer and alcohol manometer. Although it was also noted that the sensitivity of the micromanometer meant it took significantly longer for the pressure to settle on the digital reading than on the alcohol manometer, making the latter more suitable for this experiment.

Comparison of the Candaq pressure measurements when flow was determined alternately by precision manometer or alcohol manometer shows good agreements, with the exception of a single measurement. Taking all measurements into account suggest there may be some bias proportional to flow rate, but the extent of this is likely to be within 5%.

Figure 77 Chart showing trans-airway pressure loss (mean of top 3 taps minus mean bottom 3 taps) at different flow rates comparing repeatability using the alcohol manometer and a micromanometer. Error bars show 3.5Pa-2SD in CANdaq error. The results show a systematic error proportional to flow rate.
6.3.2 Sensitivity of the CANdaq

We performed measurements of single taps randomly chosen comparing simultaneous pressure differences measured by the CANdaq and micromanometer through a t-piece. The results indicated a two standard deviation level of 3.5 Pa. Manufactures calibration suggests a precision of 1.5 Pa. The results are broadly compatible with this.

6.3.3 Accuracy of the CANdaq

To determine whether there is a bias in readings between the CANdaq and the micromanometer we performed a log-ratio t-test which takes into account the difference in scale and error of these two measures and is a valid technique to compare two groups when the scale of the two measures can vary. We grouped the flows into high (60, 70 and 80 l/min) and low (20, 30, 40 and 50 l/min) which correspond with high and low pressure readings respectively. Results showed a significant difference between the two groups during high flows p-value=0.6x10^{-15}. Whilst the test for the low rates was not found to be significant p-value=0.131. This may suggest a degree of bias at the higher flow rates. For the purpose of finding the range of accuracy the test was repeated including 60 l/min in the low flow rate group and in this case the test strongly demonstrated that bias occurs above flows of 60 l/min. This is likely related to the fact that at higher pressures the CANdaq is less sensitive. However, this difference between the micromanometer and candaq represented a mean 0.5 Pa difference across all flows. Specifically, in flows of 60-80L/min a mean of 1.4% of the pressure loss and for flows from 30-50L/min 2.2% of the pressure loss. Due to the small pressures measured at 20L/min the difference between the two readings makes it an outlier. For more information about the CANdaq see appendix 5.8.

6.4 Results

6.4.1 Repeatability of model

Several experiments were run on the variable glottis sizes as well as idealised glottic models. The five versions of Model X were made with 10°, 19°, 33°, 47°, 53° glotti, however the second-generation Model Y was reduced to four variances 5°, 10°, 33°, 53°.
To determine if there was a difference between first generation Model X and second-generation Model Y’s 10-degree glottis pressure readings at different flows were compared. This showed little difference between the pressure loss, demonstrating that the extra joins in the model were air tight despite the difficulties in assembly. There was no statistical difference between the trans-nasal pressure loss between the two tests as shown by a standard t-test p=<0.05.

At 20L/min there was a 0.4 Pa difference (0.8%) in trans-airway pressure loss between models X and Y, whilst in 80 L/min the difference was 3.1 Pa (5.4%). For further charts on the spread of results see appendix 5.9.

The benefit of model Y- is simply that is easier to assemble with fewer joins to potentially leak. The full nose does not appear to compromise the patency on this occasion- although in narrower geometry it may be difficult to remove the support material adequately.

6.4.2 Comparison of 4 different glottic aperture models

In order to demonstrate the spread of pressures across 4 different models a boxplot was created (see appendix 5.10). The first 11 taps were removed which represent the nasal cavity which have the same...
results throughout all 4 models and therefore cause a misrepresentation of the spread of data. Taps 12-37 were included (5 of which were sealed off as the manometer only had 32 taps).

<table>
<thead>
<tr>
<th>Degree of opening in glottis</th>
<th>Mean transairway pressure loss (Pa)</th>
<th>Minimum pressure loss (Pa)</th>
<th>Maximum pressure loss (Pa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>194.3</td>
<td>194.2</td>
<td>194.4</td>
</tr>
<tr>
<td>10</td>
<td>68.8</td>
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<td>37.1</td>
<td>36.8</td>
<td>37.4</td>
</tr>
<tr>
<td>53</td>
<td>31.0</td>
<td>30.7</td>
<td>31.3</td>
</tr>
</tbody>
</table>

Table 5 Descriptive statistics for different models at 60 l/min air flow

Figure 79 Pressure in Pascal across 32 taps in Model Y with a 5-degree glottis at varying flow rates ranging from 20-80L.min

Figure 79 (5-degree glottis) and 78 (53-degree glottis) clearly show the narrower the glottic aperture the greater trans-glottic pressure loss. The highest pressure in all models is at Tap 2, as this is situated on the posterior wall of the post nasal space and receives direct flow. For further charts related to flow distribution in the experimental model see appendix 5.10.
Primarily to determine if there was a true difference between the 4 glottic models a univariate ANOVA was performed at 20L/min to test for the equality of means in all the models. This showed a strong statistical significance that the mean pressure readings in each model are different $F(3,42)=82$, $p$-value $< 1.5 \times 10^{-17}$. However, this test only gives information about the inequality of the means but doesn’t show where the greatest difference lies, for this reason a Games-Howell post hoc test was performed (rather than a Tukey test as Homogeneity of variances was violated) to determine which means are the most different. This confirmed a significant difference between all models particularly between the narrower glottic angles. The ANOVA with Games-Howell was repeated for 80L/min and this again showed a significant difference between all models $F(3,39.7)=104$, $p$-value $< 16.5 \times 10^{-19}$. (see appendix 5.11 for descriptive statistics)

6.4.3 Experimental model versus CFD

Models Y-10 and Y-53 were compared against CFDs predictions. Both CFD and experiment provided estimates of pressure loss from the external nostrils to the carina. However, the pressure at the nasopharynx was significantly lower in the experiment than in the CFD. The most likely reason for this is incomplete clearance of support material within the narrow nasal passages in the experimental model,
possibly compounded by alignment error where the two parts of the nose joined, although the latter is less likely. However, the trans-nasal loss is not of concern for this investigation. In all cases therefore, the experimental and computational pressure losses are compared assuming equal pressures in the nasopharynx.

The raw data from CFD and experiment do differ as the CFD utilised a reference value of zero as the outside pressure, whereas the CANdaq value was air pressure of 101325 Pa. Thus, the experiment has largely negative values and the CFD largely positive. To normalise the scales a mean was taken from the first 3 taps which lie in the nasopharynx for each model and added to each respective value for the experiment and taken away for the CFD.

For each model at each flow, the CFD and experimental results were compared using an independent t-test where there were no outliers, there was equality of variances, however the Shapiro-wilks test did not demonstrate normal distribution, however due to the small sample size and equal numbers in groups this was not deemed important (see appendix 5.1). A p-value of <0.05 indicates a difference between the two models, however all p-values were above 0.05 indicating no statistical difference between the CFD and experimental model. The only outlier is for the 10-degree model at 30 l/min, where the pressure loss is far greater across the glottis. This suggests a leak at the glottic join and for this reason

![Figure 81 Comparison between CFD and experimental data for 20 l/min in a 10 degree and 53-degree glottis](image-url)
the p-value is > 0.05. For this particular study it was noted that all pre-flow CANdaq readings are equivalent and the experimental data follows the same flow pattern as in previous studies.
Figure 82 Comparison between CFD and experimental data for 60 l/min in a 10 degree and 53-degree glottis

Figure 83 Graph showing transairway pressure loss from nasopharynx to carina (average of the top 3 taps minus an average of the bottom 3 taps) with error bars showing 1 standard deviation + 3.5 Pa error from CANdaq reading
Figure 84 Log of trans-airway pressure loss versus log of flow in different glottic apertures

Figure 85 Graph showing LOG trans-airway pressure loss versus log of glottic area at different flow rates
The log plot of trans airway pressure loss suggests a constant power law scaling for loss versus flow rate. Applying linear regression analysis to the data for all flow rates and comparing results for flow rates above 40 yields a larger exponent especially in larger glottic areas. Whereas the work of Brouns (Brouns et al., 2007b) considered a different form of restriction, namely that of a modelled tracheal stenosis, it is of interest to compare their findings for pressure loss-flow rate variation.

Figure 86 Graph showing LOG trans-airway pressure loss versus log of glottic area at different flow rates. The log of pressure loss is not consistent with area as the lines begin to diverge as the area becomes smaller.
<table>
<thead>
<tr>
<th>Degrees</th>
<th>Glottic area mm²</th>
<th>Exponent for the full line</th>
<th>Exponent for flows above 40L</th>
<th>Exponent for flows above 60L</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
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<td>1.62</td>
<td>1.67</td>
<td>1.62</td>
</tr>
<tr>
<td>53</td>
<td>181.9</td>
<td>1.55</td>
<td>1.68</td>
<td>1.57</td>
</tr>
</tbody>
</table>

Table 6 A table showing the exponent of a line for different glottic areas

For a glottic area of 76.9 mm² the pressure loss was found to scale to the flow rate by 1.91 in comparison to an exponent of 1.55 in a glottic area of 181 mm². Brouns et al (2005) derived pressure loss across their circular glottis with an area of 45 mm². For their model, at 30L/min there was a 38 Pa pressure loss compared with 51 Pa in our smallest model. Using the exponent for our model we derived a pressure loss of 13.2 Pa at 15L/min which would correspond to 10 Pa in Brouns et al’s model.

Thus, it can be noted that the exponent in the power law scaling for pressure loss was found to change according to the degree of restriction in both this study and that of Brouns. Secondly the value of exponent found in the Brouns study for their severe constriction is close to the value of 1.91 found here; both values being close to the factor of 2 associated with the theoretical loss in a sudden expansion.

