A SIZE AND SHAPE ANALYSIS
IN OBSTRUCTIVE SLEEP APNEA PATIENTS

by

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ABSTRACT

Obstructive Sleep Apnea (OSA) is related to an abnormal configuration of the upper airway. Since it presupposes a complex pathogenesis, studies on the disease usually require the analysis of many variables. This makes it difficult to obtain an adequate sample size. Further, the size of the upper airway structure often overwhelms the data matrix, and thus may be a source of multicollinearity or noise. More seriously, the strong size effect may hide an underlying biological factor. Landmark data and their analytic tools were employed in this study to partial out the size factor, and to decompose shape changes into uniform and non-uniform components. The non-uniform deformation was quantified in terms of bending energy by the Thin-Plate (TP) spline analysis. The Partial Least Square (PLS) method was applied to summarize the intricate data structure.

The tongue was the unique upper airway structure for which size presented a significant association with OSA severity. In accordance with symptom severity, the hyoid bone and the submental region moved inferiorly and the fourth vertebra moved posteriorly with respect to the mandibular plane. This caused a fan-like configuration of the lower part of the upper airway in upright and supine body positions. Body position changes generated significant tongue deformation. TP splines revealed that the distinct tongue deformation caused by a body position change enable one to distinguish the asymptomatic group from the OSA subjects. Pharyngeal length was found to be proportionally associated with OSA symptoms. Results from the PLS analysis confirmed that the pharynx variables obtained in the upright position may best predict symptom severity. Overall, the new morphometric tools adopted here were found to be viable in OSA analysis.
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INTRODUCTION

Obstructive Sleep Apnea (OSA) is characterized by recurrent upper airway obstruction during sleep, usually in the supine position. Upper airway patency depends upon a balance of forces between the intraluminal negative pressure produced by contraction of the thoracic inspiratory muscles, and the opposing upper airway dilating muscles. Any anatomical or functional factor that breaks this balance may predispose the upper airway to occlusion during sleep. To examine the association between anatomical predisposing factor change, and its effect on the symptom severity from a new perspective, the current project relied on two approaches: first, statistical modelling which abstracts logical relations between the antecedents and consequences of the disease; second, geometrical presentations which provide an intuitive understanding of the abnormal configuration of the anatomical structures. The study was performed in light of landmark data analysis concepts, which are rooted in D'Arcy Thompson’s philosophy of morphometrics, the study of shape analysis. Observation of location and quantity of a shape difference or shape change may aid comprehension of the biological process. A morphometric analysis may start with the question of whether shape differences exist. If the shape differences are shown to be significant, the next step would be a scrutiny of the deformation. Interpolation of one-to-one mapping in a Cartesian space visualizes the shape changes between two biological structures. As a new powerful tool in spatial statistics, the Thin-Plate (TP) spline method envisions a transient stage of shape changes in the context of Thompsonian philosophy and quantifies the amount of the deformation in terms of bending energy. OSA is a disease with uncertain etiologies and diverse manifestations of symptoms. Previous studies have described an association between
symptom severity and complex anatomical anomalies in OSA subjects. Partial Least
Square (PLS) is a statistical technique which deals with undefined heterogenous data in
a block design. PLS conveniently summarizes the intricate relationships between upper
airway structures and the symptoms of OSA. PLS does not provide an explanation based
on causality; however, it explains the relation between indicators and outcomes in the
notion of prediction. The present study mainly concentrates on shape changes of the
upper airway in OSA subjects. Decoding of encoded multi-correlations between
antecedents and consequences in the pathogenesis of OSA was attempted with new
morphometric tools.
LITERATURE REVIEW

1. Obstructive Sleep Apnea and Background

Obstructive Sleep Apnea (OSA) may be defined as more than five episodes of recurrent upper airway occlusion for longer than ten seconds per hour of sleep (Thorpy 1990). OSA may be one of the most prevalent diseases in modern society, which may affect approximately 2% or more of the adult male population (Partinen and Telakivi, 1992). Signs and symptoms of OSA can be summarized chiefly by diurnal hypersomnolence, nocturnal dyspnea and myoclonus, and also by the accompaniment of various associated pathophysiologic sequelae (Granton and Bradley, 1991). Upper airway patency is thought to depend upon balanced forces along the ventilatory conduit. The intraluminal negative pressure produced when the thoracic inspiratory muscles contract, tends to occlude the upper airway unless adequately opposed by the dilating upper airway muscles (Remmers et al., 1978). Any increase in inspiratory resistance in the upper stream level above the obstruction site would predispose toward an upper airway occlusion during sleep. Previous studies have evidenced there may be two main predisposing local factors leading to airway obstruction in patients with OSA: a narrow airway and reduced upper airway muscle activity.

In the book "Posthumous Papers of the Pickwick Club" in 1837, Charles Dickens described an extremely fat boy who suffered from persistent somnolence. In 1918, Sir William Osler coined the term "Pickwickian" referring to obese and hypersomnolent patients. Gastaut and his associates (1964) reported the presence of repetitive obstructive apnea during sleep in the "Pickwickian" patient. In 1966, the same group evaluated the sleep, respiration and blood gas chemistry of the patient by means of
polygraphic registration. They employed the EEG (Electroencephalogram), the spirogram and the EMG (Electromyogram) of diaphragmatic and mylohyoid muscle activity to hypothesize the pathogenesis of obstructive sleep apnea and distinguished central apnea from obstructive apnea. The term 'sleep apnea' was first used in 1971 by Kumashiro et al.. In 1972, Walsh et al. reported obstruction of the upper airway in three obese patients with sleep disturbance and somnolence. In 1973, Guilleminault et al. reported insomnia with Sleep Apnea as a new syndrome and named it the Sleep Apnea Syndrome.

1.1 Anatomical characteristics of OSA patients

There is ample evidence that OSA patients have a number of anatomical anomalies. Numerous two- or three-dimensional imaging studies attest that there are constrictions in the airway or abnormal geometrical relations in it and its parastructures. Proctor’s (1977) exhaustive review on the upper airway illustrates that the airway size around the pharynx is unsteady in normal conditions. Some of the OSA symptoms are induced by specific etiologies (Langevin, et al., 1992), yet most patients do not reveal specific anatomical or physiological abnormalities. The majority of airway obstructions seem to occur in the retrovelopharyngeal and retroglossal area, viz. the base of the tongue and hypopharynx respectively (Hudgel, 1986; Lowe et al., 1986; Shepard Jr. and Thawley, 1990). However, a more recent somnofluoroscopy study by Pepin (1992a) evidenced that the obstruction site may progress from the oropharynx to the hypo- or laryngopharynx as the airway collapse proceeds. One important anatomical structure considered to be a contributing factor in the pathogenesis of OSA is the soft palate. The soft palate and the associated redundant tissue are known to behave like a cork in a long-
neck bottle at the oropharynx while airway occlusion is occurring. Several investigations have reported a long and thick soft palate in patients with OSA symptoms (Fujita et al., 1985). After an extensive review on the role of the soft palate in OSA by Rodenstein and Stanescu (1986), some researchers including Ryan et al. (1990, 1991), have shown a correlation between the volume of the soft palate and symptom severity. Several groups (Hudgel et al., 1991; Launois et al. 1990; Sher et al., 1985) supported a usefulness of localization of the narrow site in upper airway before uvulopalatopharyngoplasty (UPPP). A recent review paper by Rodentein (1992) was sceptical toward the effectiveness of UPPP.

A large tongue in combination with a narrow pharyngeal airway has been speculated as another primary causal factor in OSA. The airway size has been measured in either 2D (two-dimensional) areas (Strelzow et al., 1988; Lyberg et al., 1989; Kuna et al., 1988) or 3D (three-dimensional) volumes (Lowe and Fleetham, 1991). The pharynx of OSA subjects was reported to be smaller than that of normal subjects in general; however, the size of the tongue may vary depending on the visualization techniques which differ from study to study. Furthermore, several radiographic studies have shown that the size of the pharynx does not necessarily predict the presence of airway occlusion (Horner et al 1989; Hoffstein et al., 1991). Another distinctive anatomical characteristic of OSA patients may be an inferiorly positioned hyoid bone (Riley et al., 1983; DeBerry-Borowiecki et al., 1988; Maltais et al., 1991). The hyoid bone position is known to be closely related to upper airway patency (Brouillette and Thach, 1979; Roberts et al., 1984). According to an investigation by Sasaki and associates (1977), the epiglottis of human newborns in their neonatal period appeared to be close to the soft palate to protect the lower airway,
which may allow respiration and deglutition to occur simultaneously. The position of the epiglottis descends with aging and stabilizes at the age of 12 to 18 months. The hyoid bone position was observed to change with age as well (Stepovich, 1965; Maltais et al., 1991). Vertical hyoid position alteration was reported to be proportional to the upper airway resistance (Athanasiou et al., 1991).

Abnormalities in the tissue proper comprise another aspect of OSA pathophysiology. Upper airway compliance may be another local problem of the upper airway. Previous studies denoted that the human oropharynx is inherently collapsible when compared with higher order primates. Upper airway collapsibility was suggested to be quantified by \( P_{crit} \), which is defined by the negative nasal pressure below which the airway occludes (Schwartz et al., 1988; Gleadhill et al., 1991). These studies demonstrated elevations in \( P_{crit} \) in apneic patients. Not only the pharyngeal tissue proper contributes to upper airway collapsibility, muscle tone (Wiegand et al., 1989; Brouillette and Thach, 1979) and vascular tone (Wasicko et al., 1990) may also be involved.

1.2 Functional characteristics of OSA patients

Several studies suggest that behavior of the upper airway dilating muscles, and the airflow through the airway conduit, both play a crucial role at the moment of airway occlusion. Since the size of the upper airway is insured mainly by tonicity of the upper airway muscles, which tend to oppose the negative intraluminal pressure created by kinetic energy of the airflow, the relationship between airway size and shape, muscle tonic activity, and airflow should all be considered simultaneously. Genioglossi (GG) have been considered as a safeguard in the upper airway. The GG, a protrudor, consists of three
compartments in accordance with its anatomy: the anterior, middle fan-shaped oblique portion, and inferior, almost horizontal portion which inserts into the posterior one-third of the tongue, the main protruder (Doran and Bagget, 1972). Interestingly enough, 75-81% of the tongue extrinsic muscles histochemically consist of type II fibers (Hellstrand, 1980). Since the GG muscle in humans contains proportionately more type II fiber than other mammals (Doran, 1975), it can be fatigued. Remmers et al. (1978) described the role of the GG muscle in upper airway obstruction during sleep, and assumed that GG atonia contributed to the inspiratory upper airway obstruction. A myriad of studies on GG followed. Brouillette and Thach (1980) found that the GG response to chemoreceptor stimulation may be quantitatively different from diaphragm responses. Önal and colleagues (1981) observed that GG and geniohyoid muscles maintain upper airway patency by pulling the tongue and hyoid bone forward during inspiration. Many groups also suggested that the respiratory function of hyoid muscles and the hyoid arch affect upper airway resistance. They postulated that the strategic location of the hyoid arch may contribute to the patency of the upper airway, and that the decreased or poorly coordinated function of the hyoid muscle may induce upper airway occlusion. This hypothesis was suggested by Mathew (1984), as well as by Roberts et al. (1984) and advocated by Van de Graaff et al. (1984) and van Lunteren et al. (1987ab). It was applied to treatment of OSA by Miki et al. (1989).

An imbalance of neural inputs or feedback (Remmers, 1990) may also cause imbalanced or poorly timed muscle function, in turn inducing an airway occlusion. St. John et al. (1984) reported that activity in the phrenic and hypoglossal nerves in cats increases or decreases in parallel fashion with the hypercapneic condition. In contrast, Parisi et al.
(1988) observed that hypercapnia effects the GG differently from the diaphragm, which suggested this might be due to the different threshold characteristics of the hypoglossal and phrenic neurons. Many studies (Van Lunteren and Strohl, 1986; Hudgel and Harasick, 1990; Adachi et al., 1993) reported that the inspiratory activity of the upper airway muscles slightly precedes that of the diaphragm in normal situations. Cherniac and Longobardo (1986) assumed that disturbance of the feedback rhythm may trigger recurrent apneas. Mathew (1982a, 1982b, 1984) hypothesized the presence of an afferent pathway which regulates GG activity in response to upper airway pressure loads. The presence of afferent limbs of this reflex in humans was confirmed by several groups (Chadwick et al., 1987; Horner et al., 1991ab). McNicholas et al. (1987) verified this by an experimentally induced OSA in topically anesthetized upper airways of normal adults. Moreover, a recent animal study proved the connection between hypoglossal activity and negative intraluminal pressure in vagotomized and artificially ventilated cats (Haxhiu et al., 1992). Reflex stimulation was suggested for one of the treatment modalities (DeBaker, 1993).

1.3 Interactions between anatomy and muscle function

Tongue position is thought to determine the volume of the oropharynx and the hyoid bone position may govern the hypopharynx volume. Contraction of the GG and hyoid muscles advances the tongue base and dilates or stiffens the upper airway. However, such activity does not always indicate actual muscle shortening since the muscle shortens only when contractile forces overcome an external load (Pae, 1989). Therefore, the airway volume, supposedly determined by the orientation of the upper airway muscles, is not necessarily proportional to the muscle activity. As Mezzanotte and
his associates (1992) demonstrated, augmented GG activity in awake OSA patients may be a neuromuscular compensatory response to abnormal airway anatomy that is required to maintain airway patency. A simple mechanical outcome produced by upper airway muscle geometry without any neural inputs may modify the upper airway volume as well. Van Lunteren and his group (1987ab) studied the relationship between hyoid muscles and hypopharyngeal volume. They observed a significant linear correlation between increases in the upper airway tidal volume and geniohyoid muscle shortening during the inspiratory phase. Upper airway volume may be altered by various reflexes which have afferent arms in upper or lower airway structures. Fouke and Strohl (1987) demonstrated that lung volume change did not affect pharyngeal volume in anesthetized animals. A recent observation by Burger and colleagues (1992) confirmed that lung volume, upper airway size, and GG EMG activity are mutually proportional at Total Lung Capacity in normal subjects. In contrast, there were significant changes in the upper airway size without any significant change in GG activity at low lung volume from tidal breathing, to exhalation, to residual volume. They postulated biomechanical interactions rather than a vagal reflex between thoracic structures and upper airway dimensions.