6.5 Conclusions

There are multiple challenges facing researchers attempting to model the airway. Primarily there lies acceptance of variability in anatomy, change in qualities of the tissues and variation in intrinsic function. Secondly, all physical models whether simulated or cadaveric have short comings related to their material and its direct similarity to a living organ. In order to create a more bio-realistic model, one can focus on maximising the similarity of material and structural likeness.

Excluding cadaveric models, the structural element of a model can be derived either from geometrical measurements or patient specific scans. Whilst there are benefits that can be derived from idealistic models, such as the ability to make broader assumptions about flow surrounding specific geometric
features, as well as ease of inter-study comparison. The advancement in the quality and speed of segmentation means that there is greater opportunity to capture more realistic features. From a medical perspective there is now a trend towards patient-specific treatment, using individual genomic sequences and anatomy to tailor make therapies. The comparisons between the CFD, idealistic and simplified models show little difference in the pressure detected at individual taps validating the CFD method we are currently using. Whilst there was one anomaly in the 10-degree model at 30 l/min, this is more likely to relate to experimental error caused by a leak at one of the joins or problems related to the CANdaq manometer.

The scope of this validated CFD protocol is to develop programs which can determine specific airflow characteristics in individual patients. Through compiling pre-operative and post-operative data related to goitre removal for example, treatment guidelines can be developed to assist surgical decision making. Reducing the amount of surgical subjectivity will promote greater consistency in the treatments offered by different centres and provide patients with validate evidence to support their choices.

There may be added opportunity for surgical simulation, to manipulate geometry and re-run a CFD to determine effect prior to operating. The next section will explore the merits of adaptable geometry in a simplified model.
6.6 An idealised glottic model

An MSc student (Alex Makalliwa) developed an idealised computer-aided design (CAD) model of the glottis which had areas of geometry which could be manipulated for CFD analysis. The model designed in STAR CCM™ was based around geometry from the literature and the glottic apertures modelled to be comparable the glottic model Y used for the flow studies. 35 pressure taps were added to the model using the same co-ordinates as model Y taps and printed in 3D to run experimental flow simulations on.

Figure 87 Left full realistic model Y with 37 pressure taps, Nose, nasopharynx, larynx, trachea and carina.

Below purple idealised larynx and trachea with 10° glottis from front and side (Model A10). Then again with pressure taps placed at the same co-ordinates as model Y
The experimental results were then compared to realistic glottic models as well as CFD data for both models. Due to differences in the number of taps between models and the ability to record measurements from those taps—some have been occluded or used twice to allow results to be compared. (see appendix 5.13)

The glottic area in A10 was 45.6 mm² and in A53 232.73 mm², in comparison to the realistic glottis of Y10 101.7 mm² and Y53 181.9 mm² respectively. We have therefore compared A10 to Y10 as well as Y5 as their glottic areas are more comparable (A10 = 45.6 mm² Y5 = 79.6 mm²).

Figure 88 Above idealised glottis, Left A53 degrees, Right A10 degrees. Below realistic glottis Left Y53 degrees, middle Y10 degrees and right Y5 degrees.

The superior portion of the trachea has been removed revealing the internal and external walls of the model. Pictures not to scale.

Figure 89 Model A10 from anteriorly and left side. 3 taps (17, 22 and 25) can be seen to be covered with adhesive silver tape and rubber cover. The seal was tested with a flow meter to determine if there was any leak.
6.6.1 Methods and results of airflow in an idealised glottic model

Due to outliers in the data a Mann-Whitney test was favoured over a t-test. This was performed on both idealised and realistic models at 5, 10 and 53 degrees all at 60 l/min, which is the flow rate at which the corresponding CFD was run. To allow a fair comparison the first 11 taps data were excluded to prevent the nasal resistance affecting the results, thus all measurements were taken from the glottis and below.

Whilst the pressure distributions between models appeared similar, a Mann-Whitney test demonstrated there was a statistically significant difference in medians between A10 and Y10 ($p=0.031$) and A10 and Y5 ($p=<0.005$) which had more comparable glottic areas. However, Figure 91 shows a close correlation in trans-airway pressure loss when comparing A10 to Y5, suggesting that the difference lies in a scaling error secondary to the presence of the nasal cavity which results in a more negative starting pressure.

The pattern of loss in A53 and Y53 bares similarites, however the pressure values are very different.

![Figure 90 Experimental data: Pressure at taps in idealised 10-degree glottis versus realistic 10-degree glottis at different flow rates (20-80L/min) excluding all supraglottic taps. The differences in taps 12-13 are caused by the higher supraglottic resistance in the full airway models](image-url)
Figure 91 LOG plot of the transairway pressure loss for the idealised and realistic models (Y = realistic model, A= idealised model, numbers refer to glottic angle)

Figure 92 Increase in trans-airway pressure loss above the loss at 20L/min from supra-glottis to carina plotted against flow with 5 different glottic apertures. Grey (A) = idealised models, Blue (Y) = realistic models
A CFD was run on the same idealised geometry at 60 l/min. An independent 2 sample T-test was performed to compare the pressure distribution across all taps between the idealised 10 degree and 53-degree models versus their CFD equivalents at 60L/min. For the both glottic angles, no statistical difference was found between the pressure distributions of the idealised model and the CFD. (10-degree p=0.923, 53-degree p=0.319).

Figure 93 CFD versus idealised model with a 10-degree glottis at 60L/min

Figure 94 CFD versus experimental data for 53-degree model at 60 l/min
Figures 95 and 96 demonstrate that scaled, results between idealistic and realistic models do follow a trend but there is a distinct difference in pattern of pressure recovery between smaller glottic apertures and large apertures.
6.7 Conclusions

When comparing the 3 types of models: idealised, realistic and CFD, we can see despite geometrical differences below the glottis they are broadly comparable. The presence or absence of a supraglottic airway effects scaling, due to high intranasal resistance, but the same pattern of pressure loss is observed from the subglottis to carina.

This suggests that simplified or idealised models may not significantly differ from realistic models, thereby permitting models with minimal pre-processing needs to be used accurately. There us further scope for a deformable model that could mould itself into the broad shape of the host trachea based on specific landmarks. This may be faster and more efficient than manual segmentation and may remove the slight surface variation that require a more complex mesh and therefore increasing time cost for an engineer. This again highlights the importance of appreciating individual sections of the upper airways in the context of the whole airway.
Summary and key findings

This work comprises an investigation of the use of virtual geometric reconstructions of the upper respiratory tract in experimental and CFD studies in order to further our understanding of airflow with respect to geometric change. Whilst the application of CFD to model flows in realistic human geometry has become quite common, there are notable gaps in the validation of this technique. Firstly, prior to this investigation there was a lack of clear information pertaining to the effect of inter-user variability when segmenting images of the upper airways and the impact of this on CFD accuracy. Secondly, few studies have investigated the effects of glottal aperture on trans-tracheal pressure loss in realistic geometries. Investigation of these deficits in understanding are important for the development of clinically acceptable models and are discussed both in the context of validating CFD results and in terms of streamlining the process of patient specific airflow studies.

Key findings

Chapter 2: The effects of inter-user variability of segmentation were assessed with respect to clinical experience (anatomical knowledge) and complexity of the target geometry. Threshold selection was seen to be a fundamental step in determining the overall airway calibre which in turn affected overall accuracy of the representation. Medical personnel, particularly those experienced with the specific anatomy, captured the geometry more accurately and faster however with more segmentation errors results in more pre-processing to complete the model.

Chapter 3: To determine the effect of geometric variability on flow within the nasal cavity, four variations of the same anatomy extracted from a single MRI scan were compared using CFD. The airway resistance did change but the pattern of airflow relative to the lower, middle and upper regions of the nose did not. This is surprising when considered within the context of the volumetric data from the different models which showed an average of 2.3% between the volume of the two congested models, and a mean of 10.5% in the decongested models. Interestingly, variations to the geometry of
the external nose (crucially anterior to the internal nasal valve) was found to alter the pressure loss across the nasal cavity.

**Chapter 4**: As the narrowest point of the adult airway, the glottis is the main modulator of airflow into the lower airways. To allow objective quantification of changes in the glottic aperture, videos of the glottis were segmented in Mimics to extract glottic area and identify patterns of respiration. A single patient with COPD was compared against a patient with no respiratory illness, demonstrating a greater percentage change in glottic area at restful breathing in the patient with Chronic lung disease compared with a healthy patient (40%/12%). Comparing multiple videos of the same healthy male with CPAP applied at different levels showed a negative correlation between glottic angle and mouth pressure, the correlation becoming weaker the higher the CPAP pressure. This suggests that the higher the pressure at the mouth the narrower the glottis becomes potentially to regulate airflow. Importantly glottic angle is a good surrogate for glottic area, thus even in poor quality videos where areas of the glottis are obscured by the supraglottis- meaning can still be derived. Evaluation of a semi-automated segmentation programs created by a previous MSc student showed sufficient promise in terms of rapidity and accuracy of segmentation comparable to manual techniques, which suggests viability for it to become a clinical applicable.

**Chapter 5**: To further investigate the role of the glottis in airway modulation, in vivo CT data from a healthy male was transformed into modular replicas using rapid prototype manufacture. This allowed multi-level pressure measurements to be made of tracheal pressure for varying glottic apertures and flow rates.

Although the purpose of model creation was directed towards in-vitro validation of CFD modelling, determining how to define and construct such a model in itself can be seen as relevant to the broad field of airway surgical intervention. Engineered prosthetic implants such as intra or extra-luminal support devices or stents are becoming more common, with the creation of biocompatible and cell scaffolds apparently offering considerable promise. This work has demonstrated the comparative ease with which a surgeon, given appropriate software can transform patient-derived data into replica geometries, which
can then be further translated into engineered structures and manipulated to provide various attachments for assembly or incorporation of instruments.

Here the replica model was used to compare with CFD predictions, since the trans-tracheal flow regime is too complex for affordable, exact numerical simulation. Further studies were also made on the role of glottis shape by comparing experimental measurements for real and idealised model geometry. Statistical analysis found no significant difference between results for the experimental models (realistic/idealised) and the CFD (realistic/idealised), validating the accuracy of this specific CFD protocol for the determination of trans-tracheal pressure loss. The merit of this is that CFD protocols once established are significantly faster and less costly than ex-vivo experimentation. For a glottic area of 43.8mm² (5 degree glottis) the pressure loss was found to scale to the flow rate by 1.91 in comparison to an exponent of 1.57 in a glottic area of 220mm². Brouns et al (2005) derived pressure loss across their circular glottis with an area of 45mm², at 30L/min there was a 38 Pa pressure loss compared with 51 Pa in our equivalent model. Using the exponent for our model we derived a pressure loss of 13.2 Pa at 15L/min which would correspond to 10 Pa in Brouns et al’s model.

The scope of this validated CFD protocol is to develop a program which can automatically determine specific airflow characteristics in individual patients. Databases of pre-operative and post-operative airflow simulations, related to goitre removal for example, would allow treatment guidelines to be developed to assist objective surgical decision making. Through the reduction of clinician’s subjectivity, treatments provided by different centres will be more consistent and patients will be provided with validated evidence to support their choices. Furthermore, there may be prospect for surgical simulation, whereby patient specific geometry is manipulated digitally to may a pre-operative predictor of outcome.

**Future work:**

In order to develop an automated program which would segment, analyse CFD and summarise results. This work would benefit from further studies quantifying the effect of specific geometric changes on
mass flow rate and pressure loss throughout the airway which could be correlated with clinical outcome data. Specific areas of interest include:

- The geometry of the nasal septum and its influence on mass flow rate through the nose, correlated with patient’s subjective symptom score.
- The internal nasal valve with airflow studies before and after surgical intervention
- Extraluminal compression of the trachea secondary to thyroid masses and the influence on pressure loss and tracheal airflow

The same would go for further geometries of pathological and non-pathological CLE tests. A clear difference was seen in this pilot study which suggests % glottic aperture change may correlate to severity of airway disease. Automated segmentation programs, or better still Glottic motion detection software would allow larger numbers of patients to be recruited and compared to determine if the glottic aperture can be used as a prognostic indicator.

Patterns of mass flow rate variation in these areas would possibly identify trends that would provide objectivity to surgical decision making. Rapid, automated segmentation to an acceptable range of accuracy will be crucial to reduce the cost associated with manual segmentation and this will become increasingly easier as the quality of image increases.

One of the limiting factors of any airway model is the inability to re-create factors such as pliability, moisture at the mucosal air interface and temperature. The ever-increasing range of 3D printing materials may offer an opportunity to create more biorealistic models to determine the influence of factors such as temperature and pliability on airflow within the trachea for example.
References


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Appendix

1.1 Imaging

The long-term cancer risk from CT scans is sufficiently small that the correct identification of pathology should outweigh the risk in routine clinical use. However despite this the numbers of MRI and CTs requested are increasing per head of population, with 274 K scans per million per year in 2012 in the United States, in comparison to 47 K scans per million of the population in the UK (Brenner, 2012). This difference does not appear to reflect national mortality rates, which are broadly equivalent in both countries; this has raised questions regarding the quantity of scans needed, (Gawande, 2009), though simplistic measures do not necessarily provide a complete picture.

1.2 Thresholding

Choosing a threshold to start from is a compromise between an initial moth-eaten mask (threshold of 101) with many holes to fill and overspill which needs to be manually excluded (threshold of 301). Whilst a threshold of 201 still has some holes- it is a compromise between which errors take more time to fix. We have found small numbers of both seem to result in the most accurate anatomical representation. If anatomy is selected but omitted in a middle slide- a gap will appear. This is a true

![Figure 97 Threshold choice in the nasal cavity demonstrating the compromise between the types of errors the user will encounter. 101 has a box showing multiple holes in the mask. 301 shows no holes but overspill into the maxillary sinus.](image)
slice-continuity error and does not reflect the actual anatomy present, its important once the first rough segmentation is done to create a 3D model and correct these gaps.

1.3 **Accuracy of segmentation**

Accurate segmentation can be affected by several factors: the resolution of images, the software package for segmentation and software for CFD. The process of translation of images to 3D models is further varied by the anatomical knowledge and capabilities of the operator and engineer. Quadrio et al comment upon the critical point in segmenting, where an ENT surgeon is required to select the threshold at which the boundary between airway soft tissue appears (Quadrio et al., 2014). From this variable threshold point a model can undergo further specific modifications. Zhu et al looked at variations in nasal airflow between ethnicities using 3D models created from CT scans. A fixed threshold was decided upon and the mask then manually modified to ensure accuracy. To ensure patency of lumens a ‘region growing’ tool was used to expand their mask to any pixels within an operator-chosen threshold range. This tool will lead to a generalised expansion of the model arguably effecting the sensitivity of the geometry (Zhu et al., 2011). Other studies alluded to ‘smoothing’ tools which reduce the stepped appearance of the threshold boundary resulting in a higher quality mesh. There are multiple modalities of smoothing and many result in some volume loss, each individual study should comment on this (Ishikawa et al., 2006, Chen et al., 2009).
The smoothing module in Mimics works by choosing a ‘smoothing factor’ of which the baseline is 0.4, then the number of iterations over which the tool is run. The parameters chosen affects the surface area and may effect the volume. In the trachea with a smooth factor of 0.4 with 1 iteration reducing the surface area by 0.000003%, and a further reduction of 0.000007% with 100 iterations. The role of smoothing is to make the surface more regular, akin to that of human tissues.

Figure 98: Laryngeal model showing process of smoothing. Left: no smoothing note surface defects. Middle: smoothing factor 0.4 x 1 iteration. Right: smoothing factor 0.4 x 100 iterations. The volume change is less than 1 mm³ between these 3 models. Volume is 67486 mm³

Figure 99: These nose models are smoothed by the same factors. Left - no smoothing, middle - 1x0.4, right - 100x0.4. The volume of the model is 46743 mm³ and changes by less than 1 mm³ even up to 100 iterations.
1.4 Errors in segmentation

To avoid or repair errors our protocol set out several steps:

1. Repair holes within the mask
2. Delete areas of overspill
3. Manually include any areas that weren’t picked up in the original thresholding
4. Identify corner to corner pixels and expand that area

![Figure 100 Types of errors which can lead to faults in the mesh](image)
1.5 Errors in segmentation

Figure 101 Slice continuity errors where in the inferior meatus has been missed in one slice

Figure 102 Where the slice continuity errors have been addressed and repaired
1.6 From Segmentation to airway models: the nose

<table>
<thead>
<tr>
<th>Hahn’s planes (our plane)</th>
<th>Plane 1 (5)</th>
<th>Plane 2 (4)</th>
<th>Plane 3 (3)</th>
<th>Plane 4 (2)</th>
<th>Plane 5 (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hahn et al</td>
<td>173</td>
<td>135</td>
<td>145</td>
<td>162</td>
<td>258</td>
</tr>
<tr>
<td>Our experiment</td>
<td>-</td>
<td>59</td>
<td>68</td>
<td>69</td>
<td>321</td>
</tr>
<tr>
<td>% difference</td>
<td>-</td>
<td>56</td>
<td>53</td>
<td>57</td>
<td>-24</td>
</tr>
</tbody>
</table>

Table 7 Comparative table of Hahn versus our study for the cross-sectional area of Right nasal cavity. Plane 1 was not comparable to our experiment, plane 2 was most comparable to our plane 4 - though taken on an oblique course.

Figure 103 This is an example of the polyhedral mesh with a clear hole in the superior portion.
2.1 Clinical example of contours and partial volume effect

This is of specific clinical relevance when creating radiation fields for 3D conformal radiotherapy. The volume of the anatomical area delineated is fundamental to delivering a fixed amount of radiation to a cancerous tissue region. During the planning process, ‘organs at risk’ (OARs) must be isolated to manipulate the radiation field to minimise radiation to healthy organs; thereby preventing unpleasant side effects and long-term organ dysfunction. Typically, an initial higher resolution CT will be performed, and planning will take place, then at regular intervals during treatment further low-resolution scans will be taken, to update the ‘dose grids’, to allow for patient movement and change in organ sizes.
The use of T1 and T2 weighted images, with and without the addition of contrast has not yet been evaluated as a method by which to improve contours but may be source of interest as some MRI sequences can result in distinct contrast between adjacent tissues which may assist the speed and accuracy of segmentation.

CT scans tend to have homogeneity in the Hounsfield units expressed by different tissue types between slices, MRI is more susceptible to artefacts which alter this. Magnetic susceptibility artefacts, seen in Figure 106, lead to significant distortion of the image and are typically caused by metallic implants; the most common of which is dental fillings. To a lesser degree, a similar process occurs at air-tissue interfaces as air is deemed ‘paramagnetic’ due to the oxygen content which leads to a concentration of the magnetic field at that point. ‘Ferromagnetic’ compounds such as metallic implants can strongly concentrate the field and distort an image.
The capability of a computer in terms of speed, memory and graphics heavily impacts on the processing speed during segmentation and 3D image processing. Most segmentations for this study took place on a computer with an Intel ® Zeon ® 2GHz processor. Comparatively Haas using a single Pentium IV 3.4GHz personal computer (Haas et al., 2008). If CFD and patient specific models are to be integrated into surgical care provision, then it is fundamental to be able to run these systems on computers which are readily available in a healthcare setting. This may mean accepting that processing speed may be reduced in a clinical environment.
2.2 Automated segmentation systems

Semi-automatic systems, such as Atlas-based automatic segmentation (ABAS) relies on *priori* information programmed from normal scan data. Such methods require some user input to orientate the software: in the case of Mimics™ this involves ensuring that the front, back, top and bottom of the patient are correctly marked. Then defining a threshold within which pixels are to be included and narrowing a field of view for maximal accuracy.