1.4 Supine cephalometric OSA studies

In spite of the obvious limitations of looking at 3D structures with a two-dimensional method, cephalometrics has recently become an auxiliary diagnostic tool for evaluating the size of the tongue and airway. Since Riley and co-workers (1983) introduced the conventional upright cephalometric analysis to OSA research, several groups have applied cephalometric analysis to OSA (Tsuchiya et al., 1992; Pepin et al.,
However, only a few studies have been undertaken in the supine position (Pae et al., 1993; Yildirim et al., 1991, Hoffstein et al., 1991). Since the supine cephalometric techniques utilized by each laboratory were developed by their own philosophies and protocols in accordance with their own facilities, obtained results drew diverse conclusions. Pae (1989) first attempted this modified cephalometric technique and reported preliminary data. His study suggested that the supine cephalogram may be a more logical tool and may deliver more physiological information. However, in their extensive review on lateral roentgenograms in the upright and supine positions, Hoffstein et al. (1991) concluded that the supine roentgenogram did not differ from the upright in linear measurements of the upper airway. Moreover, it did not provide any diagnostic clue to distinguish apneic from nonapneic snorers. In contrast, Yildirim et al. (1991) advocated that the supine cephalogram during wakefulness may be the best practical diagnostic tool. Furthermore, they observed many significant differences between the upright and supine positions in the linear measurements and also between the normal and apneic patient. The study by Pae et al. (1993) actually observed several dynamic changes in the upper airway structure. However, there were inevitable limitations to demonstrating the dynamic change by means of distance and area measurements. A great deal of imagination may be required to figure out what has occurred and how it occurs in the upper airway in accordance with the symptom severity and during body position changes. Each separate measurement of linear distance or area only informs whether each measurement is changed or different. It does not show either overall relationships between structures dynamically, or how much of the change has occurred. Several recent reports strongly
emphasized the role of pharyngeal shape on modification of OSA severity (Rodenstein et al., 1990; Brooks et al., 1989). Hudgel (1992) argued that anatomic narrowing actually contributes to OSA in some but not all patients, and pharyngeal size per se may not be a primary etiologic factor. Nevertheless, the literature postulates that there may be substantial differences between OSA patients and normal subjects in their upper airway structures. The inner structural difference and its morphologic expression in OSA patients may originate from genetic characteristics (Redline et al., 1992; Guilleminault and Quera-Salva, 1990) or from a pathophysiologic compensation (Davies and Stradling, 1991; Zucconi et al., 1992). Whichever is the case, scrutiny of the anatomical expression of symptomatical anomalies must be the first step in approaching the question. Function is important in understanding the pathogenesis of OSA, as is form and structure. Approaching the pathophysiology of OSA from the aspect of shape not size might uncover a veiled aspect.

2. Landmark Data

2.1 Landmarks and homology

Landmarks in biology may be defined as generally identifiable discrete loci which usually carry biological meaning (Bookstein, 1991; Lele and Richtsmeir, 1990). Homology is an important concept in morphometrics since it is the unique notion which bridges biology to geometry using landmarks as a medium (Bookstein, 1991). Homology may be defined as correspondence caused by a continuity of information (Van Valen, 1982). In traditional biology, homology may be used to indicate corresponding structures of apparata or organs; for instance, the homologous organ to the human arm in the bird
is the wing. Roth (1988) subclassified homology into two types. First, phylogenetic homology exists between characteristics of different organisms or taxa. Second, iterative homology is a correspondence between different structures within a single individual; for instance, α and β chains of haemoglobin. The concept of homology in the context of morphometrics, however, is a linear mapping function which relates points to corresponding points instead of a part to a part (Bookstein, 1991). The points are landmarks. Therefore, landmarks that are considered biologically homologous depict a spatial structural configuration. A group of spatial structures denoted by landmarks must have a biologically explicable covariance amongst themselves or with other exogenous phenomena. A landmark set in one organism should be homologously related to another set of landmarks in another organism where the morphological relationship may be smoothly linked by a mapping function in the context of deformation (Bookstein, 1991). Thompson (1917) stated that transformations may be a process of size and shape changes relative to others, so our descriptions of form may be equivalent to describing relations among those forms. To recap, deformations may be a substrate in which we search for evidence of explicable biological process (Bookstein, 1991). As deformation is redefined as the smoothly altering rearrangement of configuration described by landmarks in Thompson’s notion, biological process or morphological difference between two structures may be delineated by smooth mapping from one form to another and interpolation between them. The role of homologous landmarks may be to link first, the geometry of data, second, the mathematics of deformation, and third, the explanation of biology.
2.2 Why landmark data?

2.2.1 Why not inter-landmark data?

The inter-landmark data that refers to measurements of distances has been employed in conventional morphometrics. As a counter expression of the inter-landmark data, landmark data analysis and its application to biology was enriched recently with the development of an imaging technique (Bookstein, 1984). Bookstein first provided a statistical ground for analysis of landmark locations as raw data. While advocating the advantages of landmark data analysis, he abridged several shortcomings of the inter-landmark data analysis into two arguments. Primarily, the inter-landmark data abide with multicollinearity. Multicollinearity indicates the condition which arises when some or all of explanatory variables are so mutually correlated that it becomes difficult to disentangle their influences and obtain a reasonably precise estimate of their effects (Elliot, 1985). Previous morphometric studies on OSA subjects evidence a strong multicollinearity amongst variables (Bliwise, 1991) which presumably comes mainly from size allometry, and also from redundancy of the variables (Bookstein, 1990). Inter-landmark distance variables inevitably bear a mixed concept of size and shape and cannot escape from size allometry. Conventional methods utilize distances and angles as variables in analyzing actual landmark locations. Therefore, to measure a biological object may be to know the relative locations of the landmark points of the object. Distance is comprised of two landmark points and an angle requires that three landmark points be measured. If the substantial purpose of the measurements of a biological configuration is to numeralize the relative positions of the landmark points, then there is no reason to measure them redundantly. Redundant variables yield redundant eigenvectors of the matrix without
providing any further information, and thus make an eigen structure of the matrix unstable (Bookstein, 1991). More crucially, there is a conceptual reason to avoid inter-landmark measurements. In morphometrics, biological configurations are measured and compared in the context of homology. This concept is a crux which sustains whole ontogenic and phylogenetic studies. Conventional inter-landmark measurements carry this concept only implicitly. As soon as the form of a structure is altered to interlandmark variables, the geometry is eliminated. The only geometrical remnant is a statistical vector space which cannot be easily translated into two- or three-dimensional morphological space. Multivariate analyses utilizing the traditional distance measurements simply link the linear combination of variables to biological form changes whatever its meaning may be (Bookstein, 1990). Therefore, biologists should rely on their imaginations for much of the interpretation rather than simply reading the numbers given to them. Since it is hard to register the absence of geometry, it is hard to localize changes or differences (Moyers and Bookstein, 1979; Moss et al, 1980). Furthermore, linear measurements can also lead to spurious correlations. The morphometric correlation matrix composed of inter-landmark measurements may contain the arbitrary geometry of the linear dimensions in addition to the biological structures (Cheverud and Richtsmeier, 1986).

2.2.2 Why landmark data?

As well as the theoretical advantages of the using landmark method, analyses employing landmark points affix some more pragmatic reasons which are to be recommended. The role of landmark points in morphometrics is to mediate between homology in biology and geometry in mathematics. Morphometrics and geometry share
a common root in their inceptions. The term morphometrics is a compound word which originates from Greek 'morph-' which means shape and 'metron' which means measure. Geometry is a branch of mathematics which deals with form. Geometry has evolved since the Pythagorean age or maybe earlier, and has developed numerous paraphernalia for the analysis of forms. Recent conceptual advancement in topology and technical progress in computer graphics grant boundless applicabilities in diverse fields. Morphometrics may share a large part of its domain with geometry. Appropriately determined homologous landmark points correlate biology and geometry, and readily provide visual presentations.

Another reason for recommending the use of landmark data analyses is that position change of landmark points denotes physical vector change. In other words, interlandmark variables indicate scalars, whereas landmark variables represent actual vectors that accommodate physical distance and direction as well. Vector changes provide more direct information than scalar expressions of quantities. Statistical evaluation of the landmark variables supplies information in the context of vector changes, therefore it is more direct. The spatial statistics, that is the study of spatial patterns by statistical means, visualizes hidden patterns and smoothenes the landmark data to summarize the image (Ripley, 1982). Even for researchers who have an adequately trained mind in mathematics and statistics, the advantage of visual presentation cannot be over-emphasized (Newton, 1978). Modern computer geometry enables researchers to see the contents of a theoretical exposition which was invisible a few years ago, thereby suggesting new postulation by the eyes rather than the mind. The statistical tools integrated with landmark data may mean virtual advantages in this regard and play versatile roles in the field of biology.
2.3 Outline data

When Lestrel (1989) explained a Fourier function method, he suggested a significant advantage of this technique, which was applicable to morphologies having no discernible homologous landmarks. Straney (1990) summarized that there are three basic strategies to use to overcome the inappropriateness of measuring forms which lack landmarks: first, mathematical modelling of an outline itself; second, using arbitrary pseudolandmarks of convenience; third, constructing proxy landmarks on the mathematically transformed outline. Methods in the first category model the shape of an outline mathematically. Examples for the first strategy are Fourier Analysis (Lestrel and Kerr, 1992; Rohlf, 1990) and its cousins. Euclidean distances between corresponding homologous points on an outline are presumed to bear homology. However, the arbitrariness of the correspondence in reality is inevitable. The second approach takes landmarks which measure the longest, widest or shortest dimensions between the extreme points on an outline. This arbitrariness confounds errors, which limits this method to the comparison of similar shapes. Another form of the method categorised in this type utilizes derivatives. Eigenshape analysis, (Lohmann, 1983; Lohman and Schweitzer, 1990) which is an improved form of Zahn and Roskie's (1972), takes the first derivative from a certain segment of the outline as a homologous measurement. However, eigen analysis of the linear function of first derivatives could not always generate the same eigenshape, particularly in complex biologic objects. Moss et al. (1993) recently utilized a similar type of method for facial profile analysis. The third type is an improved form of convenience landmarks. By invocation of the power of geometry, the arbitrariness of these methods can be minimized. The medial axis method (Grayson et al., 1986; Daegling, 1992) utilized
for the current study is an example. The medial axis method employs outline data but creates a set of reproducible landmarks and they still carry a homological meaning.

3. Basic Concepts in Landmark Data Analysis

3.1 Circular normal model

To analyze data gathered in the form of landmarks, the concept of a circular normal model provides a theoretical ground for all hypothetical tests for statistical inference. Bookstein (1984) assumes a null model in which every landmark is distributed about an unobservable centroid by independent, identically distributed (i.i.d.), normal perturbation (which is defined as a slight change in the values) in each x- and y-coordinate separately. The isotropic distribution of errors may not be observable in real situations, yet it is convenient to assume them normally distributed like normally distributed residuals in ordinary statistical cases (Goodall, 1991). This circular error perturbation includes instrumental errors and measurement of error of landmark locations like Baumrind and Franz pointed out (1971) but excludes inter-individual variation as proposed by Goodall (Goodall, 1986). Upon this model, one can apply any conventional multivariate statistical method to test the significance of group differences in shape, or association of shape with size, without ambiguity. The isotropical random distribution of shape coordinates indicates that the two shape coordinates have the same variance and no covariance regardless of the mean shape of the triangle and the choice of baseline. In order to perform any of the landmark data analyses, we need to assume a probability model which comprises a set of three fixed points of the population mean landmark locations, about which the observed data perturb by i.i.d. measurement errors.
in each Cartesian coordinate individually.

The assumption of circular normal residuals in a null model implies that signals which might carry a biological meaning are likely to be associated with a deviation from circularity, e.g. elliptical distribution. Elliptical distributions may be generated from the superimposition of two sources: first, normally distributed values, along a line in variable space; second, circularly distributed noise (Bookstein, 1991). The source of the second variation may be digitizing error and random biological variability, etc. In order to interpret the first factor appropriately, one must account for the effect of size variation, or sometimes, the effect of an exogenous covariate such as severity of OSA which is the target of the current project.

3.2 Distances in morphometrics

All linear multivariate statistics utilize summed-squared distances as a basic metric device to measure likeliness or difference between groups and variables like physical distances in physical space. Association in ordinary statistics is measured by the squared distance between variables in different cases, which is usually transformed into an array of cross-products of the distances, i.e. a matrix. In most cases of statistical analysis, this notion of distance cannot be observed or measured directly; for instance, distance between an achieved grade in biology and the attitude of patients in dental clinics. In landmark data, however, distance denotes a physical distance. Therefore, the statistical distance between two structures in landmark data indicates differences in the physical form between two configurations. Morphometric distances express the patterns of relative location among the landmarks and between the organisms.
4. Morphometrics

4.1 Background, shape and size variables

4.1.1 Background

The relationship between size and shape has long been an arduous subject for researchers working in systematics and taxonomy (Medawar, 1945). Assessing the relationship of size to shape (size allometry) often clarifies the results of morphometric studies. Moreover, when one wants to study shape only, size variation may be a mere noise. From such a viewpoint, a clear differentiation of size and shape must be the basic goal for every morphometrician. Needham (1950) introduced a useful distinction of the term "shape" from "form" and conveniently symbolized it by the equation: form = shape + size. Before the 1950's, however, morphometrics in a modern concept was only scouted in sporadic fashion by a few scholars including Thompson (1917, 1952) and Wright (1932). In 1960, Jolicoeur and Mosimann attempted to separate size and shape variation in one-dimensional measurements by a principal component analysis and their work was pursued by others (Jolicoeur, 1963; Burnaby, 1966). Along with the development of multivariate statistics, multivariate morphometrics emerged as a branch of morphometrics in the early 1970's. Mosimann continued a quest for size and shape variables (1970). Blackith (1960) and Reyment (1971) brought in ordination techniques in taxonomy. Blum cultivated the field of morphometrics in his own philosophy (1964, 1973) and invented medial axis methods (Blum and Nagel 1977). Around this time, Bookstein quantified the Cartesian transformations and linked statistics to geometry (1977). The past two decades could be said to have been a period of re-evaluation and refinement of the ideas already developed (Reyment et al., 1984).
Thompson's transformation grid (1917) provided rational substrata for three different streams of morphometric approaches all of which were built upon landmark data; Procrustes methods, finite element methods and Bookstein's statistical transformation models. Procrustes methods have their origin in Sneath's trend-surface analysis of transformation grids in 1967. Two objects were expressed in terms of x,y-coordinates set and translated, rotated and scaled to find the best fit. Gower (1970, 1971) retreaded the idea by means of matrix operations and further developed it into a generalized method (1975). Rohlf and Slice (1990) developed an algorithm of resistant fitting rooted in the idea of nonparametric analog in order to rectify one of the frail points of the Procrustes method. Recently, Procrustes analyses were authenticated as multivariate shape analyses. Goodall (1991) consolidated Procrustes theoretical foundation on the basis of the Gaussian model and provided a ground for inference tests. The second stream consists of finite element methods (FEM). The finite element technique was initially developed for the field of engineering. Niklas (1977) first brought this technique into the field of biology to describe changes in the continuous non-linear growth and geometry of plants. Cheverud and associates (1983) applied this technique to morphometrics by incorporating it into the scaling method (Lew and Lewis, 1977). This anthropometric scaling method conveniently normalizes size, location, and orientation while describing a homogenous deformation with arbitrary principal directions. The finite element scaling method arbitrarily divides a biological object into elements and quantifies the transformation from one form into another. The third one is Bookstein's shape coordinates and Thin-Plate (TP) spline method. In 1977, Bookstein implemented landmarks and his famous biorthogonal grids that displayed integral curves of principal strains to investigate hominid skull phylogeny.
He invoked geometry to equip Thompson’s transformation grids with a mathematical ground. However, the biorthogonal method was not a popular morphometrical technique due to analytical difficulty (Cheverud et al., 1983). Bookstein’s new morphometric tools (Bookstein, 1986, 1989a; Bookstein and Sampson, 1987) surmounted the problems of the biorthogonal method and other morphometric methods. Bookstein suggested a more simple approach to shape analysis which is grounded in the assumption of a spherical Gaussian distribution of landmarks, and therefore is theoretically solid and versatile (1986). He proposed a convenient method to decompose form and variables based on the assumption of a circular normal model. Particularly, the TP spline method quantifies deformation with ease (Bookstein and Sampson, 1987, 1990), and it was found to be facile (Albrecht, 1991).

4.1.2 Shape and size variables

Angles or ratios may be the most common and oldest tools used to quantify shape (Mosimann, 1970). However, a ratio has several shortcomings. According to the empirical study by Atchley et al. (1976), a ratio does not eliminate the effect of scaling variables but rather increases the correlation between the ratio variables and the original scaling variables. Secondly, a ratio increases the non-normality of the distributions of data and the spurious correlation. Lastly, a ratio inflates the first eigenvalue of the correlation matrix together with changes of the coefficients on principal components too large in magnitude and direction. The next technique dealing with shape changes may be the ordination technique (Blackith and Reyment, 1971). This technique maximizes the differences among groups with respect to within group covariance by means of
discriminant functions and canonical axes. However, size or shape variables must be assigned *a priori* (Humphries, 1981). Therefore, these techniques do not contribute to partition of size and shape. Thirdly, techniques grounded on principal component analysis or factor analysis, which basically utilize linear combinations of variables, have been introduced (Flessa and Bray, 1977; Mosimann and James, 1979). When all measurements employed are *a priori* to be lengths, the principal factor score of factor analysis may indicate General Size (GS) (Bookstein et al., 1985). GS may be a fairly legitimate size variable derived from factor analysis (Bookstein, 1989b). Factor analysis computes a latent variable in relation to the observed covariance matrix. The first explanatory factor which usually corresponds to joint increases of variables is interpreted as GS. GS is usually comprehended as an underlying growth trend due to its consistent positive loadings. Allometry embedded in the coefficients is indicated by unequal loading of variables on GS. Nevertheless, shape does not necessarily appear explicitly in a factor model (Bookstein, 1989). If the residual errors of regressions on the factor score do not reveal meaningful covariances with other variables, then they should be considered as noise. Overall, GS cannot differentiate shape from residuals. Likewise, principal component analysis cannot cleave size and shape either. Although there are several modifications such as sheared principal component analysis (Rohlf and Bookstein, 1987) and size-constrained principal component analysis (Somers, 1986), principal component analysis simply rotates the data set from the measured original variables to new variables along the principal axes. Nonetheless, one hopes that the first principal component will inevitably express size. However, what we observe may, in fact, be arbitrary (Mosimann and James, 1979). Furthermore, the ubiquity of negative signs for the second component are not shape
components but mere artifacts.

Bookstein introduced a simple geometrical manoeuvre to decompose size and shape (1986). Assume a simple morphometric structure: a triangle, ABC digitized in a Cartesian table, where landmark A is at \((x_A, y_A)\), B is at \((x_B, y_B)\) and C is at \((x_C, y_C)\). (Fig. 1).

1. Choose one pair of any homologous landmarks, for instance A and B.

2. To normalize scale and orientation, the two landmarks, A and B, are fixed at a constant separation. The coordinates \(x, y\) of the point A are fixed at the location \((0,0)\), and the coordinates of the point B are fixed at the point \((1,0)\), so that we standardize the scale of the cartesian coordinates table accordingly. By restricting two landmarks in this way, the size of the triangle ABC is partialed out and its shape is encoded in the remaining aspect of the data, \(i.e.\) the third point remains free to vary, and thus uniquely carries the characteristics of the triangle.

This third point C is called "the shape coordinates of landmark C to the AB baseline". Goodall (1991) expressed it \(\rho_{2k-4}(U_k, V_k)\) and named it as Bookstein's shape coordinates. Each of the shape coordinates \(\delta_1, \delta_2\) where

\[
\delta_1 = (x_B-x_A)(x_C-x_A) + (y_B-y_A)(y_C-y_A) / (x_B-x_A)^2 + (y_B-y_A)^2,
\]

\[
\delta_2 = (x_B-x_A)(y_C-y_A) - (y_B-y_A)(x_C-x_A) / (x_B-x_A)^2 + (y_B-y_A)^2.
\]

They are employed as variables, and so variation in location of the third landmark in a certain space conveys a message. This method elegantly separates shape from the mixture of the concept of size and shape.
Figure 1: Construction of the shape variable. The upper panel shows a triangle ABC arbitrarily located in a Cartesian table. The lower panel demonstrates a position and orientation normalized triangle ABC with respect to the baseline AB.
The simplest size variable may be the distance between any pair of \( K \) landmarks. As long as the selected landmarks describe the entire form of a biological object faithfully, the sum of all squared distances between the landmarks in pairs \((s|X_i - X_j|)\) can be employed as a size variable (Bookstein, 1986). Standardization of size by any variable explicitly measured, regardless of its unit, confounds variation of that unit (Bookstein 1990). Bookstein (1986) introduced a geometric size variable, Centroid Size (\( S \)), which may be statistically equivalent to the sum of distances from each landmark to their joint centroid \((S = \sum d_j)\) which is much less redundant. (Fig. 2). Centroid Size supersedes other size variables such as area, perimeter, truss, and first principal component in the aspects of simpleness, robustness and versatility. The Centroid Size is uncorrelated to shape coordinates, and it explains nothing but size, therefore we can test the existence of allometry. Bookstein demonstrated this in a geometric way (Bookstein, 1991). Instead of showing the relationship between Centroid Size and shape coordinates directly, Bookstein demonstrates the covariance between shape coordinates and baseline first. He then positions the coordinates in a special location to the baseline which yields a zero covariance vector between them. The specific location is the unique position at which the covariance vector of the coordinates and the associated baseline pass through the centroid.

Allometry is the study of differences in shape associated with size (Spernt, 1972). When Cock (1966) discussed growth and form in animals, he introduced the term "static data" from which the element of true ontogenic growth is completely absent. Cheverud (1982) statistically confirmed Cock's idea and suggested a new term "intraspecific static phenotypic allometry" which infers mere changes in shape in static
Figure 2: Construction of the size variable. The sum of all the interlandmark distances, $z_iX_j - X_i$, is utilized as the size variable. This variable is equivalent to the sum of the distances, $d_1, d_2, d_3,$ and $d_4$, where the point $S$ is a centroid of the rectangle $X_1, X_2, X_3,$ and $X_4$. 

The sum of all the interlandmark distances, $z_iX_j - X_i$, is utilized as the size variable. This variable is equivalent to the sum of the distances, $d_1, d_2, d_3,$ and $d_4$, where the point $S$ is a centroid of the rectangle $X_1, X_2, X_3,$ and $X_4$. 

26
data. If it is assumed that the size factor is something linear, on the assumption of circular landmark location error, the existence of size allometry can be tested by the multiple regression of Centroid Size on any shape coordinates. However, the significance of the coefficients of this regression does not necessarily describe whether there is allometry or not. Allometry, which will be dealt in the current project, may be static.

For shape measurement, the scale of morphology need not be taken into account, for once the geometric size of a landmark configuration is registered as a form of Centroid Size, one may select a baseline and standardize the scale and orientation to it. If the null model is assumed, the baseline is recommended to be the longest diameter of the form through the centroid. Yet all baselines are statistically equivalent and differ only in the amount of nonlinearity. Bookstein (1991) proved the invariance of changes in shape coordinates regardless of a baseline in complex space. This trait conveniently allows application of the multivariate statistical analysis. As long as a statistical method is invariant in variable space, a minimal change of a shape triangle vertex produces nearly the same findings regardless of the landmark pairs chosen for the baseline. MANOVA (Multivariate Analysis of Variance) and Hotelling’s $T^2$ are invariant for rotation and rescaling, yet factor analysis and canonical covariate analysis are not, since their axes are variant. Therefore, MANOVA and Hotelling’s $T^2$ test can be employed in morphometrical analyses using landmark data without ambiguity.

4.2 Transformations, topological mapping and interpolation

To analyze the array of shape variables by means of geometrical tools, some concepts need to be borrowed from the field of geometry. To interpret biological meaning
of form changes by means of statistics, a form should be expressed in a numerical manner in order to be pervious to morphometrical analysis, and this is a landmark. Form change, viz. transformation or deformation of K-landmarks is statistically analyzed in the context of K-2 vectors, for at least three landmarks are required to construct a form. However, vector space must not be confused with real space. What we want to observe in the data matrix is a biological process physically occurring in three-dimensional real space, not vector changes in algebraic vector space. For this, Lele (1991) constricted the rank of a shape matrix to two for 2D data and three for 3D data. Morphometric landmark data comprises two kinds of system structures: spatial ordering of landmarks and covariance matrix which carries some biological meaning of interrelationship among the landmark points. Bookstein (1991) surmised that the covariance matrix manifests the spatial structure of forms which include size and shape. Analyzing the covariance structure is the same as analyzing the physical spatial patterns of the landmarks of configurations.

Topology is a relatively new mathematical field which was not discovered until the 18th century. Topology deals with the geometrical facts of the continuous connectedness between the points on forms (Borowski and Borwein, 1989). The simplest topological mapping of a surface consists of a continuous distortion which transforms the entire surface into another form. This type of mapping is called a deformation (Hilbert and Cohn-Vossen, 1952). A point that is mapped onto itself under a mapping is called a fixed point of the mapping, and may be analogous to a homologous landmark mapping in biology. Since the mapping is continuous by assumption, the direction change of arrows from point to point must be continuous. Interpolation is defined as an approximation of a function between the values known a priori (Sard and Weintraub, 1971). Spline
interpolation techniques are based on fitting a curve within each of the intervals between the data points and choosing the parameters of the curve giving continuity at each data point (Ripley, 1981; Greville, 1969).

When one describes two different forms, it may be more obvious to explain them by employing the concept of deformation rather than a precise description of each one (Thompson, 1952). Thompson rationalized that form changes may be a process of size and shape changes relative to others. He also postulated that the direction and magnitude of the force which affects transformation may imply hypotheses of biological causation. Likewise, our descriptions of form may conduce to descriptions of relationships among those forms in terms of geometric deformations, i.e. relations between two forms may be expressed as deformations. Deformations may be a substrate revealing evidence of biological processes (Bookstein, 1991). Bookstein introduced the concept of a "factor" to substantiate the concept of deformation (1991). Deformation behaves much like a factor in the notion of a latent variable which accounts for simultaneous changes in several conceivable variables as a whole. As a number of variables change simultaneously with each other, we may be able to model each one as if it varies according to a regression upon the factor score which bears their global characteristics, where the regression coefficients are called loadings. However, the deformation factor is different from an unobservable latent variable since it is observable in the same plane where the data are scattered. Accordingly, their loadings also have a spatial and statistical structure. The loading is the standardized change in length i.e. change per original unit of length, and is therefore dimensionless. Deformation scatters may be decomposed based on this philosophy.
5. Components of Shape Changes

Bookstein (1985) asserted that any deformation is composed of a uniform part and non-uniform part in the notion of geometrics. In other words, any sample variation about a mean configuration has a uniform part and non-uniform part. These two parts occupy complementary subspaces within the entire vector space of the covariance matrix. Regardless of where the phenomenon lies, a covariance structure of the deformation can be decomposed into a global and a local shape change which is depicted in a coordinate-free way. The term "global" indicates "uniform" throughout a form graded smoothly from edge to edge. The term "local" is limited to a group of particular landmarks. The term "global" may be substitutable with "homogeneous", yet "inhomogeneous" may not totally correspond to the term "local." The term "inhomogeneous" may be closer to the term "non-uniform." The term linear (affine) or non-linear (non-affine) transformation bears a more differential geometrical notion of transformation. Uniform transformations in the current project may indicate gradients of shape changes.