Broadly, fully automatic segmentation can be split into 3 methods: Model fitting, image registration based and rule-based systems (Haas et al., 2008). These segmentation methods are heavily reliant on stark contrast between tissues- either through contrast media or on anatomy that is distinct from other tissue around it. In this study we have explored both manual segmenting and semi-automated segmentation with respect to the nasal and tracheal airways; as there has been little evaluation of this previously. Mimics™ offers multiple tools which allow automated pixel selection based on restrictions that the user can apply, i.e. region-growing tool, where there is an option to limit or edit the selection made.

2.3 A table evaluating inter-user variability papers
### Evaluating subjective identification of geometric features

<table>
<thead>
<tr>
<th>Summary of the study</th>
<th>Number of observers</th>
<th>Any criteria used against which to score</th>
<th>Variability or concordance between groups</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(Sims et al., 2009a)</strong></td>
<td>Compared Atlas based automatic segmentation tool (ABAS) against manual segmentation in the parotid, brain-stem and mandible classified as ‘organs-at-risk’ (OARs)</td>
<td>Study 1: OARs manually segmented by 2 ‘experts’&lt;br&gt;Study 2: The ABAS drawn contours of OARs were reviewed and edited.&lt;br&gt;13 CT head’s in 2-3 mm slice thickness were used in each study.</td>
<td>Both manually derived OAR segmentations were considered gold standard against which to compare the ABAS tool.</td>
<td>This automatic tool was prone to over-estimating the size of the parotids, yet the inter-observer difference was less likely owing to contours lines already existing. The authors suggest that in semi-automatic methods; there may be a reluctance to re-draw contours or deviate from what is marked.</td>
</tr>
<tr>
<td><strong>(Tingelhoff et al., 2008)</strong></td>
<td>To examine the inter and intra user variability of segmentation of the maxillary and ethmoid sinus from a CT using a line drawing method to outline the structures.</td>
<td>Study 1: 10 ENT surgeons (5 specialists, 5 juniors), 10 Medical students (5 junior, 5 senior) and 1 engineer (no segmentation experience), with varying experience of anatomy and segmentation outlined the maxillary and ethmoid sinuses. They compared time to segment and volume of the segmentation.&lt;br&gt;Study 2: 1 surgeon (anatomical expert) and</td>
<td>The model’s volumes were compared against each other as well as time taken to segment. A software demonstration was given, and a written protocol was given to all observers for both methods. Then the paranasal sinuses and nasal cavity were outlined according to the mucosal-bone interface.</td>
<td>The authors speculated the variance between the two sinuses was secondary to more complex anatomy as well as the clarity of bone borders between individual cells picked up on CT. Of note study 2 showed that with experience segmentation times became quicker for the inexperienced observer, however this did not affect variability. This paper clearly says that due to the inter-user...</td>
</tr>
<tr>
<td>Study (Haas et al., 2008)</td>
<td>To clinically and quantitatively validate a fully automatic segmentation software for CT for radiotherapy planning for prostate cancer. The segmentation algorithm was based on data from 600 CTs of the thorax and pelvis. Studies 1 &amp; 2 rated the quality of automatic segmentations. Study 3: Seven experts manually segmented specific structures in 7 randomly selected scans, the results of which were compared to the mean of the automated segmentation.</td>
<td>1 medical student (segmentation expert) outlined the maxillary and ethmoid sinuses 5 times consecutively.</td>
<td>Clinical validation was performed with 2 studies: Study 1: 66 randomly selected pre-segmented images were rated by 6 dosimetrists (radiation technicians who calculate radiation doses). Study 2: 52 scans were rated by 5 radiation oncologists from a pool from 3 different departments. Study 3: For quantitative validation 7 ‘experts’ manually segmented the prostate in 7 scans to be compared against automatically segmented scans.</td>
<td>Studies 1 and 2 required automated segmentations to be rated from 1-4 based on accuracy of the contours and requirement to make corrections, a score of ≤3 = time saved. The manual segmentations were compared against a mean of all the segmentations as well as the automated version.</td>
</tr>
<tr>
<td>Study (Song et al., 2006)</td>
<td>To determine inter-user variability when contouring with two types of image data:</td>
<td></td>
<td>Study 1: inter-observer study consisted of 7 observers (4 oncologists, 1 physicist</td>
<td>The contours were compared against a mean from all the user’s contours.</td>
</tr>
</tbody>
</table>
Kilo-voltage CT (KVCT) versus Mega-voltage CT (MVCT) to determine if this had a clinical impact of the deliverance of radiotherapy. and 2 radiation therapists) contoured the seminal vesicles and prostate in 5 patients whom had had 2 CTs one in each modality (Total scans interpreted=70). Study 2: long-term intra-observer study, 7 observers segmented a prostate from a single study twice but with a mean 2-month interval. (Total scans interpreted=14). The volumes and radial distances were compared. resulting in consistent over-estimation of volume of the prostate and seminal vesicles in comparison to KVCT with a ratio of 1.1 and 1.2 respectively. Study 2: The intra-observer variability was much less than the inter-user variability, but the authors appreciated the limited numbers 2 observers versus 7 in study 1. (Mazonakis et al., 2001) To determine the inter- and intra-user variability of region-growing segmentation versus manual segmentation techniques. Study 1: a single experienced radiotherapist. (Total scans interpreted=30). Study 2: 4 observers (a second radiotherapist and 3 medical physicists). (Total scans interpreted=40). This study does use a protocol for region growing which allowed repeatability of technique- although the initial seed pixel has to be placed by the observer which introduces variability. Additionally, during region-growing if there was leakage from the organ of interest as the threshold was Inter and intra-user variability was consistently lower in the region growing technique. Inter-user coefficient of variable values of volume between region growing vs manual, Prostate (7.5% vs 9.6%), Bladder (4.4% vs 5.3%) and rectum (5.9% vs 7.3%). Difference in the segmentation time was reduced by a third using Although the region growing technique was more reproducible than manual tracing, a good correlation was found between the volumes in both methods. Manual corrections did need to be applied to some areas where leakage had occurred into surrounding structures that had similar Hounsfield units to the target organ; this was reduced with the
segmentation was repeated 3 times, a week apart, to determine intra-user variability. The organ volumes were compared. Study 2: Inter-user variability saw 4 observers segment the prostate, seminal vesicles and rectum from 10 CTs using contouring versus semi-automatic segmentation using the region growing technique. increased the observer had an option of placing a limiting contour which would prevent the leakage any further into adjacent structures. region growing (8.4 minutes) versus manual contouring (12.3 minutes). application of contrast media within the bladder. This group’s experience of using region growing has been the same particularly in the nasal cavity where fine anatomical detail where a single pixel may represent the difference between two anatomical boundaries.

| (Fiorino et al., 1998) | To determine the inter-and intra-user variability of clinical contouring of the prostate and seminal vesicles from CT data for planning for radiotherapy of the prostate. | 5 radiotherapists contoured 6 patient CTs (Total scans interpreted=30). One CT was segmented twice by the 5 radiotherapists in the same sitting to determine intra-user variability (Total scans interpreted=5). | Inter-user variability was compared to the mean of all results. Intra-user variability was determined by comparing the two scans against each other. The inter-user variability in volume of the prostate and seminal vesicles was 5% (range 1.5-9%). The intra-user variability between the distance between two contours drawn was low; with a mean=0 mm±SD 0.8 mm-1.8 mm depending on the direction the discrepancy. Both Fiorino and Song (above) mention a tendency to make errors at the superior border of the prostate where the interface between it and the bladder make the border hard to identify. There was repeatable significant difference at certain points of the prostate- namely the superior and inferior margin. |
To evaluate a computerised deformable model for semi-automatic segmentation of 3D Doppler ultrasounds of the carotid artery in comparison to standard manual segmentation of a 2D ultrasound of same patient. To start the semi-automatic tool the observer must place a starting point in the centre of the lumen. The 2D ultrasound image was segmented 8 times by one 'user' (Total scans interpreted=8). No comment is made on the technical skills of the user. These segmented images were stacked, interpolated and reconstructed into a 3D image registered in a co-ordinate based space to extract the geometry data. There was an absence of gold standard thus an average of all segmentation was used. The degree of carotid stenosis was confirmed as 72% based on angiography. The semi-automatic method segments the carotids with less variability than the manual method. There was a 65% agreement between semi-automatic methods and manual segmentation. The semi-automatic segmentation takes 20 seconds in comparison to 30 minutes for manual segmentation. A limitation of this model is that like CT and MRI imaging, ultrasound is subject to the same variation in grey-values and image noise which can prevent the model working.
2.4 Comparison of inter-user variability methodology

In all the studies greater numbers were used for the inter-user experiments than the intra-user experiments. Tinglehoff’s (2007) average time to segment was 75 minutes for a whole scan and ours was 30 minutes for 5 slices; however, it was difficult to get volunteers to engage for that long and we noticed a correlation between speed of segmentation and the number of errors. This suggests that as the task becomes boring segmentation accuracy may decrease. They noted that in their intra-user variability study their segmentation times improved with practice but plateaued at a certain level of experience. An inevitable limitation of this study is volunteers time and how long they are willing to spend on the task.

The effect of training or experience on rate and accuracy of segmentation has not been clearly evaluated, whilst half of Tinglehoff’s surgical group were advanced specialists he does not make specific comment on whether their experience of anatomical knowledge effected the accuracy of their segmentation. Additionally, the critically of variability has not been formally assessed in any of these papers.

This study used a mean of two segmentations performed by surgeons with both anatomical knowledge and experience with segmentation as a gold standard. Whilst the highest number of users was compared in comparison to any other study, the users segmented comparatively fewer scans, in addition only of slices of scans not whole images.