5.1 Uniform deformation

Uniform deformation may represent gradients of shape change. However, what it actually indicates is a common global shape change in all coordinates between two configurations. Bookstein (1990) represents a suggestive figure to visualize the distinctions of differences between uniform and non-uniform transformations (Fig. 3A). In uniform transformation, a square in broken line is tipped with respect to the original picture in solid line, and it creates a projected image of the original form. The non-uniform transformation appears to bend the square, therefore the axis is also bent. The geographic presentation
of uniform transformation may be perceived in a visual metaphor. All uniform changes of shape coordinates are parallel to each other (see Fig. 3B). The length of each uniform vector change in a solid arrow is proportional to the distance from the baseline. The direction of the displacement vectors below the baseline are reversed. As depicted in the figure, the original polygon looks like it has been tipped or flipped, and lengthened with respect to the baseline AB. Uniform changes are all multiples of a single vector $\alpha(a_1,a_2)$ by a factor representing the means of the y-coordinate which corresponds to the distance from the baseline to each landmark. Uniform deformation can be computed from a decomposition of the covariance matrix of a shape change by means of the least squares technique. As previously noted, deformation behaves like a factor (Bookstein, 1991) i.e. a global tendency of shape changes. A single vector $\alpha$ can be considered as the factor.

For any change $(x_i,y_j)$ of shape of a coordinate pair, from the previous observation or its mean, the single factor prediction will be $(\alpha x_i,y_j) \cdot y_i \alpha$, where $\alpha = (a_x,a_y)$ is a standardized factor score. In a Factor analysis, the factor is standardized to have a variance of 1. Analogously, the vector $\alpha$ is standardized to match the expected displacement of distance at 1 from the baseline. If a factor $\alpha$ is denoted as the normalized factor score $F$ to the baseline length 1 and distance 1 from the baseline, the remaining errors around the factor score can be estimated in a fashion such as in psychometrics. If $x_i = a_i F + \epsilon_i$. Here, $a_i$ corresponds to $y_i$ in the current application which is the distance of each landmark from the baseline. This viewpoint may be directly relevant to Bookstein’s version of PLS (Partial Least Square) analysis.

In spatial statistics, a deformation study may be a study of landmark patterns that vary in a systematic way. This landmark pattern change sometimes exhibits preferred
Figure 3: Uniform and non-uniform transformations, and a common factor. The upper figures contrast uniform (left) and nonuniform (right) deformations. In uniform transformation, a square in broken line looks as if it is tipped with respect to the original square in solid line. The axes in a non-uniform transformation are bent (right). The lower figure demonstrates a common factor $a$ which is parallel to all uniform vectors. Each vector length is proportional to the distance from the baseline AB.
directions. This is called anisotropy (Ripley, 1982). Anisotropy is a simple quantification of small shape changes in Bookstein's tensor description (Bookstein, 1884). A tensor is a coordinate free form of a mathematical operator upon vectors (Moss, 1986). Likewise, anisotropy is the scalar quantity of a uniform transformation. Bookstein (1984, 1985) implements this numerical value to describe uniform shape changes. When one lets a general form of geometric anisotropy be $C(h)$, where $h$ is a small change, then $C(h)$ is a function of $(h'_{1} + h'_{2} + ... + h'_{k})^{1/2}$.

5.2 Non-uniform transformation

After extracting the uniform part of the shape change, a residual part of shape variation remains. When the uniform part comprises a small portion of general variation, the residual part should contain some biological explanation. Localization of deformation is, in a sense, a matter of whether or not neighboring landmarks move together with respect to others. In order to quantify and depict the non-uniform part of the shape variation, Bookstein (1987) suggested the use of a TP spline (Fig. 12). The TP spline method may demonstrate a canonical form of a non-uniform deformation in a coordinate free way. Thompson (1917) considered deformation to be a dynamic relation between two related configurations. He invoked the Method of Coordinates to express form changes. He delineated his work as follows: "We obtain a new figure, which represents the old figure under strain, and is a function of the new coordinates in precisely the same way as the old figure was of the original coordinates $x$ and $y$." (1917, p724). This quotation strictly describes the process of splining methods (Sard and Weintraub, 1971). If we presume a shape change as a deformation, then we can express it in a form of mapping function.
As deformation is re-defined as a smoothly altering rearrangement of the landmarks in the configuration, morphological difference between two structures may be depicted by the smooth mapping of one form to another and the interpolation between them (Bookstein, 1991). TP Spline demonstrates location of deformation and quantifies the deformation in terms of bending energy (E). The grid system conveniently depicts the gradation of localized bending E change. Two sets of coordinates before and after the change are fitted in the context of a surface spline interpolation. This method is mathematically robust and may encompass all the possible expressions of a pure inhomogeneity by a rigid translation of the coordinates. Uniform deformation effects equally all parts of the form and the second derivative of the change is the same everywhere, whereas the second derivative of the change in TP spline is different (Bookstein, 1991). A residual from uniformity is displayed by the TP spline in this manner regardless of what the uniform component of deformation is.

5.2.1 Thin-plate spline

The term spline originated from a tool known as a mechanical spline used by draftsmen due to the resemblance between the two (Wahba, 1990). The mechanical spline is a thin reed-like strip used to draw curves needed in the fabrication of cross sections of ships' hulls. Weights were placed on the strip to force it to go through given points. The free portion of the strip assumes a position in space that minimizes the bending energy. In general, splining is applied for smoothing or approximating scattered data. However, Bookstein utilizes a TP spline function for a general-purpose interpolation function which expresses a mapping that models a certain biological homologous organism sampled by
pairs of landmark points. The term interpolation means finding an intermediate term. Bookstein (1991) also demonstrated that the TP spline technique is adequate for the visualization of statistical analyses. TP spline interpolation is a synonymous term of surface spline interpolation, which is a method of fitting appropriate surfaces to arbitrarily scattered data (Meinguet, 1984). Micchelli summarized Franke’s interesting conjecture as follows (1984). Given any distinct points \( x^1, \ldots, x^k \) in the plane

\[ (-1)^{k-1} \det(1 + |x^i - x^j|^2)^{1/2} > 0 \]

Here \( |x|^2 = x_1^2 + x_2^2, x = (x_1, x_2) \) is the Euclidean norm of \( x \). Then, there is a unique surface

\[ f(x) = c_1 (1 + |x - x^1|^2)^{1/2} + \cdots + c_k (1 + |x - x^k|^2)^{1/2} \]

which interpolates data \( y^1, \ldots, y^k \) at \( x^1, \ldots, x^k \). Further, Meinguet proposed that the term \( |x^i - x^j|^2 \) may be physically interpreted as the bending energy of a thin plate of infinite extent.

The TP spline and its bending \( E \) has been applied in the field of computer vision and animation since 1983 by Terzopolus. Bookstein’s TP spline does an interpolation of a linear mapping function of two sets of coordinates by a surface splining technique. The algebraic crux of the TP spline method is provided in Appendix I. The next explanation about TP splines and bending energy may be a summary of Bookstein’s proposed conjecture in 1989. Deformation of the TP spline occurs in a direction orthogonal to the lie of the plate. One may imagine this displacement \( z(x,y) \) occurs on the coordinates \( x \) or \( y \). Hence, the scheme of the metal plate may be interpreted as the interpolation function between before and after distortion. For example, the \( x \)-coordinate is transferred from one scheme to another without change, whereas the \( y \)-coordinate is altered by the value \( z(x,y) \) which was the \( z \)-coordinate originally on the metal plate. Therefore, the
mapping function becomes

\[(x, y) - (x', y') = (x, y + z(x, y)),\]

where \(z(x, y)\) is the function \(z(-)^{k+1}U((x, y) - (i^k))\) in three dimensions. If a spline sheet is merely tilted, no bending occurs. To bend a plate requires energy; the sharper the bending, the greater the second derivatives of the surface \(z(x, y)\) and the greater the energy (bending \(E\)) required. Bending \(E\) is a metaphor which indicates the percentage of net displacement of landmarks but is not a function of the displacement. Bending \(E\) is the integrated scalar quantity uniquely determined between two shapes. It actually is a matrix of squared distances between notes on the flat plane and notes on a warped plane. Since the matrix is symmetric and orthogonal, we can perform the eigen-analysis with it. A bending \(E\) matrix produces a number of set of eigenfunctions in accordance with the number of involved landmarks. Each subset of the matrix is orthogonally projected toward each other, which may provide distinctions between each different landmark configuration. Bookstein (1989) termed them principal warps. The matrix \(L^{-1}_k\) (see Appendix I) was defined as bending \(E\) by Bookstein. This matrix has \(K-3\) non-zero eigenvalues. Each eigenvalue has a corresponding set of eigenvectors. The set of eigenvectors are coefficients for \(K\) of the function \(U\) based at \(K\)-landmarks. Each eigenvector may be interpreted as coefficients of a TP spline. Each spline expressed by each eigenvector set can be visualized as a pattern of deformation. Thereby, a bending \(E\) matrix bears \(K - 3\) number of warped splines each of which is lofted into the third dimension. The height of these surfaces at each landmark corresponds to the coefficient of an eigenvector. Therefore, integration of each spline constitutes a full spline. Although the net amplitude of vertical changes of the landmarks remains the same, the larger eigenvector, derived
from an eigenvector set, requires more bending $E$ than others. The eigenvector set, which
reveals more localized deformation, exhibits a higher rate of change in its grade system,
thereby accounting for higher eigenvalues.

In summary, morphometric data comprised by landmark coordinates may
provide more information than do conventional interlandmark data. Moreover, ample
geometrical tools e.g. the TP spline, enhance the versatility of landmark data. For
instance, an increment or decrement of an actual measurement can easily be displayed
on a Cartesian coordinate plane. Morphometric tools and their underlying assumptions
employed for the present study may enable the incorporation of diverse requirements from
researchers and clinicians and may legitimize applying multivariate techniques to a
morphometric study.

6. Partial Least Squares (PLS) Analysis

6.1 Background and characteristics

PLS analysis is a blend of regressions and principal component analysis, and
is simpler than other structural models. PLS has its origin in path models (Wright, 1960)
with latent variables (Wold, 1985). Since PLS does not require any assumption about the
population, scaling of measurements, or distributional requirements, Wold named it PLS
soft modelling as a general Least Squares (LS) counterpart to LISREL (Linear Structural
Relations) rather stringent modelling which uses Maximum Likelihood (ML) that was
originally developed by Jöreskog (Jöreskog and Wold, 1982). Wold (1982) explained that
PLS soft modelling is primarily designed for causal-predictive analysis of complex
problems that are usually data-rich but theory-primitive. The basic mechanics of PLS
analysis are the construction of latent variables, (LVs) by aggregation of common indicators which are directly observable variables and the simultaneous estimation of relations between the LVs, and each LV and manifest variables (MVs). Therefore, the analysis is initiated from the arrow scheme which relates MVs and LVs, and thereby constitutes a model. The arrow scheme is crucial, for it shows the theoretical-conceptual design (Wold, 1985). In general, the model structure comprises three components (Wold, 1982): blocks, inner relations, and outer relations. Linearly assembled indicators by definition constitute a block, the characteristic of which is manifested by an LV (Fig. 4A). The LVs are assumed to be interconnected by one or more relations called inner relations (empty arrow). An LV which is called 'exogenous' and its relation to MVs is defined as an outer relation (filled arrow). The two-block model has one inner relation and two-outer relations. LVs in Wold’s PLS models predict other LVs and MVs. Weight relations may be the most basic elements in PLS modelling. As the inner relations act as a vehicle which conveys information between blocks, the weight relations exploit the content of information involved in this process. Each LV is estimated as a weighted sum of its indicators, where weights are determined by the weight relations. The PLS estimation algorithms accord with various inner and outer relationship modes.

The PLS estimation algorithm is composed of three stages (Wold, 1982). The first stage is an iterative procedure to obtain explicit estimates of each LV by linearization of each weighted, centered value of indicators. The ensuing LV and loadings are numerically the same as the first principal component. To determine weights, one of the modes must be determined a priori for the weight relations. The iterative procedure starts with arbitrary values. The weights are computed by simple and multiple OLS (Ordinary
Figure 4: Command diagrams for two- and three-block analysis. A. X1, X2, and X3 represent indicators. I1, I2, I3 indicate outcome variables. LVx and LVy indicate latent variables in each block. LVi indicates the latent variable for apnea index variables. B. Opt symbolizes the optimization process of one block to another.
Least Squares) regressions. The iteration is subject to a conventional rule for cessation; for instance, $|w' - w''| \leq 10^{-5}$, where $w$ is a value of the weight. In the second stage, using the estimated values of LVs obtained from stage one, the multiplicative parameters of the block structure, the inner relation, and the causal-predictive relations are estimated. The simple OLS regression estimates the block structure without location parameters and also estimates the multiplicative parameter of the linear correlation between two LVs. The inner relations are determined with minimum variance. Estimated causal-predictive relations at this stage will provide several inferences for different situations. In the third stage, the standardized indicators to zero mean at the first step are now released, hence the location parameters are obtained for the entire model structure.

As remarked previously, the version of PLS analysis employed in the current work is somewhat different from the one originally designed by Wold. The crux of algebraic computation for the two-block PLS is explained in Appendix II. Multi-block modelling is an extension of the two-block modelling computation, but shows a combination of principal components and canonical correlation in its characteristics. What the PLS model tries to determine are two series of coefficients: first, regression weights (saliences) for inner relations whereby the latent variable affects the value of others. Second, item weights for outer relations which describe the manner in which the indicators determine their own latent variables. This effort is driven by two philosophies: inter-block suboptimality and simplicity (Bookstein, 1980). Each block in a model may be interpreted in the notion of a submodel which consists of one block and another block or blocks. Each block is communicated by explicit arrows which denote the association between the indicators of the one block and the other block variable(s). Since those submodels
overlap with each other, the results should also be interpreted as an interdependent system between latent variables, and also between LVs and items in the other block. Each interdependency seeks a most optimal association. For simplicity, an LV is characterized in terms of a projection of LVs upon the indicators of its own block. The unique principle in PLS computation for optimization is the minimum distance projection of the LV onto block variables. The optimization operation keeps replacing each tentative LV by a new linear combination of the indicators in its block. The new LV is always a new orthogonal projection. The command diagram in Fig. 4B illustrates the relationships amongst latent variables and the optimization operator. The arrows express not causation but associations of inputs and an output. The thick arrows stretching from LVi, i.e. the latent variable for the index block to each LVs comprised by indicators, are associated by optimization of each operator. The algorithm to obtain saliences and item coefficients for Bookstein’s version of the PLS procedure may be as follows:

1. Define each LV as an arbitrary linear combination of the indicators in its block.
   Reasonable starting values might be LVx = eX, for instance.

2. Determine the form of each Opt. command, e.g. a short sequence of regressions and linear combinations.

3. Execute all the Opt. command once.

4. Iterate the command until it arrives at where the LVs are consistent to some preset tolerance.

5. Replace each LV by the output, and return to step 3.

In summary, PLS conveniently summarizes inter-relationships among variables within a complex data matrix. Variables are to be gathered in a block manner in priori. In
a block, the PLS algorithm computes the most optimal linear combination of the variables in order to have the most optimized relationship between these variables and the LV of variables in the opposing block. PLS may be a useful tool to abstract the logical relation between the anatomical characteristics of OSA subjects and the severity of symptoms. Appendix III provides some fundamentals in multivariate data management.
STATEMENT OF THE PROBLEM

There has been ample evidence that OSA is strongly associated with an anomaly of upper airway morphology. Previous studies conjectured that size may be one of the main contributing factors of the pathophysiology of OSA. Even if the current data are sampled with no growth effect, variation around the measurements is expected to be large since it is presumed to be size confounded. Numerous studies on OSA subjects utilizing conventional cephalometrics have reported morphometric characteristics of the patients in numerical values of mixed sense of size and shape. However, one tends to take notice of the shape of a biologic form rather than its size, for it is the shape which delivers the impression of the biologic object promptly. When one wants to observe shape, size is mere noise. No study has attempted to weigh the effect of pure size on the severity of OSA. However, if size is over-emphasized as an etiologic factor, it may be hard to explain the existence of slim OSA patients and obese heavy snorers without OSA symptoms. Without quotienting this presumed overwhelming component out, one could not elucidate the other covert biological process, e.g. shape change which may be more important. Other than morphologic factors, numerous studies have proposed malfunction of the upper airway dilators as one etiologic factor which may be exposed in the supine body position during sleep. Cephalometrics in the supine position may facilitate a more physiologic interpretation of shape changes of the vulnerable airway upon the exogenous condition. The morphologic characteristics of OSA patients could be appreciated as a deformation from the normal state. In order to investigate whether deformations are significant or not, multivariate statistics must be implemented, since one perceives shape differences from a global view. Only a few morphometric studies have been undertaken.
on this notion. Geometry is analogous to a tool box that provides paraphernalia which facilitates intuitive understanding and summary of form. The conventional statistical morphometric studies which utilize interlandmark measurements deprive this emblematic advantage of geometry. As well, the traditional interlandmark data include a mixed sense of size and shape in their variables which are not readily separable. In contrast, landmark based morphometric techniques maintain the relative position between landmarks, thereby the position of each landmark depicts a geometry of its own configuration. Due to this advantage, abundant apparata in geometry can be applied to morphometric studies. Conventional statistical tools measure a statistical distance in interlandmark data, whereas what they evaluate in landmark data is a physical distance change in physical space. By virtue of this attribute, a form change can be decomposed into several features that are incommensurate to each other, yet can be dealt with using statistical tools in a separate dimension. The summary of landmark data from OSA subjects by PLS may abridge the intricate aspects of OSA.

This study proposes to answer the following questions by means of new morphometric techniques.

1. Are size and shape of the upper airway structures associated with OSA severity?
   After a simple geometric manoeuvre is used to decompose the anatomical structure into size and shape, the influence of each aspect upon OSA severity will be weighed.

2. Does a body position change evoke size and shape differences in the upper airway?
   Assessment of size and shape change in the upper airway will be carried out in the context of spatial statistics as the body position changes from upright to supine.
3. Are these new morphometrical tools versatile enough to answer these questions?

Versatility of the analysis techniques will be visually displayed and statistically proven.
MATERIALS AND METHODS

The current chapter is comprised of two major sections: data collection and data analysis. Data were collected over a four year period at the UBC Faculty of Dentistry and the Respiratory Sleep Disorder Clinic at the University Hospital. The data were analyzed by means of several custom made mnemonic biostatistics programs and a number of commercial statistics software programs.

1. Data Acquisition

1.1 Experimental subjects

To diagnose OSA, overnight hospital monitoring quantified electroencephalogram (EEG), electrocogulogram (EOG), electromyogram (EMG) and electrocardiogram (ECG) variables, naso/oral airflow and respiratory effort, oxygen saturation levels, anterior tibialis EMG and sleep position. The anthropometric, pulmonary function and overnight sleep study data utilized in this study were provided by the Respiratory Sleep Disorder Clinic. Subjects with ongoing respiratory infections, on any medication known to affect muscle activity, those who required orthognatic surgery, or edentulous subjects were excluded from the study. A total of 80 subjects were selected from patients referred to the clinic. The subjects were classified into four subgroups according to OSA severity: asymptomatic, mild, moderate and severe (Hoffstein et al., 1991). The severity of sleep apnea was evaluated by a combination of Apnea Index (AI), defined as the total number of apneas divided by the total sleep time in minutes, and Respiratory Disturbance Index (RDI), defined as the total number of apneas and hypopnoeas divided by the total sleep time in minutes (Quera-Salva, 1988). The
asymptomatic group included subjects whose AI ranged from 0-4 or whose RDI ranged from 0-9. The mild group included OSA subjects who showed an AI of 5-15 or 10-30 for RDI. The moderate subjects demonstrated 16-25 for AI or 31-50 for RDI. The severe group included subjects who had values higher than 25 for AI or 50 for RDI. The asymptomatic group consisted of 20 subjects who had no apnoeic symptoms. The mild group, the moderate and the severe group included 26, 17 and 17 subjects respectively.

Table 1 and 2 summarize the anthropometric data of the entire sample and of each subgroup. The average age of eighty subjects was 45.86 years. The weight ranged from 56 Kg to 148.5 Kg and the mean was 88.75 Kg. The average Body Mass Index (BMI = Weight (Kg) / Height² (m²)) was 29.39. The mean AI was 11.20, and the mean value of RDI was 26.63. Total Apnea Time (TAT) showed the mean value of 9.83 and a somewhat wide range of the standard deviation (s.d. = 14.15). Table 2 illustrates the mean values of demographic variables and their standard errors in each group. The mean value of age shows a weak tendency of increment as the apnea becomes more severe. ANOVA analysis confirms a P level of 0.05. Measurements on BMI (P = 0.002) and Weight (P = 0.001) increase in proportion to severity.

1.2 Cephalometry

A pair of cephalograms were obtained for each subject with the same cephalostat (Counterbalanced Cephalometer Model W-105, Wehmer Co.) under identical conditions with a source target distance of 165 cm, a film target distance of 14 cm, 90 kvp, 15mA, 1.25 sec in the upright standing and supine positions. To obtain upright lateral cephalograms, natural head posture was determined by visual feedback in a mirror.
<table>
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<th></th>
<th>mean</th>
<th>s.d.</th>
<th>min</th>
<th>max</th>
<th>median</th>
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</thead>
<tbody>
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<td>6.21</td>
<td>21.08</td>
<td>53.04</td>
<td>27.18</td>
</tr>
<tr>
<td>WT</td>
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<td>16.89</td>
<td>56.00</td>
<td>148.50</td>
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<tr>
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<tr>
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<td>23.88</td>
<td>0.00</td>
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<td>21.32</td>
</tr>
<tr>
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<td>0.00</td>
<td>83.60</td>
<td>4.81</td>
</tr>
</tbody>
</table>

**TABLE 1: Demographic variables and apnea index variables.** s.d. indicates the standard deviation. min and max indicate minimum and maximum values.
<table>
<thead>
<tr>
<th>AGE</th>
<th>ASYMPTOMATIC</th>
<th>MILD</th>
<th>MODERATE</th>
<th>SEVERE</th>
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<tbody>
<tr>
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<td>s.e.</td>
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<td>mean</td>
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<tr>
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<td>1.27</td>
<td>27.34</td>
<td>1.14</td>
<td>31.84</td>
</tr>
<tr>
<td>WEIGHT</td>
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<td>3.50</td>
<td>84.33</td>
<td>3.07</td>
<td>95.15</td>
</tr>
</tbody>
</table>

TABLE 2: Group differences in demographic variables. s.e. indicates the standard error.
Natural head posture in the standing position for each individual has been demonstrated to be highly reproducible and distinctive. The subject was required to stand 1.5 m away from and in front of the mirror. In a relaxed and natural body posture, the subject was instructed to swing his head back and forth and gradually reduce the magnitude of the swing. Finally, the subject stopped at his own natural head posture determined by his own feeling of a relaxed posture and sight. This procedure was carried out with the eyes closed first, then the second time with the eyes open and gazing in the mirror. A lead marker with a diameter of 5.0 mm was placed on the midpoint of the tongue tip with biocompatible adhesives (Iso Dent, Ellman Dental Inc.) to register the exact position of the tongue tip. The midsagittal junction of the tongue dorsum and the inferior mucous membrane was regarded as the anatomical tongue tip. After natural head posture in the upright position was decided, one tablespoon of the Microtrast Esophageal cream (Esobar, Therapex Inc.) was given. The dorsum of the tongue and upper pharyngeal airway were coated with the radiopaque cream to enhance radiopacity of the outline. Subsequently, the subject was instructed to stand on the footprint in the cephalostat and to reproduce his own natural head posture determined previously. A metal chain was suspended from the surface of the cassette to register a true vertical plane on the film. To obtain the supine cephalogram, the subject was instructed to lie down on a stretcher and to assume his own usual sleeping position. Pillow height was adjusted in accordance with each subject's testimony. The head position was determined after the patient had established his own comfortable, natural sleeping position. The supine cephalogram was taken with the jaw in a completely relaxed position. Finally, cephalograms were taken in the instructed position in both up-right and supine positions.
Figure 5: Supine cephalometric technique and a supine cephalogram. An arrow in the upper figure indicates a chain for true horizontal.
at the end of the expiration phase. Fig. 5 illustrates the posture maintained for
taking the supine cephalogram and an example of the supine cephalogram with the
anatomical outlines emphasized.

1.3 Landmark variables for the face (Fig. 6)

Landmarks were determined to best sustain the distinction of the upper airway
structure in subjects. Seven landmarks considered to best depict the facial configuration
were determined; Sella, Nasion, Gnathion, Gonion, Hyoidale, 4th vertebra, and
Submentale. All landmarks were coordinated with X and Y axis values, and these two
coordinates were employed as variables.

S Sella: The estimated centre of the sella turcica.
N Nasion: The most anterior point of the naso-frontal suture.
Gn Gnathion: The most inferior and anterior point of the mandibular symphysis
determined by a midpoint between Pog and Me on the bisecting line
of the angle formed by mandibular plane and facial plane.
Go Gonion: The most inferior, posterior and outer most point of the mandibular
angle, determined by a bisector of the angle formed by the tangent
to the posterior and inferior border line of the mandible.
H Hyoidale: The most anterior and superior point of the hyoid bone.
C4 4th Vertebra: The most posterior inferior point of the fourth vertebral corpus.
Subm Submentale: The intersect point of the inferior chin profile in the submental area
and a line through RGN parallel to the true vertical line.
Pog Pogonion: The most prominent point on the anterior surface of the mandibular symphysis with respect to the mandibular plane.

Me Menton: The most inferior point on the mandibular symphysis.

1.4 Landmark variables for the tongue (Fig. 6)

A total of eight landmarks were designed to be utilized for tongue shape change analysis.

TT Tongue Tip: The center of the lead disc attached on the transition border from ventral to dorsal surface of the tongue tip.

T1: A tangential point on the dorsal surface with the true horizontal line.

TH Tongue Height: The highest point of the tongue curvature relative to a line from E to TT.

T2: A tangential point on the dorsal surface with the true vertical line.

E Epiglottis: The deepest point of the epiglottis.

H Hyoidale: The most anterior and superior point of the hyoid bone.

RGN Retrognathion: The most posterior point of the mandibular symphysis along a line perpendicular to the FH (Frankfort Horizontal) plane.

C Tongue Centre: The arithmetic means of x,y coordinates of the rest of the seven landmarks.
Figure 6: Landmarks on the face and tongue. S (Sella), N (Nasion), Gn (Gnathion), Go (Gonion), H (Hyodale), C4 (4th Vertebra), and Subm (Submentale) are landmarks for the face. TT (Tongue Tip), T1, TH (Tongue Height), T2, E (epiglottis), H (hyoidale), RGN (Retrognathion), and C (Tongue Center) are landmarks for the tongue. An arrow on the left indicates the true vertical chain.
1.5 Interlandmark variables for the pharynx

Due to the difficulty of determining homologous landmark points for the pharynx, an intermediate geometric transformation of an outline configuration which supposedly still carries the traits of the original shape was utilized as a proxy of an archetype. The pharyngeal outline was defined as a soft tissue boundary of the posterior surface of the soft palate and tongue dorsum, posterior margin of the epiglottis, a line parallel to the palatal plane through C4, posterior boundary of the upper pharynx, and posterior margin of the posterior nasal aperture.

1.5.1 Medial axis

There may be several strategies to overcome the possible inappropriateness of placing landmarks. The medial axis method is an improved form of convenience landmarks which the current project invoked (Strany, 1990). Arbitrary forms of convenience landmarks can be improved in a sense of preciseness by means of a geometrical transformation without losing the concept of homology. The medial axis is the line constructed on the inside of an outline which is equidistant from the segmented outline on an object. The basic idea is that as the line segments of the outline are given, their tangents at the middle of the segments can be assessed directly and their medial symmetric axis line segments can be derived by a simple calculation. A closed outline of the pharynx can be transformed into a tree-like line skeleton in the middle of an outline of the pharynx. The algorithm of the medial axis program currently employed is as follows (see Fig. 7):
1. The outline segments \( O_i \) and \( O_j \) are extended as lines until they intersect at point A.
2. The line that bisects the interior angle at this intersection is calculated and named as \( L \). This line extends into the interior of the outline and runs midway between the outline segments.
3. The lines bisect the interior angles at each endpoint of the segments \( O_i \) and \( O_j \). These four lines (\( P_1, P_2, P_3, \) and \( P_4 \)) are called as pseudonormals to the outline.
4. The intersection points of each pseudonormal and the line \( L \) are calculated. The distances between these intersections and point A are calculated and ordered.
5. The middle two points of the ordered set are to be considered as the end points of a line skeleton segment defined by the two outline segments.
6. The outline segments for calculation of the next line skeleton are determined.