<table>
<thead>
<tr>
<th></th>
<th>Inter-user variability</th>
<th>Intra-user variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papers</td>
<td>Us</td>
<td>Papers</td>
</tr>
<tr>
<td>Mean users (range)</td>
<td>6.6 (2-21)</td>
<td>22</td>
</tr>
<tr>
<td>Mean scans segmented (range)</td>
<td>33.7 (21-70)</td>
<td>22</td>
</tr>
<tr>
<td>Mean scans segmented (range)</td>
<td>9.6</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 8 Table showing the average number of users and scans segmented in each inter- and intra-user variability study in comparison to our study
2.5 The effect of automatic mask expansion tools on volume

A single slice of an MRI nasal cavity in Subject D (healthy male) was segmented using different techniques by a single experienced user.

- The first mask (blue) was created using thresholding alone (Threshold of 201).
- The first mask was subject to mask expansion by 1 pixel in all directions to become the second mask (pink). The Mimics ‘Mask expand’ tool allows the expansion of a mask by either 8- or 26-connectivity, connectivity being the type of relation neighbouring pixels have to the seed pixel. 8-connectivity; used in this study; only expands to pixels bordering the edges and corners of the seed pixels, whereas 26-connectivity includes faces as well thus expanding in 3 planes. (See figure 108)
- The first mask was then duplicated to create a third mask (yellow). This was manually modified by adding or removing pixels using a ‘multiple slice edit tool’. This allows the user to include or exclude pixels using a pencil/rubber technique.

![Diagram showing mask expansion](image)

Figure 108 Using Boolean operations tool to expand the whole mask either by 8-connectivity where the mask is expanded into pixels adjacent to edges and corners or 26-connectivity where pixels adjacent to the edges, corners and faces in 3D are included.

Figure 109 shows the 2D polylines which trace the contour of the 3 different masks. Lines are drawn from the masks onto the histograms below to demonstrate how the gray-value of each pixel corresponds to its inclusion in each mask. The blue mask closely corresponds to the yellow mask in most areas which is why it’s not particularly evident on the diagram, however you can see where the polyline identifies a hole in the centre of the mask. The red line which travel horizontally corresponds to the
pixel gray-values in the histogram. Simple changes in the tools used to segment or using automated mask expansion tools can affect which pixels are included and whilst in a single slice the effect is marginal- cumulatively the volumes increased can be large. Whilst during thresholding- pixels are included based on fixed parameters, mask expansion indeterminately expands the whole mask irrespective of gray-values.

The completed segmentation in all 3 techniques were made and their volume extracted. Mask expansion gave a 1 pixel increase on every border resulting in a 23.6% increase in the overall model volume. The manually modified mask increased model volume by 15.3%.
<table>
<thead>
<tr>
<th>Volume of 3D model (mm³)</th>
<th>First mask pre-expansion surface area (mm²)</th>
<th>Second mask expanded area by 1 pixel (mm²)</th>
<th>Third mask duplicate modified area (mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>35759</td>
<td></td>
<td>46756</td>
<td>42183</td>
</tr>
</tbody>
</table>

Table 9: An example of different model volumes associated with different segmentation techniques from one user on the same geometry.

2.6 Acquisition data for MRI

MR images were obtained using a GE discovery 3-Tesla MR750 series scanner. A series of 120 slices of 1.2 mm thickness and 1.2 mm spacing between slices were acquired in the coronal plane using a fast-spin echo sequence called ‘CorCube’ in T2. This technique allows the scan to be reformatted in any plane in high resolution (Lien et al., 2015). These were obtained with a repetition time (TR) of 2500, Echo time (TE) 85.4 and a matrix 512x512. For the tracheal study a CT thorax was captured in a Philips iCT 256 scanner. A series of 323 slices 2 mm thickness with a 1 mm slice increment were acquired with a FOV of 430 mm.

2.7 Models and segmentation

Creating a virtual model in mimics can done in multiple ways using a variety of tools on the software. The objectives are as follows:

- To make an anatomically representative model
- To interpolate to prevent slice continuity errors which result in holes in the mesh
- To avoid underestimating or overestimating the volume of the model
- To exclude anatomy irrelevant to the project

The following process demonstrates through screen shots the process of segmentation of an MRI nose:
1. DICOM files from CT or MRI are uploaded into Mimics™ and processed according to the file type. Orientation markers ‘superior/inferior’, ‘anterior/posterior’ and ‘left/right’ are placed.

2. The full scan is displayed in 3 planes. The user decides on an initial threshold which selects the area of anatomy being segmented. This creates a coloured ‘mask’ which reflects the area being delineated.

3. The mask can be cropped to minimise the area being worked on. This helps prevent spillage outside the anatomical area when using the ‘region growing’ tool.
4. The area in question can be zoomed. Then ‘dynamic region growing’ tool can be used. This selects all pixels within designated threshold.

5. Underlying masks can be made invisible to show the quality of the working mask. Note there are still multiple holes where pixels have not been included in the segmentation.

6. By using the ‘smart expand’ tool, this expands the mask to include any pixels within the same threshold for up to 5 pixels in any direction. However, this does generally increase the surface area of the mask. Pre-expanded Yellow=241 mm² to Post smart-expand Cyan=265 mm².
7. Another option is initially to choose a higher threshold which has fewer missing pixels but greater overspill of the mask into adjacent tissues. Using a manual editing tool, these spills can be deleted, leaving the selected area.

8. Following the deletion, the anatomy in question is isolated and can be selected using the ‘region growing’ tool.

9. The green mask can now be switched off, leaving the purple mask delineating the anatomy. Pixels can be added at the top (in yellow) to fill out some missing areas.
10. Once each slice has been segmented, a 3D model can be formed in varying qualities. The finer the detail of the model the longer it takes to create it.

11. The 3D image will then be viewed from all angles in the right lower quadrant of the screen. It can be examined for errors which will affect the eventual mesh and boundary layer.

12. The model can then undergo smoothing. This image has been smoothed using factor 0.4 with 50 iterations. The 3D model can then be examined for errors.
2.8 Detailed methodology for inter-user variability

For the inter-user variability study any user that had used Mimics™ before or had inadequate English language to comprehend the instructions were excluded. All users performed their segmentation on Mimics Research 17.0™ on HP monitors. 90% (9/10) of medics used an HP Elitebook with a 15.6-inch screen with 1920 x 1080-pixel resolution. All other users used an HP 24-inch desktop monitor with 1920x1200 pixel resolution. All users had an optical mouse. Contrast was on maximum and gray-scale adjusted to 1500 gray-values to maximise definition of the soft tissue.

The investigator was present during the segmentation to help with software queries only. No extra information was given to the user regarding anatomical inclusion or exclusion criteria, threshold levels or error correction.

Users decided upon a fixed threshold and then manually delineated anatomy based on the instructions given. Maxillary sinuses, which receive little airflow at rest, were excluded so as not to significantly affect the 2D surface area (Xiong et al., 2008).

Data collected was 2D mask area, time taken to segment, error rate and mask diameter. 2D mask area is calculated by a Mimics tool and expressed as mm². Time taken to segment was determined using the segmentation log provided by the Mimics interface. Time from first click of ‘threshold’ to final ‘save document’ were recorded. Error rate was calculated by visual inspection of the masks, observing for 3 negative qualities which result in poor CFD simulation. Mask diameter was measured at a single co-ordinate across the slices using the Mimics measurement tool.

**Variability in segmentation throughout the nose**

Previous studies have shown the distribution of airflow through nose is not uniform, predominantly travelling through the lower and middle sections. The superior nasal cavity extends into a labyrinth of sinuses, where the anatomical detail increases making the areas prone to variations in segmentation. To
determine the difference in segmenting between the upper, middle and lower nasal cavity, a grid was used to divide the cavity into within a box made of 4 anatomically located lines formulated by a radiologist.

The inferior horizontal line corresponds to the palatal line (PL) midway between the centre of the hard palate bone and its two cortices. The vertical posterior line corresponds to the posterior septum (PS). The anterior vertical line lies perpendicular to PL from the anterior nasal spine (AS) extending superiorly. A final superior horizontal line (TOP) ran parallel to PL from the posterior wall of the sphenoid sinus to the nasal bony septum. This was then divided into 12 equal segments with 3 vertical lines labelled 1V, 2V and 3V from anterior to posterior and 2 horizontal lines splitting the cavity into inferior, middle and superior. (As per Cetto et al- In press)

**Consequences of geometric variability on nasal airflow distribution**

To determine the effect of inter-user variability on CFD results. The same subject D was segmented by two expert users R and L. The mean surface areas for the 5-slices in our inter-user variability study were extracted from the full data sets. The full 3D models were subject to the same smoothing and CFD, then compared against one another to evaluate the impact of small geometry changes on flow field and shear wall stress.

**Assessing inter-user variability in segmentation of the trachea**

The aim of this study was to determine the inter-user variability between speciality groups when segmenting tracheal anatomy from CT data.

Four user groups were identified: Radiologists (n=10), Non-medics (n=10), ENT Surgeons (n=7) and Medics (n=10). A normal CT trachea was uploaded to Mimics™ segmenting platform where users could view the scan in sagittal, coronal and axial sections. In a single slice, they were asked to identify an ideal threshold which best captures the tracheal lumen in its maximum dimensions, once in the axial plane and once in the sagittal plane.
Users were informed that air was black and soft tissue grey. Their aim was to choose a threshold which coloured in the air within the trachea so that the mask neither over- nor under-estimated the anatomical size. They first chose a threshold in the sagittal section and then with a new mask chose a threshold in the axial section. The trachea was then selected using tool ‘mask-selection’ which only colours in pixels which have been picked up by the threshold and are in direct continuity with each other. The resulting anatomy was made into a 3D model and the model volume extracted. Sagittal and axial thresholds were also recorded.