Elements of the line skeleton always position on an angle bisector of two outline segments. To extend the skeleton, the algorithm consumes the outline segments one at a time, and applies process 1 through 6 each time. The algorithm connects the additional elements in a chain-like fashion until it is completed.

Digitized outlines were divided into the same distance (2 mm) segments by a customized interactive program. Each pharyngeal boundary was preliminarily smoothed out and made to contain different numbers of segments after this process. The digitized numbers were formatted into fortran files and clustered in such a way as to feed into the medial axis program in the MTS system. The program MEDIAL.OBJ+*IG 8 computed a medial axis for a certain outline and provided outputs.
Figure 7: Construction of a medial axis. A is a point outside of the structure constructed by an intersection of the extended lines of the segments $O_i$ and $O_j$. A line skeleton segment locates on an extension line from the point A.
1.5.2 Determination of variables (Fig. 8)

A primary axis and three or four landmark points (P1, P2, P3, and P4) on the primary axis were utilized to constitute pharyngeal variables. In most medial axes of the pharynx, the rostral and caudal end of the primary axis were promptly identified. In the middle of the two points, frequently two, occasionally one constricted area was revealed. Four interlandmark distance variables and four ratio variables were measured by a ruler and protractor on the outputs of the medial axis program. Measurements were rounded-off by 1/2 millimeters or degrees.

LT Total Length: The total length of a primary axis.
LM Mid Length: The length between the two points at the constricted area.
W1 Narrow Point: The width at the most narrow point.
W2 Wide Point: The width at the most wide point caudal to W1.
WR Width Ratio: The ratio of W2 to W1.

\( \theta_1 \): The angle constructed by a line that connects P1 P2 and a line that connects P3 P4.

\( \theta_2 \): The angle constructed by a line that connects the anterior point of W1 and W2 and a line that connects the posterior point of W1 and W2.

LT/W1: The ratio between LT and W1.
Figure 8: Measurements on the pharynx. Points P1, P2, P3, and P4 are determined on the primary skeleton. Four linear lengths (LT, LM, W1, W2) and two angles ($\Theta_1, \Theta_2$).
1.6 Data transformation

2D structures of the face, tongue and pharynx were traced on acetate paper with a 0.5 mm pencil for each of the landmarks and outlines. Boundaries were outlined in the middle of tissue transition zones to take into account averaging. A data entry program was written to permit digitization (HP Model 9874) of the cephalograms. A cross-hair cursor was used to enter the points and contours of each structure into the PC computer (HP Vectra). Grouping programs were utilized to cluster the data files into four subgroups for each of the anatomical structures. The grouped landmark data files for the face and tongue were standardized with respect to the designated baseline with a converting program. The data files for the pharynx were subgrouped as well. All the files were manipulated in the commercial program LOTUS and transferred into the commercial statistical package SYSTAT.

2. Data Analysis

2.1 Analysis of the landmark data

To obtain biologically meaningful interpretation by statistical analyses, determined landmarks must bear some explanation of the biological process. Landmarks provide information about the relative position of biological structures. The relative position of each homologous landmark is maintained in a form of coordinates which carries the spatial information in a certain dimension, thus landmark points carry information about size and shape. When one attempts to analyze morphology of a biologic structure, size and shape may be a major concern. According to the purpose of the current project, size and shape were decomposed.
2.1.1 Construction of the size variables

Numerous works have attempted to disjoint shape and size for two main reasons: to develop a variable which immaculately expresses the growth factor and to avoid the multicollinearity problem among variables when size contamination is believed to be a main cause. Size may be more explicitly clarified after a definition of shape is determined. Shape may be what remains after the size, position, and orientation effects are filtered out (Kendall, 1989). Therefore, size variables must be independent from shape variables. Bookstein (1991) ascertained the independence of these two variables as described in the literature review. When there are associations between size and shape, the association may be interpreted as the existence of size allometry. A constructed landmark variable, Centroid Size (S), which is the root-summed-squared set of interlandmark distances, was employed as the size variable for the current project (see Fig. 2). The root-summed-squared set of interlandmark distances employed as Centroid Size variables were calculated on the face and tongue using the program LOTUS. The number of segments of the pharyngeal outline was employed as a size variable in the pharynx. Allometry conjuncts the relationship between size and shape. It is assumed that size behaves like a linear factor. On the assumption of circular landmark location error, the existence of size allometry was tested by the multiple regression of Centroid Size on shape coordinates. The equation used was:

\[ \text{Centroid Size} = \text{constant} + x_i + y_i, \]

where Centroid Size and shape coordinates are mutually independent by definition. Significant associations indicate the existence of a size effect on shape changes.
2.1.2 Construction of shape variables and baselines

Decomposition of size and shape was attempted. A customized computing program that standardizes landmark points with respect to a baseline executed a simple geometrical manoeuvre (Fig.1). To determine an appropriate baseline, circular normality of each raw coordinate data was evaluated. In accordance with the principles of baseline selection, a few pairs of candidates which represented the most random circular normality were selected. In general, a long baseline that crosses close to the centroid of the structure tends to exhibit a better understanding of the mean vector changes. Preliminary examination by TP spline interpolation of the mean vectors of the landmarks with respect to a predetermined baseline also aided baseline selection.

2.1.3 Evaluation of average shape changes

The method to obtain averaged forms of homologous landmark configuration includes:

1. Select a baseline to construct shape coordinates.
2. Normalize scale and orientation of the configuration in accordance with the baseline.
3. Compute the vector of mean shape coordinates to the determined baseline.
4. Draw out the configuration of landmarks with the baseline scaled to its size.

Since one perceives shape difference from a global view point, the appropriate tests for shape difference should be multivariate methods. The appropriate test for differences between two groups may be Hotelling's $T^2$. The test for more than two groups may be MANOVA (Spielman, 1973). If shape scatters look roughly circular without striking outliers, and one can safely assume normal circular perturbation, one can employ
multivariate statistical methods which do not generate distorted matrix space such as MANOVA or Hotelling’s $T^2$, as mentioned previously. The statistic $T^2$ is called Hotelling’s $T^2$, named after Harold Hotelling who first obtained its sampling distribution (Johnson and Wichern, 1988). The $T^2$ is an alteration of the notion underlying the Student’s $t$ test. $T^2$ is the squared ratio of an observed mean difference to its own standard error analogous to $(t^2)$. If the observed generalized distance $T^2$ is too large, the observed mean $X\bar{}$ is too far from the population mean $\mu_0$, thus the $H_0: \mu = \mu_0$ is rejected. Special tables of $T^2$ percentage points may not be required for formal tests of hypotheses, since $T^2$ follows an F-distribution. The $T^2$-statistic is invariant with changes in units of measurements (Rao, 1973). MANOVA investigates whether population mean vectors are the same, and if not, which mean components differ significantly. Assumptions regarding the structure of the data for inference are (Johnson and Wichern, 1988):

1. All samples are randomly selected from an independent population.
2. All populations have a common covariance matrix $\Sigma$.
3. Each population is multivariate normal.

Condition 3 may be relaxed by invocation of the assumption of the circular normal perturbation. Observation vectors may be decomposed into variation between (B) groups and within (W) each group. $\Lambda = |W|/|B + W|$ When the quantity $\Lambda$ is too small, we reject the null hypothesis $H_0$. $\Lambda$ is read Wilk’s lambda. For large sample sizes, $\Lambda$ has approximately a chi-square distribution. Thus, we test the null hypothesis accordingly.

The statistical package SYSTAT was utilized to execute Hotelling’s $T^2$ and MANOVA tests. Both tests employed F-test as a significance test in SYSTAT. The PRINT = LONG command provided standardized estimates of effect, total and residual sum
of squares and cross product matrices, mean, and standard deviations for each cell. The multivariate hypothesis test of ANOVA in SYSTAT generated three statistics i.e. Wilk’s Lambda, Pillai’s trace, and the Hotelling-Lawley trace. Wilk’s Lambda is a likelihood ratio criterion which varies between 0 and 1. A small value of $\Lambda$ indicates no significant difference between groups in terms of variance. F approximation substituted the distribution of all three statistics.

2.1.4 Analysis of uniform shape changes

When a number of variables change simultaneously, we may model each change on the simplest form of factor analysis upon factor score, which conveys their global characteristics. The covariance matrix of deformation to be decomposed is based on this philosophy. Bookstein (1985) proposed decomposition of any sample variation-covariation about a mean configuration into a uniform part and a non-uniform part. The uniform part is assumed to be a factor. Uniform changes are assumed to be multiples of a single vector $\alpha$ by a factor of the means of the $y$-coordinates. Thus, the image of a uniform part of deformation in shape space is a set of $2K-4$ landmark vector changes, where $K$ indicates number of coordinates. The program Project developed by Bookstein and revised by Kim (Kim, 1990) computes the new coordinates for the uniform part and the single vector. The single factor prediction will be $(\alpha x_i, \alpha y_i) = y'x$, where $\alpha = (\alpha_x, \alpha_y)$ is a standardized factor score. As the factor is standardized to have variance 1 in factor analysis, the vector $\alpha$ is standardized to match the expected displacement of distance at 1 from the baseline, thereby we can substantiate the interpretation of the quantity of the single vector as anisotropy. The significance of the linearity and the single vector itself is
examined by F distribution.

To format the input files as indicated, files were prepared in the program LOTUS and transferred into Turbo C. The files were formatted as fortran files ($T_3, I_2, 16F6.2$). The baseline was determined prior to running the program Project. The program allows one to use the covariance observed matrix or the null model covariance matrix. For the current project, the null model was decided upon as the model of choice. Rationalities for using the null model are as follows (Kim, 1990):

1. There are insufficient cases in the data to invert the sample covariance matrix $S$ reliably.

2. The observed scatter of shape coordinates includes a strong single exogenous factor whose expressing effect could not be disregarded. In this circumstance, it would be better to estimate the effect of this factor, partial it out, and consider the true residual correlation of shape coordinates.

The data employed for the current study were sorted, analyzed and interpreted based on the single strong exogenous variable RDI. The output of a uniform model fitting provided mean locations of landmarks for the first group and observed mean shifts of the second group against the first. Using null model covariances, a uniform deformation was fitted. This linear term was conveniently parameterized by a single common vector ($F$). The uniform fit corresponds to a shift of landmarks at height 1 by the common vector. The program also computed the fitted mean landmark shifts and residuals of each landmark. Based on these numbers, the residual sum of squares and fitted sum of squares were calculated. Under the null hypothesis of an exact linear model, the standardized lack of
fit shows Hotelling's $T^2$ distribution. The model can be tested by Rao's $F$ approximation instead of the Hotelling's $T^2$ distribution, for they are equivalent. If the $T^2$ statistics accepts the null hypothesis of no deviation from the linear fit, we can proceed to test the fitness itself against zero, i.e. $\alpha = 0$. If the residual sum of squares is significantly large, then the linear model may not explain the whole variation, hence there is no point in testing $\alpha = 0$. The test for the significance of the common vector $F$ is same as $T^2$ test in Srivastava and Carter (1988) for a fitted mean. Since the estimate $\hat{\alpha}$ is a projection of the sample mean onto a subspace, we can interpret the fraction of the fitted sum of squares to a generalized sum of squares as the fraction of mean landmark shift explained by this linear model. Anisotropy of the deformation was also calculated in the same manner as the case of small changes in the principal axes construction. For $\alpha = (\alpha_x, \alpha_y)$, the anisotropy was calculated as follows:

$$\left(\alpha_x^2 + \alpha_y^2\right)^{1/2}.$$

The anisotropy quantifies the total amount of uniform shape change of a deformation.

2.1.5 Analysis of non-uniform shape changes

Thin-plate spline interpolation was used to extricate the non-uniform, local part of a deformation. If the uniform part of a deformation does not explain much about general variation, the biological process should contribute to the residual counter part. The TP spline method depicts a deformation on the grid system and quantifies the non-uniform part of the shape variation in terms of bending $E$ which corresponds to anisotropy in uniform change. As deformation is assumed to be a smoothly altering rearrangement of landmarks in a configuration, morphological difference between two structures can be
described by the smooth mapping of one form into another using interpolation techniques. Under the assumption of a circular normal perturbation, each mean value of the x- and y-coordinates of two separate structures were incorporated in the TP spline program. Each specimen file containing a mean shape was constructed and transferred separately. Two sets of coordinates corresponding to each other were matched in the context of a linear mapping procedure and the spline sheet was deformed to yield minimum bending E, and thereby a full spline was generated.

TP spline

Landmarks \((x_1, y_1), (x_2, y_2), \ldots, (x_K, y_K)\) in the Euclidean plane represents a certain biologic form. When this form changes to another, the \(K\) landmarks are still on the form, but they have now changed their relative spatial locations. In the case of an extreme transformation, we can imagine an intermediate shape between an original and a new form. We could still match these and interpret the intermediate shape as a transition process. This is the basic concept behind the TP spline interpolation process. As interpolation mapping is undertaken, the transformation must be smooth rather than abrupt. The intermediate point set in between the pair of corresponding landmarks must be allocated at the positions which generate minimal deformation of the global shape of the original form. To visualize this 2D-intermediate change as if it were in three-dimensions, we invoke the complex space for convenience and use an imaginary axis. The coefficients of the function \(f_x\) and \(f_y\) are obtained from the matrix \(L^{-1}V\) that were incorporated by the inverted matrix of the flat spline surface. This includes the original landmark points and the column space of new landmark points corresponding to the
original landmark points. The actual algebraic computation is a pseudo-projection process of the original shape \( L^{-1} \) onto the x- and the y-subspace of the new landmark \( V \) separately. The x components and y components of the new deformed spline \( f_x \) and \( f_y \) are now composed to construct a full spline

\[
f(x,y) = (f_x(x,y), f_y(x,y)),
\]

where each component reveals the form of a complex vector not scalar. This is how a 2D transformation is animated in a 3D space.

Compared to the algebraic intricacy of TP spline interpolation, its illustration is straightforward. For the sake of an easy explanation, a spline was divided into nine local regions. Anteroposteriorly a spline is divided into three regions: anterior, middle, and posterior. Likewise, it is divided into three regions in a superior-inferior direction: superior, middle, and inferior. The middle region is called "the center" (Fig. 9). Accordingly, local distortion of a warp is described in terms of "strain gradient" in a region of the spline such as the "posterior inferior region." A TP spline warp bears its own bending \( E \) which is a net percentage of the landmark displacement. Bending \( E \) measures the information local to the proper subsets of the landmarks. Each full warp was compared in terms of the magnitude of bending \( E \). The matrix \( L^{-1}_K \) which was introduced in the previous section, is defined as the bending \( E \) that can be orthogonally decomposed. This matrix contains \( K-3 \) non-zero eigenvalues, therefore yielding \( K-3 \) sets of principal warps in accordance with its corresponding eigenvectors (see Appendix I). Each principal warp was described and analyzed in a similar fashion as in full warps.
Figure 9: Sub-division of a TP spline. A spline is sub-divided into 9 regions by imaginary lines.
2.1.6 Profile analysis of the shape vector changes

Profile analysis may be a useful tool for cases which have more than two treatment groups (Johnson and Wichern, 1988). It is assumed that the responses for the different groups are independent of one another, yet all responses must be expressed in the same unit or at least similar units. Originally, this technique was designed to examine whether the population mean vectors were the same. In landmark data analyses, profile analysis is a powerful method to demonstrate mean vector changes. The program SYGRAPH, an auxiliary program of SYSTAT, was utilized to display the mean value changes of the significant landmarks. The shape variables for the face and tongue, which significantly contribute to the mean vector differences of symptom severity, were recruited for profile analysis. The program SYGRAPH generated profiles of the mean value changes for each landmark.

2.2 Analysis of interlandmark data

To assess form differences of the pharynx in accordance with severity, MANOVA was employed. Paired t test and Hotelling’s $T^2$ were implemented to investigate if there were differences that occurred due to the body position changes.

2.3 Regression analysis

Simple and multiple regression analyses were undertaken on each data set. Simple $r$, multiple $R$ and adjusted $R^2$ were accommodated to describe relations. SYSTAT was utilized to obtain these coefficients and the inferences base on them. The quantity $R^2$ explains the proportion of the total variation attributable to the predictor variables. The
adjusted value Adj $R^*$ is calculated from

$$Adj \ R^* = R^* - \frac{p}{n-p-1}(1 - R^*),$$

where $p$ is the number of predictors (Johnson and Wichern, 1988). $R^*$ equals 1 when the fitted equation passes through all the data points so the random error equals 0. At the other extreme, $R^*$ equals 0 when predictor variables have no influence on the response.

The multiple correlation coefficient $R$ equals $\sqrt{R^*}$. MGLH (Multivariate General Linear Hypothesis) option in the program SYSTAT (SYSTAT, 1990) estimates the parameters of a model and tests a general linear hypothesis by establishing the following form:

$$A\beta = D,$$

where $A$ is a matrix of linear weights on coefficients across the independent variables, $\beta$ is the matrix of regression coefficients and $D$ is a null hypothesis matrix. For each fitted model, the command MGLH reports: $R^*$, Adj $R^*$, the standard error of the estimate. A result of ANOVA computation includes the estimate of the regression coefficient, the standard error of the coefficient, the standardized coefficient, tolerance, and $t$ statistic for measuring the usefulness of the variable in the model. Tolerance here indicates multicolinearity. Regression analyses were employed to find a variable or a combination of variables that best delineate the severity of OSA.

2.4 PLS analysis

2.4.1 Model Design

PLS analysis was employed to summarize the results and to provide an overview of the morphological characteristics of OSA patients. Primarily, structural equation models were diagrammed and outlined. Multiple measurements were
reorganized into several blocks to obtain an indirect but better integrated assessment of underlying factors. Nine predictor blocks and one outcome block were utilized. Each block was composed of its own indicator variables. Predictor blocks included face blocks, tongue blocks, pharynx blocks, size blocks in the upright and supine position, and a demographic variable block. The outcome block was the index block. Each block yields an LV which implies its own unobservable property. LV in the current PLS analysis indicates a linear combination of indicators weighted in proportion to their correlations with other LVs. Arrow diagrams illustrate an example of a framework of a two-block model structure (Fig. 4A). Indicators in the model are employed in a formative mode since the objective is the explanation of the combinations of indicators as an integral abstract e.g. facial shape change or pharyngeal form change (Fornell and Bookstein, 1982). However, the indicator coefficients are based on simple regressions, and loadings rather than regression weights are engaged for interpretation, which allows us to escape from the distress of multicolinearity. The four-block analysis currently employed is the simplest method (Tabashnick and Bookstein, 1990) amongst all PLS versions for multi-blocks (Fig. 4B). It simply disregards the covariances of the latent variables for each block and combines them according to a factor mode strategy. The LVs for each block were computed separately with respect to the opposing outcome blocks i.e. the sum of the means of all simple regression functions, indicator by indicator.

2.4.2 Execution procedures

To execute the PLS program in the MTS system, the input files were first manipulated into the format of a Fortran file. The variables to be employed were clustered
as a block. Two or more block variables were combined for design to constitute a
covariance or correlation matrix. For the current study the correlation matrices between
two or four block variables were incorporated. The correlation matrices were constructed
in SYSTAT and compiled in LOTUS. The program TURBO-C imported these files before
the Fortran files were formatted in the software. The files thus created were transferred
into MTS and plugged into the PLS program PLS.OBJ+ Na:slatec3. The program allows
a maximum of 20 indicators for each latent variable. The program provides several
modules such as two-, three-, or four-block analysis of factor regression and multiple
regression types. The modules employed in this study were the two-block factor
regression type and the four-block multiple regression type.

2.4.3 Statistics in PLS

The two-block analysis yields three basic statistics on which our determination
depends (Ketterlinus et al., 1989). Saliences (s) were calculated, which describe the
patterns of correlation between the indicators of either block and the LV score of the
opposing block. The singular-value ratio (rsv) assesses how effectively a single pair of the
vectors consumes the correlation matrix. A two-block correlation coefficient (r) is the
ordinary Pearson correlation between two LV scores as weighted by their saliences. The
PLS computation process is iterated twenty times until the final values of the statistics are
determined. R² and rsv values manifest the soundness of the model. Before accepting r
values as a correlation between the blocks, one determines whether this particular pair
of LVs summarizes a sufficient fraction of the correlation information. A 2:1 ratio between
the first and second singular values, corresponding to a 4:1 ratio of the explained
summed squared correlations, was suggested as a threshold in order to determine whether the first pair carries meaning. An rsv value lower than 2.0 implies that the first and second pairs of singular vectors are not sufficiently distinguished. Therefore, the linear representation of the cross-correlation matrix might not be adequate even if the Pearson’s correlation shows a high value. This threshold is basically arbitrary. An R-value indicates what fraction of the total summed squared correlation is attributed by the first pair (Ketterlinus et al.; Sampson et al., 1989). Saliences are the most significant statistic, and play a crucial role in the PLS model system. Saliences are covariances at the root between the manifest variables and the LV of an opposing block. The saliences are evaluated, block by block in terms of magnitude and sign. Salience is proportional to correlation, but is not the absolute value with respect to zero. The correlate R in the multi-block analysis is the salience weighted sum of r values of each block.
RESULTS

2D landmark data obtained from the face and tongue, and linear measurements from the pharynx, are inspected by histograms, scatter plots and density functions. The nonparametric kernel density estimator is used to plot each variable in order to examine its distribution. The nonparametric kernel density estimator (Hardle, 1989) is a statistical tool used to estimate the density function of a measurement by means of a kernel that is a function which produces a discrete part of an integrated curve. A product between a kernel function and a measurement creates a density function. All basic statistics including mean, standard deviation, median, coefficient of variation, and minimum to maximum range are evaluated.

1. Demographical Configuration

Table 1 demonstrates the means, standard deviations, ranges, and median values of the demographic and apnea index variables. Ages range from 18 to 71. The age median (44.00) is located relatively close to the mean (45.86) when one considers the size of the standard deviation (12.47). A standardized variable BMI shows a smaller range of deviation (21.08 - 53.04) than the raw variable weight (56.00 - 148.50), yet the median value of the weight supposes a lower value of mean-variation ratio than BMI. QQ plots for the three demographic variables of Age, BMI and weight demonstrate almost normal distribution (Fig. 10). In contrast, apnea index variables, AI, RDI, TAT are distributed in a more skewed fashion than the demographic variables. However, when one takes the lower limit of range (0.00) for the apnea index variables into account, the shape of the distributions for AI and RDI may be acceptable. TAT exhibits a wide range.
Figure 10: QQ plots of the demographic and index variables.
(0.00 - 83.60) of deviation and a skewed distribution (mean 9.83; median 4.81). Group differences in demographic variables are outlined in Table 2. ANOVA examines a group effect on each variable. While age does not contribute much to the grouping effect (P = 0.05), weight (P = 0.00) and the standardized weight variable BMI (P = 0.00) strongly influence the mean vector tendency of the subgroups. The increase of BMI and weight affects the symptom severity proportionately. A simple regression analysis is also undertaken to find a demographic variable which best assesses RDI (Table 3). Weight appears to be the best single demographic variable which explains approximately 20% (Adj R^2 = 0.199) of the RDI variation at a P level of 0.000.

1.1 Summary

As observed in Figure 10, each distribution of the measurement of demographical variables approximates normal. BMI and weight present obvious group differences, yet weight may be the best OSA severity predictor among the three demographic variables.

2. Size

Correlation among the size variables is investigated (Table 4). In both positions, SIZFACE and SIZTONGUE show high correlation, but SIZPHARYNX reveals somewhat low correlations to the other two size variables. Correlation between SIZPHARYNX and SIZTONGUE demonstrates a lower value than that between SIZPHARYNX and SIZFACE. Correlations between the SIZFACE and SIZTONGUE variable in the supine position reveals the highest correlation (r = 0.668). To examine the overall relationship between
TABLE 3: Simple regression of RDI on demographic variables. BMI indicates Body Mass Index \([\text{Weight(Kg)/Height(m}^2\text{)}]\).
Multiple R, in this case, denotes the simple correlation coefficient.
TABLE 4: Pearson's product moment correlation coefficients between size variables.
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<th>GROUP</th>
<th>N</th>
<th>SIZFACE mean</th>
<th>SIZFACE s.d.</th>
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<th>SIZPHARYNX s.d.</th>
<th>SIZFACE mean</th>
<th>SIZFACE s.d.</th>
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<th>SIZPHARYNX mean</th>
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<td>110.08</td>
<td>1.60</td>
<td>287.90</td>
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</table>

**TABLE 5:** Group differences of upper airway size in both body positions. ANOVA examines group differences on each variable. MANOVA tests an overall difference among the groups and among the variables.
the severity of OSA and the size variables, ANOVA and MANOVA analyses are employed. Table 5 illustrates that there is a tongue size difference among the subgroups in both body positions at a P level of 0.004. The face and pharynx do not demonstrate size changes in accordance with symptom severity in both positions, yet SIZFACE in the supine position shows a weak indication of group differences. Wilk’s Λ values (0.749 in upright; 0.792 in supine) in both positions suggest that there may be general size differences among groups, but the significance (P = 0.01 in the upright; P = 0.04 in the supine) of these differences seems to be led by SIZTONGUE. To examine if the body position change generates size differences in any upper airway structure, a paired t test was undertaken on the three determined size variables. Table 6 exhibits no significant difference between the pairs for any variables. The variable for the tongue size changed the most, yet the change was not significant. Results from a simple regression study of weight and BMI with size variables are shown in Table 7. In general, weight reveals a more significant relationship with size variables. SIZFACE shows higher values in the supine position for both weight and BMI, whereas SIZTONGUE reveals higher correlations with weight variables in the upright position. To investigate which of the size variables in which body position shows the strongest correlation with RDI, a simple regression analysis is carried out. It is found that SIZTONGUE in the upright position best correlates with RDI and best describes the variance (11%) at the P level of 0.002 (Table 8). The size variables for the face and pharynx demonstrate less than 5 % of the Adj R² values.
<table>
<thead>
<tr>
<th></th>
<th>SIZFACE</th>
<th>SIZTONGUE</th>
<th>SIZPHARYNX</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=80</td>
<td>mean</td>
<td>s.d.</td>
<td>mean</td>
</tr>
<tr>
<td>UPRIGHT</td>
<td>289.12</td>
<td>56.93</td>
<td>213.76</td>
</tr>
<tr>
<td>SUPINE</td>
<td>289.12</td>
<td>58.67</td>
<td>211.79</td>
</tr>
<tr>
<td>P</td>
<td>0.995</td>
<td></td>
<td>0.058</td>
</tr>
</tbody>
</table>

**TABLE 6:** Size differences of upper airway structures between the upright and the supine position.
TABLE 7: Simple regression of weight and BMI on the size variables.

<table>
<thead>
<tr>
<th>SIZE</th>
<th>UPRIGHT</th>
<th></th>
<th></th>
<th>SUPINE</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WEIGHT=constant+</td>
<td>BMI=constant+</td>
<td>WEIGHT=constant+</td>
<td>BMI=constant+</td>
<td>WEIGHT=constant+</td>
<td>BMI=constant+</td>
</tr>
<tr>
<td>SIZE</td>
<td>R</td>
<td>Adj R²</td>
<td>P</td>
<td>R</td>
<td>Adj R²</td>
<td>P</td>
</tr>
<tr>
<td>SIZFACE</td>
<td>0.632</td>
<td>0.392</td>
<td>0.000</td>
<td>0.481</td>
<td>0.221</td>
<td>0.000</td>
</tr>
<tr>
<td>SIZTONGUE</td>
<td>0.564</td>
<td>0.310</td>
<td>0.000</td>
<td>0.481</td>
<td>0.221</td>
<td>0.000</td>
</tr>
<tr>
<td>SIZPHARYNX</td>
<td>0.000</td>
<td>0.000</td>
<td>0.595</td>
<td>0.092</td>
<td>0.000</td>
<td>0.421</td>
</tr>
</tbody>
</table>
TABLE 8: Simple regression of RDI on the size variables in different body positions.