All users performed their segmentation on Mimics Research 17.0™ on HP monitors. 96% (45/47) of users used an HP Elitebook with a 15.6-inch screen with 1920 x 1080-pixel resolution. All other users used an HP 24-inch desktop monitor with 1920x1200 pixel resolution. Contrast and gray-scale were on maximum and the axial image was zoomed to 50%.

The investigator was present during the segmentation to help with software queries only. The apices of the lung, oesophageal air bubble and the anatomy of the trachea were explained to all users. No extra information was given to the user regarding threshold choice.

2.9 Impact of threshold choice on error rate

Figure 110 Slice 3 with the highest mask area User F with a threshold of 566 (left), no mask (centre) and lowest mask area with a threshold of 283 User G (right).
2.10 Inter-user variability of segmentation of the trachea

<table>
<thead>
<tr>
<th></th>
<th>Sagittal threshold ± SD</th>
<th>Sagittal model volume mm³</th>
<th>Axial threshold ± SD</th>
<th>Axial model volume cm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medics</td>
<td>445±159</td>
<td>266250</td>
<td>553±320</td>
<td>6476</td>
</tr>
<tr>
<td>Surgeons</td>
<td>406±214</td>
<td>264566</td>
<td>726±163</td>
<td>13334</td>
</tr>
<tr>
<td>Radiologists</td>
<td>483±82</td>
<td>380333</td>
<td>675±238</td>
<td>9467</td>
</tr>
<tr>
<td>Non-Medics</td>
<td>390±143</td>
<td>220105</td>
<td>566±263</td>
<td>6311</td>
</tr>
<tr>
<td>Standard</td>
<td>441</td>
<td>66161</td>
<td>441</td>
<td>66</td>
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</table>

Table 10 Average thresholds and model volumes between groups

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>Std. Error</th>
<th>95% Confidence Interval for Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Std. Error</td>
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<td>Lower Bound</td>
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<tr>
<td>Medics</td>
<td>10</td>
<td>445.1</td>
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<td>Surgeons</td>
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<td>138.2</td>
<td>52.2</td>
<td>324.1</td>
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<tr>
<td>Radiologists</td>
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<td>482.6</td>
<td>82.2</td>
<td>26.0</td>
<td>423.8</td>
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<tr>
<td>Non-medics</td>
<td>10</td>
<td>386.7</td>
<td>148.3</td>
<td>46.9</td>
<td>280.6</td>
</tr>
<tr>
<td>Total</td>
<td>37</td>
<td>440.7</td>
<td>134.3</td>
<td>22.1</td>
<td>396.0</td>
</tr>
</tbody>
</table>

Table 11 ANOVA Descriptive statistics for tracheal segmentations in the sagittal plane

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>Std. Error</th>
<th>95% Confidence Interval for Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td>Std. Error</td>
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<td>Lower Bound</td>
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<tr>
<td>Medics</td>
<td>10</td>
<td>558.4</td>
<td>322.0</td>
<td>101.8</td>
<td>328.1</td>
</tr>
<tr>
<td>Surgeons</td>
<td>7</td>
<td>726.1</td>
<td>163.3</td>
<td>61.7</td>
<td>575.1</td>
</tr>
<tr>
<td>Radiologists</td>
<td>10</td>
<td>674.9</td>
<td>237.6</td>
<td>75.1</td>
<td>504.9</td>
</tr>
<tr>
<td>Non-medics</td>
<td>10</td>
<td>565.7</td>
<td>262.6</td>
<td>83.1</td>
<td>377.8</td>
</tr>
<tr>
<td>Total</td>
<td>37</td>
<td>623.6</td>
<td>258.1</td>
<td>42.4</td>
<td>537.5</td>
</tr>
</tbody>
</table>

Table 12 ANOVA Descriptive statistics for tracheal segmentations in the axial plane

Multiple linear regression analysis was performed on the data from the sagittal plane to investigate the association of volume with threshold and profession. Results showed that there is no impact of the profession factor on threshold choice, whilst there is a strong association between threshold and volume choice. The coefficient of the threshold was found to be significant with a p-value = 0.221x10^-5. However as seen in Figure 111, the data does not follow a linear pattern but rather seems to be divided into two groups making linear regression not a particularly suitable tool to analyse the association. Thus,
we looked at the difference in volume to see where the difference in volume is maximised to find an optimal threshold.

Figure 111 Scatterplot of data from sagittal plane showing threshold against volume. Note the large jump in volume between a threshold of 400 and 500 where the mask spills into surround tissue thereby including the right lung in the segmentation (see figure 23)
The coloured point in figure 113 represents the maximum difference in volume over the 37 users. It corresponds to a threshold level of 430 (441 low-threshold line), showing that the optimal threshold choice <430, above which there is a significant leap in volume which is unsatisfactory.
Similarly, we performed the same analysis on the axial data set and found that again there was no statistical link with profession but there was still a strong correlation between threshold choice and volume. The coefficient of the threshold was statistically significant with a p-value = 0.000045. As before we analysed the difference in volume and showed that the ideal threshold would be below 778 (806 = high-threshold line).

Figure 114 A plot of the differences in volume per threshold level in the axial plane.
3.1 The process of running a CFD

The process of running a CFD requires several steps as seen in Table 1. The time spent on each task can vary depending on the complexity of the task and the computational tools available to solve the problem.

<table>
<thead>
<tr>
<th>Process of CFD analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Problem statement</td>
</tr>
<tr>
<td>2. Mathematical model</td>
</tr>
<tr>
<td>3. Mesh generation</td>
</tr>
<tr>
<td>4. Space discretisation</td>
</tr>
<tr>
<td>5. Time discretisation</td>
</tr>
<tr>
<td>6. Iterative solver</td>
</tr>
<tr>
<td>7. CFD software</td>
</tr>
<tr>
<td>8. Simulation run</td>
</tr>
<tr>
<td>9. Post processing</td>
</tr>
<tr>
<td>10. Verification</td>
</tr>
</tbody>
</table>

Table 13 Process of CFD analysis from University of Dortman (Kuzmin)

When the engineer receives the STL the polyhedral volume mesh will be generated based on the original geometry. If the original mesh quality is poor, pre-processing can require a lot of manual work including fixing holes and smoothing so that the final mesh is acceptable for CFD analysis (See Chapter 1 for segmentation errors). The mesh created be compiled of multiple shapes, each point known as a cell. The more cells, the more detailed the mesh and the longer the CFD simulation takes to run.
<table>
<thead>
<tr>
<th>Model</th>
<th>Mesh size</th>
<th>Number of cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nose model</td>
<td>4mm</td>
<td>3.7 million</td>
</tr>
<tr>
<td>Trachea model (including nasal cavity)</td>
<td>3.5mm</td>
<td>7.6 million</td>
</tr>
</tbody>
</table>

Table 14 Mesh size and cell number for the two models

There is a close collaboration between the engineer and clinician segmenting the image. The segmentation produced by the surgeon is based on anatomical understanding of the nasal passage and layout of the intranasal sinuses, it also relies on an appreciation of how MRI and CT images capture different tissues. The user needs to provide the engineer with an accurate model which can be made into a mesh devoid of holes or defects. Holes can appear through slice continuity errors, made by missing adjacent pixels in a sequence of slices. When the mesh is created this leaves defects which are artefact and not true to the anatomy, importantly these can only be appreciated in 3D.

In the nasal cavity particularly, the effect of congestion and decongestion dramatically changes the airways diameter, the smaller the airway the fewer number of pixels differentiating between tissue types and therefore there may be only a single pixel delineating the airway. This particularly happens in the olfactory slit, which is anatomically narrow and the area adjacent to the inferior turbinate which is subject to large volume changes associated with congestion (Figure 115).
Figure 115 Coronal (above) and sagittal (below) showing a congested and decongested nose. Middle turbinate (MT) and inferior turbinate (IT) are labelled.
3.2 Comparison between mass flow rates between two segmentations of the same nose

Figure 116 Comparison showing percentage mass flow rate between different levels of the nose in Level 2V of the nose between two users.

Figure 117 Comparison showing percentage mass flow rate between different levels of the nose in Level 3V of the nose between two users.
4.1 Factors limiting image quality in CLE

Video quality is one of the limiting factors for this study. Not only does the endoscope and stack set need to be of sufficient quality and resolution, but the filming is affected by camera position, oro-nasal secretions and tolerance of the patient.

Light intensity is fundamental to discerning the difference between structures and can frequently be inconsistent due to the movement of the nasendoscope. This is important from a segmenting perspective as it can result in variations of grey-values of structures from frame to frame which will affect area captured during segmentation. In terms of patient tolerance, whilst their nasal cavity is numbed with topical anaesthetic, patients who repeatedly swallowed or who had a hyper-mobile larynx, were associated with videos in which the view of some or all the glottis was frequently obstructed. Equally if the patient was phonating or coughing during the test, the glottic aperture would be undetectable. This proved troublesome to quantify, whether it was secondary to swallow or phonation. In the first case series, the video equipment used a marker of time and date as a fixed watermark on the screen. As a result, the white writing from the watermark could fall over the glottis creating a bright area that is difficult to segment.
The placement of the camera is important in terms of perspective, as closer shots will result in a larger glottis area; as of yet there is no fixed protocol for camera placement since this will largely depend on the patient’s comfort and individual anatomy. Furthermore, there is little practicality in developing a fixed protocol as scaling will always be a problem, it is more likely that long-term the solution will be found in image-recognition technology, than how far an endoscope is inserted into a patient’s nose. A beneficial advance for such technology would be the ability to account for the 2D geometric change based on depth and angle of the camera, since if the camera is positioned within the post nasal space, it may tilt anteriorly, resulting in an oblique view of the larynx where tongue base or epiglottis obscure the posterior commissure. As this is the widest part of the glottis this effect will significantly reduce the recorded glottic area.

4.2 Preparation of images for segmentation

Videos were uploaded to Matlab where they were converted to DICOM images in grey-scale and cropped using a semi-automated Matlab script, which allowed the user to crop the videos to create a <40 second video- 20 second before and after a point chosen by the treating physician. (See appendix courtesy of Dr Alister Bates). If the point chosen had less than 20 seconds of footage the video was cut short. These videos were uploaded into Mimics™ and segmented by a single user. 2D mask area as well as glottic angle was exported and plotted onto a graph. The steps of segmentation of the glottis were performed using the same software and steps as nasal segmentation found in the appendix of Chapter 1.
Figure 119 DICOM file showing a still of the glottis in grey-scale. At the top of the image, an intra-oesophageal manometer seen in white measures pressure. The white watermark is seen in the upper-left corner. The telemetry trace is seen on the right-hand side.

Figure 120 A video still following conversion to grey-scale. Showing a partially open glottis, with the epiglottis featuring in close proximity to the camera at the bottom of the image.
4.3 Flow modulation at the glottis

To understand how the glottis may modulate flow during expiration, Figure 122 shows patient 32 and 34 with green lines marking maximal inspiration and orange lines during maximal expiration. In the healthy subject 34 it can be appreciated that the glottic aperture opens and closes approximately at the same rate. However, Subject 32 shows rapid widening of the glottis during inspiration, but a comparative gradual reduction on expiration suggesting the glottis is modulating the airflow by maintaining a narrower outlet and thereby higher pressures.
Figure 122 Green inspiratory lines versus orange expiratory lines showing a more gradual increase in glottic aperture during inspiration in a patient 34 who has no lung disease. No scale is provided as due to scaling the height and width of the respiratory cycles are not directly comparable.
4.4 Experiment 2 results: Linear regression analysis

A linear regression analysis was performed to analyse the association of glottic angle to mouth pressure and oesophageal pressure on Video D and T. This showed a strong negative correlation between glottic angle and mouth pressure in both videos, when pressure increases glottic angle decreases. In particular the regression coefficient of mouth pressure for Video T (Figure 123) was -6.80 (p-value <0.4x10^-7) showing that increasing the pressure by 1mmHg results in the glottic angle decreasing by a factor of 6.8. Video D’s regression coefficient for mouth pressure was -3.26 (p-value <0.2x10^-15) which still shows a strong association between glottic angle and mouth pressure. The probable cause for the difference in regression co-efficient between D and T is that on expiration the exhaled air and positive pressure from the machine combine in the mask increasing the mouth pressure recording, however the glottic aperture is typically smaller on expiration.

Comparing the data from the highest and lowest CPAP settings there is an inverse correlation which becomes stronger the lower the CPAP setting. This may be because to overcome the positive pressure at higher settings, there is an element of forced expiration which requires a less restricted glottic. It
should be noted that the volunteer was supine for Video D and sitting for Video T, but the date is too limited to clearly state what impact that may have on these results without running a direct

4.5 Glottis angle versus oesophageal pressure

The correlation between oesophageal pressure and glottic angle was found to be weaker in particular in Video D. The regression coefficient was not found to be significant whilst in video T there was slight significance (p-value = 0.01) but not to the same degree as that of mouth pressure: increasing oesophageal pressure by 1 mmHg the glottic angle decreases by a factor of only 0.53. The oesophageal pressure is surrogate marker of plural pressure but without knowing details about lung compliance there is a limitation to how much we can derive from this data.
Video H Supine patient (CPAP=14)- Glottic area against oesophageal & mouth pressure

Video H Supine patient (CPAP=14)- Glottic area against anterior commissure angle
Video M sitting patient (CPAP=9) - Glottic area against oesophageal & mouth pressures

Video M Sitting patient (CPAP=9) - Glottic area against anterior commissure angle
Video T Supine patient - Glottic area against oesophageal & mouth pressure

Video T sitting patient - Glottic area against anterior commisure angle
4.6 Automated glottic segmentation methodology

This Matlab script was developed to segment the glottis from a video of a flexible nasendoscopy. Whilst Mimics™ only works in grey-scale, Matlab is not constrained and therefore colour images can be used. The script works by uploading a video into Matlab frame by frame and converted each frame to an array of numbers, where each number describes the colour. A seed pixel is chosen manually, and the code searches the surrounding pixels to find a change in colour suggesting the presence of a boundary. The code takes 15 minutes to get the glottic area of 657 frames and takes approximately 75 minutes to perform glottic area, anterior commissure angle and curve of the cord measurements.

During the development of this program, different channels of colour including grey-scale were explored to see if they enabled better edge detection, by increasing the dominance of either the Red, Green or Blue colouring within the images.

The first image is then displayed, a user clicks somewhere within the centre of the area that is trying to be defined- in this case the centre of the glottis where it appears most black. The code then scans upwards and downwards across the 2D image looking for a large change of colour which may represent the edge of a region. The degree of the colour change at which the program stops is pre-defined by the user, there is a degree of adjusting that needs to take place to get the right parameters. The seed point for the first frame is critical, as the boundary parameter may be 100 grey-units above the seed pixel, therefore if a pixel will be excluded if its 101 or 200 points greater than the seed. If the first seed had a grey-value of 5 and the one adjacent a grey-value of 20- it will result in different pixels being included/excluded at the boundary. Smoothing and filtering reduces the criticality of choosing the first seed-pixel and thereby reduces the variability in the possible contour.

The code also has some other small features designed to improve accuracy. At the end of the edge detection, it expands the mask by 1 pixel to see if it detects any islands that should have been included, if none are found the mask is eroded back down by 1 pixel. Typically, the code runs automatically after the first seed-pixel is chosen until it runs into a problem such as swallowing or vocalising. An error
message will show ‘Are the vocal folds obscured?’, this requires the user to manually go through the obscured images until the glottic aperture re-appears and the code can re-start.

5.1 Models

Figure 125 Depictions of the upper airway and larynx from left to right by (Katz et al., 1997, Gemci et al., Zhang et al., 2002, Stapleton et al., 2000)
5.2 Stages in designing the joints between sections

5.3 Stages in designing the final Model Y

<table>
<thead>
<tr>
<th>Prototype</th>
<th>Sections</th>
<th>Taps</th>
<th>Joins</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-1</td>
<td>3- Nose, larynx, trachea</td>
<td>None</td>
<td>Simple peg</td>
</tr>
<tr>
<td>X-2</td>
<td>3- Nose, larynx, trachea</td>
<td>5mm</td>
<td>Simple peg</td>
</tr>
<tr>
<td>X-3</td>
<td>5- Nose, larynx, trachea, 2x bronchi</td>
<td>5mm</td>
<td>Simple peg and slotted join</td>
</tr>
<tr>
<td>X-4</td>
<td>6- Full face, nasal cavity, larynx, trachea, 2x bronchi</td>
<td>5mm</td>
<td>Simple peg, slotted join + anchoring screws</td>
</tr>
<tr>
<td>Y</td>
<td>5- External nose and nasal cavity, larynx, trachea, 2x bronchi</td>
<td>2mm</td>
<td>Simple peg in supraglottic join, slotted join + anchoring screws</td>
</tr>
</tbody>
</table>

Table 15 Table of features of the generations of models created for the airflow project. These correspond with Figure 71 in Chapter 5
The models were printed using an Objet Connex 350 3D printer. The initial prototype airway with a 53-degree glottis was printed in digital ABS-like material made of a mix of two sub-types of plastic RGD515 & RGD535. Due to a change in the material type on the printer; the anterior nose and face, as well as the 19, 33, 38 and 47-degree glotti were constructed using RIGUR RGD450. These products use a non-dissolvable wax-based support material; which was removed using a Water-Jet between 20-120 bar of pressure. A sonic-bath was used to soften some areas of material and a flexible nasendoscope was used to scope each part to ensure the internal surface was smooth. Aesthetically the two materials have similar qualities- however ABS has higher tensile strength and thermal resistance than RIGUR in areas of small calibre anatomy.

5.4 CAD models compared with endoscopic images

![Figure 127 Photograph of human glottis with a 33-degree anterior commissure angle compared with a CT derived glottis of the same angle](image-url)
5.5 Experiment set up

Figure 128 Photograph of human glottis with a 17-degree anterior commissure angle compared with a CT derived glottis which shows a 10-degree glottis

Figure 129 Inspiratory model set up with alcohol manometer set at 45 degree
A 240V vacuum pump running at variable RPM was used to mimic inspiration. The speed was controlled with a knob dial from 1-8 which did not correlate with a specific air speed, therefore in addition to using the alcohol manometer a clamp device on the inlet tube was used to fine tune the flow.

In initial experiments a 64-multichannel pressure transducer CANdaq was used, this was eventually replaced with a 32-channel transducer (MiniDAQ) due to problems related to the calibration of the instrument and persistently unreliable readings. Instead of giving a reading in Pascals, the CANdaq gives an arbitrary measure of pressure where an index of 32768 equates to zero. The maximum reading is 65536 (equivalent to 1000pa) and the lowest reading is -32768 (equivalent to -1000pa). To convert these values into Pascals the following equation was used.

\[ \text{Pa} = \left( \frac{\text{difference between max + min}}{\text{max index}} \right) \times \frac{\text{Flow mean}}{\text{Preflow mean}} \]

![Figure 130 Vacuum pump with conical attachment to enable secure fixing of the silicon tubing and a fine tuning clamp to limit flow](image)

The 64-channel pressure transducer gave consistently unreliable readings from taps 14, 16, 20, 30 and 35. In attempts to correct this, the model was de-constructed, the taps re-cleaned to ensure no support...
material was retained and the silicon pipes were replaced with newer versions that were tighter fitting. If single taps were giving inaccurate readings different manometer taps were trialled to see if this settled the problem. Eventually the CANdaq controller unit began to fail and the whole system was changed for another version with 32 taps model number ESP-32HD.

5.6 Orifice plate

The orifice plate was designed according to the guidelines issued by The American Society of Mechanical Engineers ‘Measurement of fluid flow using small bore precision orifice meters’ ASME MFC-14M-2003. This was designed by a previous student, Marcus Rose and printed in a Conex 350™ 3D printer in the material Rigur™. Orifice plates can be produced cheaply and accurately with a 3D printer and also do not require specific calibration against another device. This orifice plate has a

\[ Q = \frac{\pi}{4} C \beta \sqrt{\frac{2\Delta P_d}{1 - \beta^4}} \]

\[ C = \left[ 0.5991 + \frac{0.0044}{D} + \left( 0.3155 + \frac{0.0175}{D} \right) \left( \beta^4 + 2\beta^{16} \right) \right] \sqrt{1 - \beta^4} + \ldots \]

\[ \left[ \frac{0.52}{D} - 0.192 + \left( 16.48 - \frac{1.16}{D} \right) \left( \beta^4 + 4\beta^{16} \right) \right] \sqrt{1 - \beta^4} \frac{1}{R_D} \quad (D.2) \]

Figure 132 Coefficient of discharge for the micromanometer

3D printer in the material Rigur™. Orifice plates can be produced cheaply and accurately with a 3D printer and also do not require specific calibration against another device. This orifice plate has a

Figure 133 Orifice plate (see dimensions)
coefficient of discharge of 0.6223 (calculated according to the relation given in the appendix),
diameter=13mm and β=0.5. The orifice plate was tested in both directions and the results were the same.

\[ Q_m = CA \sqrt{\frac{2\Delta P \rho_{air}}{1 - \beta^4}} \Rightarrow Q_{vol} = CA \sqrt{\frac{2\Delta P}{\rho_{air} (1 - \beta^4)}} \]

Figure 134 Orifice plate equation

\[ \Delta P = \left( \frac{1 - \beta^4}{2 \rho_{air}} \right) \left( \frac{4Q_m}{\pi C d^2} \right) \]

Figure 135 Orifice plate equation

5.7 How the experiment was run

To start the experiment running

1. Determine the number of samples 225/second
2. Record temperature of the room
3. Tilt the alcohol manometer to 45° for lower flows to enable more accurate readings
4. Zero the pressure samples and take a pre-flow reading
5. Turn on the flow and titrate the flow to 20 l/minute
6. Start the data collection for 30 seconds
7. Repeat for 30 l/min and 40 l/min
8. Tilt the alcohol manometer back to 25°
9. Record data for flows 50-80 l/min
10. Once the fan has completely stopped take a post-flow reading to ensure that the zero’d pressure hasn’t changed during the experiment.

11. Repeat 3 times and take the mean of the 3

12. Convert CANdaq index to pascals

5.8 CANdaq pressure manometer

Sensitivity of CANdaq manometer to environmental factors- In two cases the door of the lab was open and in two cases the windows to the street were open. In two tests a silicon tube, the same length as the other tubes, was attached to the atmosphere tap. The graph below shows the impact of environmental flow is minimal, the maximal difference being 0.0076%.

![Graph showing sensitivity of CANdaq to environmental factors](image)

**Figure 136 Testing the sensitivity of the CANdaq to environmental factors such as temperature change and circulation of air through the room**

Sensitivity between experiments from individual tap readings- To determine whether there were inconsistencies in the tap readings two taps were selected (Taps 4 & 28) and measured at two speeds of airflow in 4 different glottic aperture models. Each study was run 3 times and then plotted against the mean of the 3 readings to determine if there was a significant variation between tests. Tap 4, located on
the posterior wall of the pharynx showed greater spread than Tap 28 on the posterior surface of the mid-trachea. Tap 4 is a more sensitive location thus this may explain the greater spread.
Determining accuracy of CANdaq at a single tap: To verify the quality of readings from the CANdaq at two taps, a T-piece was placed and that tap read by both the CANdaq and a FCO510 Furness micromanometer to ensure correlation. This was performed in each model and the tap number changed between each experiment. A standard t-test was performed, and this showed no statistical significance between the measurements from the micromanometer and CANdaq p-value = <0.05. The mean difference between all measurements was 0.5 pa with a maximum of 5.6 pa.
Quantifying error margin for the CANdaq- For the purpose of quantifying the accuracy of the CANdaq we assumed that the micromanometer was the perfect measure. At first when the mean relative error between the CANdaq and micromanometer was calculated it showed an 8% relative percentage error between the readings, however this is likely incorrect because it’s too sensitive to large values.

Instead the mean absolute error has been calculated as 1.3. It should be noted that the absolute error is not particularly accurate with measurements which are captured at the limit of the sensors sensitivity, however it can be used in this case as the readings are well within the manometers sensitivity range. In
order to quantify the degree of error of the CANdaq we calculated 95% confidence intervals. A histogram, seen below, was examined to determine that the error was normally distributed.

Histogram showing the distribution of Candaq error measurements with relation to the micromanometer

Error of candaq in 5 degree glottis at different flows
Error bars for the candaq in Y-10

Error bars for the candaq in Y-33
The Candaq and the micromanometers fall within the error bars. In the 5-degree model at extremes of flows the micromanometer is outside the error bars of the Candaq. This may be because the Candaq’s sensitivity is less when measuring very high or very low pressures, as would be found in a much narrower glottis.

This is more than expected but we have to consider that the micromanometer will have its own error value which we assume to be less than that of the CANdaq which is the reason why we have used it as a reference value. The micromanometer was assumed to be more accurate than the Candaq because the micromanometer is calibrated to measure smaller pressure differences.

Error bars for the CANdaq are computed as 2* the standard deviation of the difference between 29 readings taken using the micromanometer and those taken using the candaq across all models for a variety of flow rates using different taps.
5.9 Comparison of 4 different glottic apertures

Figure 137 Spread of results at 20L in 2 generations of a 10-degree model (X and Y). Results have been scaled to allow comparison.

Figure 138 Spread of results at 80L in 2 generations of a 10-degree model (X and Y).
Figure 139 Pressure across Model Y with a 33-degree glottis

Figure 140 Pressure across Model Y with a 10-degree glottis
Figure 141 shows poor correlation between the pressure loss in the wider aperture glottis. Because the 53-degree model is much wider it has less resistance, and less evidence of pressure loss at the glottic level. Whilst the full model still has the resistance of the upper airway - when plotted together the scale does not allow comparison. Therefore, the final pressure for each flow was subtracted from the pressure reading at each tap to reduce the scales.

5.10 Pressure tap distribution across 4 different models
5.11 Descriptive statistics for comparison of 4 different glottic apertures

<table>
<thead>
<tr>
<th>(I) Degrees</th>
<th>(J) Degrees</th>
<th>Mean Difference</th>
<th>Std. Error</th>
<th>Sig.</th>
<th>95% Confidence Interval</th>
</tr>
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<tbody>
<tr>
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<td>5</td>
<td>10</td>
<td>-13.73410*</td>
<td>1.38208</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td></td>
<td>-16.87256*</td>
<td>1.34406</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>33</td>
<td>-18.09209*</td>
<td>1.33722</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>10</td>
<td>13.73410*</td>
<td>1.38208</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td></td>
<td>-3.13846*</td>
<td>.48460</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>33</td>
<td>-4.35799*</td>
<td>.46530</td>
<td>.000</td>
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<tr>
<td></td>
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<td>16.87256*</td>
<td>1.34406</td>
<td>.000</td>
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<td></td>
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<td>10</td>
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<td>.48460</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td>53</td>
<td></td>
<td>-1.21952*</td>
<td>.33591</td>
<td>.004</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
<td>33</td>
<td></td>
<td>1.21952*</td>
<td>.33591</td>
<td>.004</td>
</tr>
</tbody>
</table>

* The mean difference is significant at the 0.05 level.

Table 16 A table showing pair-wise comparison (Games-Howell) between the different glottic models from the glottic taps to the carina at 20L/minute. Showing there is statistical difference between all models.

5.12 T-test p-values for experimental model versus CFD

<table>
<thead>
<tr>
<th>Flow rate l/min</th>
<th>53 degrees experiment vs CFD T-test p-value</th>
<th>10 degrees experiment vs CFD T-test p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>0.776</td>
<td>0.290</td>
</tr>
<tr>
<td>30</td>
<td>0.531</td>
<td>0.0000066</td>
</tr>
<tr>
<td>40</td>
<td>0.958</td>
<td>0.207</td>
</tr>
<tr>
<td>50</td>
<td>0.869</td>
<td>0.138</td>
</tr>
<tr>
<td>60</td>
<td>0.936</td>
<td>0.195</td>
</tr>
<tr>
<td>70</td>
<td>0.999</td>
<td>0.212</td>
</tr>
<tr>
<td>80</td>
<td>0.920</td>
<td>0.215</td>
</tr>
</tbody>
</table>

Table 17 p-values from independent t-tests showing all but one model shows no statistical difference between the CFD and experiment.
5.13 Taps recorded in the idealised and realistic glottic models

Model Y included a nasal cavity and had a total of 37 taps, compared to 35 in the idealised model, however the pressure manometer had 32 probes thus 3 taps in the idealistic model were sealed off. These were chosen based on their similarity to the Model Y - Taps 17, 22 and 25. On CFD data 33 taps were measured as the first two were not used. To ensure the glottis was lined up, the 1st tap from the CFD data is used twice, and the results between missing taps (17,22 & 25) are joined to create a smooth line. On experimental versus CFD data 35 taps are used.

To compare idealised model versus CFD. The full model of both A10 and A53 were compared as neither CFD nor model had an upper airway. Each model had a single tap that was giving a poor reading, and 3 taps were sealed during the experiment due to insufficient space on the Candaq manometer which had a limit of 32. For these 4 taps- an average of the other 3 taps at the same level have been taken to allow comparison.