<table>
<thead>
<tr>
<th></th>
<th>UPRIGHT</th>
<th>SUPINE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>Adj R²</td>
</tr>
<tr>
<td>SIZFACE</td>
<td>0.185</td>
<td>0.022</td>
</tr>
<tr>
<td>SIZTONGUE</td>
<td>0.346</td>
<td>0.108</td>
</tr>
<tr>
<td>SIZPHARYNX</td>
<td>0.196</td>
<td>0.026</td>
</tr>
</tbody>
</table>
Size allometry is also investigated (Table 9). The location of the hyoid bone manifests a strong correlation with the face size in both body positions (P = 0.004 in the upright, P = 0.002 in the supine). Most of the tongue variables reveal significant correlations with the tongue size in the upright and supine position. T1 (P=0.002), Tongue Height (P=0.000), Hyoidale (P=0.002) and Tongue Centre (P=0.002) in the upright position show strong correlations with SIZTONGUE, whereas T1 and Hyoidale are significant in the supine position at the P level of 0.005 and 0.000 respectively. Instead of measuring size allometry in the pharynx, simple correlations between SIZPHARYNX and variables in the pharynx are assessed (Table 9). The table exhibits that all of the variables in the supine position show significant correlations, yet the variables LT/W2 (P = 0.002), W2 (P = 0.000) and Wr (P = 0.004) reveal significance in the upright position.

2.1 Summary

The tongue size is found to be the most significant size variable. However, it explains only a small fraction of the RDI variation (11 %). Weight reveals a better correlation with the structure size than the constructed variable BMI did. The face size in the supine position better predicts the weight of the patients, while the tongue size correlates more with the weight variable. The body position change does not yield significant size changes for any of the variables. Many shape variables of the face, tongue, and pharynx demonstrate a strong relationship with each size variable. In general, the size factor of each upper airway structure appears to be less strong than initially expected.
### TABLE 9: Regression of the size variables on the shape variables

The size variables of the face and tongue are regressed on x and y shape coordinates, and the pharynx size variable is regressed on the pharyngeal measurements.

<table>
<thead>
<tr>
<th>Variable</th>
<th>UPRIGHT</th>
<th>SUPINE</th>
</tr>
</thead>
<tbody>
<tr>
<td><code>SIZFACE</code></td>
<td>( R )</td>
<td>( P )</td>
</tr>
<tr>
<td>constant +</td>
<td>0.227</td>
<td>0.271</td>
</tr>
<tr>
<td><code>Sx + Sy</code></td>
<td>0.130</td>
<td>0.054</td>
</tr>
<tr>
<td><code>Nx + Ny</code></td>
<td>0.193</td>
<td>0.283</td>
</tr>
<tr>
<td><code>Hx + Hy</code></td>
<td>0.233</td>
<td>0.040</td>
</tr>
<tr>
<td><code>C4x + C4y</code></td>
<td>0.022</td>
<td>0.004</td>
</tr>
<tr>
<td><code>Submx + Submy</code></td>
<td>0.013</td>
<td>0.000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>UPRIGHT</th>
<th>SUPINE</th>
</tr>
</thead>
<tbody>
<tr>
<td><code>SIZTONGUE</code></td>
<td>( R )</td>
<td>( P )</td>
</tr>
<tr>
<td>constant +</td>
<td>0.254</td>
<td>0.392</td>
</tr>
<tr>
<td><code>TTx + TTy</code></td>
<td>0.076</td>
<td>0.002</td>
</tr>
<tr>
<td><code>T1x + T1y</code></td>
<td>0.035</td>
<td>0.036</td>
</tr>
<tr>
<td><code>THx + THy</code></td>
<td>0.955</td>
<td>0.005</td>
</tr>
<tr>
<td><code>T2x + T2y</code></td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td><code>Hx + Hy</code></td>
<td>0.236</td>
<td>0.518</td>
</tr>
<tr>
<td><code>Cx + Cy</code></td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>UPRIGHT</th>
<th>SUPINE</th>
</tr>
</thead>
<tbody>
<tr>
<td><code>SIZPHARYNX</code></td>
<td>( R )</td>
<td>( P )</td>
</tr>
<tr>
<td>constant +</td>
<td>0.235</td>
<td>0.164</td>
</tr>
<tr>
<td><code>LT</code></td>
<td>0.036</td>
<td>0.146</td>
</tr>
<tr>
<td><code>θ2</code></td>
<td>0.375</td>
<td>0.332</td>
</tr>
<tr>
<td><code>LT/W1</code></td>
<td>0.001</td>
<td>0.003</td>
</tr>
<tr>
<td><code>LT/W2</code></td>
<td>0.477</td>
<td>0.477</td>
</tr>
<tr>
<td><code>W1</code></td>
<td>0.318</td>
<td>0.318</td>
</tr>
<tr>
<td><code>W2</code></td>
<td>0.477</td>
<td>0.477</td>
</tr>
<tr>
<td><code>WR</code></td>
<td>0.004</td>
<td>0.433</td>
</tr>
</tbody>
</table>
3. Shape

3.1. Face

3.1.1. Determination of baseline

To select an appropriate baseline for the facial shape analysis, a preliminary study is undertaken. Ten landmarks thought to best express the anatomical characteristics of OSA are chosen (Fig. 11). Each of the digitized x and y landmark values obtained from 73 cephalograms are standardized to a baseline Sella-Gnathion. Each cloud of landmark points in a scattergram contains 73 landmark points. To investigate mean vector changes of each landmark upon the severity, a TP spline analysis is undertaken. The TP spline promptly displays a localized rostrocaudal downward moving tendency of the hyoid bone accompanied with the Go location change upward (Fig. 12). This observation illustrates that the occurred vector changes are local not global. Go-H-Gn might be the triangle in which shape changes related to the severity of symptom mostly occur. To investigate the appropriateness of the preliminary baseline, Go-Gn, the normality of the distributions of the non-standardized Go and Gn are examined. The density functions smoothed by the nonparametric kernel density estimator for each Go and Gn appear to approximate the normal distribution (Fig. 13). Therefore, the baseline S-Gn should be changed to Go-Gn so that the vertical change in the hyoid and submental region can be observed more directly. In addition, some insignificant landmarks are deleted.
Figure 11: Scattergrams of face variables and of Hyoidale. Landmark variables for the face in the scattergram on the left are shown with respect to the S-Gn baseline. The enlarged scattergram for Hyoidale on the right uses a different scale from the scattergram on the left.
Figure 12: A preliminary TP spline analysis for the baseline selection. Arrows indicate a vector movement of variables. C3 indicates the landmark for the 3rd vertebra which is excluded afterward.
Figure 13: Kernel density functions of the variables for the baseline. Density functions of the variables which were tentatively selected for the baseline are examined.
3.1.2. Overall configuration changes

To investigate whether there is a group difference in the face shape, MANOVA analysis on the standardized landmark coordinates with respect to the baseline Go-Gn is implemented. Amongst 10 x,y variables from 5 landmarks (two coordinates Go and Gn are fixed as a baseline), the variables C4x, Hy and Submy reveal significant association with the group effect in both body positions (Table 10). MANOVA evidences overall landmark vector changes in accordance with OSA severity at a P level of 0.038 in the upright position (all MANOVA tables included in the present dissertation present significant variables only, but in statistics such as Wilk’s Λ, F and P are obtained from the calculation including all variables). There is an obvious tendency for the hyoid bone (P = 0.009) and the submentale (P = 0.001) to migrate down, yet less of a tendency for the 4th vertebra (P = .035) to move posteriorly. Such tendencies are stronger in the supine body position (P = 0.000 in the hyoid bone, P = 0.002 in the 4th vertebra and P = 0.002 in the submentale) than they are in the upright position. Thus, the entire face shape change becomes more significant in the supine (P = 0.000) than in the upright position. Facial shape changes between the upright and the supine positions are also investigated by Hotelling’s T² in total and in each group (Table 11). None of the groups reveal a significant face shape change upon the body position change. Body position changes do not cause facial shape change in any group or in total.
<table>
<thead>
<tr>
<th></th>
<th>UPRIGHT</th>
<th></th>
<th></th>
<th>SUPINE</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HYOIDALE</td>
<td>C4</td>
<td>SUBMENTALE</td>
<td>HYOIDALE</td>
<td>C4</td>
<td>SUBMENTALE</td>
</tr>
<tr>
<td></td>
<td>Hx Hy C4x C4y</td>
<td>Submx Submy</td>
<td>Hx Hy C4x C4y</td>
<td>Submx Submy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASYMPOMATIC</td>
<td>0.463 -0.288</td>
<td>-0.238 -0.613</td>
<td>0.943 -0.266</td>
<td>0.462 -0.218</td>
<td>-0.208 -0.625</td>
<td>0.944 -0.262</td>
</tr>
<tr>
<td>MILD</td>
<td>0.470 -0.339</td>
<td>-0.234 -0.625</td>
<td>0.940 -0.301</td>
<td>0.500 -0.341</td>
<td>-0.200 -0.631</td>
<td>0.922 -0.295</td>
</tr>
<tr>
<td>MODERATE</td>
<td>0.474 -0.402</td>
<td>-0.272 -0.669</td>
<td>0.962 -0.351</td>
<td>0.473 -0.364</td>
<td>-0.256 -0.678</td>
<td>0.950 -0.338</td>
</tr>
<tr>
<td>SEVERE</td>
<td>0.458 -0.385</td>
<td>-0.336 -0.636</td>
<td>0.967 -0.371</td>
<td>0.441 -0.350</td>
<td>-0.344 -0.650</td>
<td>0.953 -0.361</td>
</tr>
<tr>
<td>P</td>
<td>0.927 0.009</td>
<td>0.035 0.551</td>
<td>0.355 0.001</td>
<td>0.261 0.000</td>
<td>0.002 0.450</td>
<td>0.551 0.002</td>
</tr>
<tr>
<td>Overall Face</td>
<td>Wilk's A=0.534</td>
<td>F =1.566</td>
<td>P =0.038</td>
<td>Wilk's A=0.389</td>
<td>F =2.496</td>
<td>P =0.000</td>
</tr>
</tbody>
</table>

**TABLE 10: MANOVA analysis of facial shape differences in two different body positions.** Mean value difference of x- and y-coordinates of each landmark are examined by ANOVA. Statistics from the MANOVA analysis shown in the bottom row indicate the result which includes all variable.
TABLE 11: Comparison of facial shape differences between the upright and the supine position.

<table>
<thead>
<tr>
<th></th>
<th>N=</th>
<th>Wilk’s Λ</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASYMPTOMATIC</td>
<td>40</td>
<td>0.695</td>
<td>1.270</td>
<td>0.292</td>
</tr>
<tr>
<td>MILD</td>
<td>52</td>
<td>0.764</td>
<td>1.269</td>
<td>0.279</td>
</tr>
<tr>
<td>MODERATE</td>
<td>34</td>
<td>0.811</td>
<td>0.539</td>
<td>0.847</td>
</tr>
<tr>
<td>SEVERE</td>
<td>34</td>
<td>0.814</td>
<td>0.526</td>
<td>0.854</td>
</tr>
<tr>
<td>TOTAL</td>
<td>160</td>
<td>0.906</td>
<td>1.548</td>
<td>0.128</td>
</tr>
</tbody>
</table>
3.1.3. Uniform Changes

Overall shape changes are decomposed into uniform changes and non-uniform changes. The program PROJECT abstracts out a common linear vector of shape changes and tests if the vector change is significant or not. Linear parts of shape differences (or uniform deformation) of the face between the symptom-free group and the groups with apnoeic symptoms in the upright and the supine positions are presented in Table 12. Uniform deformations are computed and vectors are determined in proportion to distances from the baseline Go-Gn. Each common vector of the uniform change is calculated among the vectors for each deformation. In all cases, the anisopropy changes of the uniform deformation appear to be minimal and contrarily the residuals are large. The linear models of the facial shape changes show only a small change and seem to explain only a part of the overall shape changes. The residuals from the regression of the linear model is tested by Rao's $T^2$ equation. The high Rao's $F$ values indicate that the linear modelling of the face shape difference between the asymptomatic group and each OSA subgroup may not be possible. To recap, there may be a significant signal remaining in the residual from the fit. Null linear models of the face shape difference explain from 1% to 30% of the generalized variances in both body positions. Therefore, it is concluded that the difference in facial shape between the OSA subjects and the asymptomatic group cannot be modeled in a linear fashion. In other words, the facial shape changes between the apnoeic group and the asymptomatic group are not global or uniform.

The uniform shape changes of the face which occurred during the body position change from upright to supine are also modeled (Table 13). The residuals from the null models of the mild, moderate and severe groups are not significantly large (Rao's $F$ are
TABLE 12: Uniform shape differences of the face in both body positions. ssq indicates the sum of squares. Tables demonstrate uniform shape differences of the face of each group from the face of the symptomatic group.
TABLE 13: Uniform deformation of the face between the upright and the supine body position.

<table>
<thead>
<tr>
<th>Difference between Upright &amp; Supine</th>
<th>$\boldsymbol{\alpha}$ Common Factor</th>
<th>Residual $ssq$</th>
<th>Fitted $ssq$</th>
<th>Rao's $F$</th>
<th>% of Linear model explains</th>
<th>Sriv-Cart's $F$</th>
<th>Anisotropy $%$</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASYMPTOMATIC</td>
<td>-0.003 0.008</td>
<td>1.511</td>
<td>0.030</td>
<td>6.198</td>
<td>1.9</td>
<td>0.178</td>
<td>0.9</td>
</tr>
<tr>
<td>MILD</td>
<td>-0.015 0.028</td>
<td>0.322</td>
<td>0.352</td>
<td>1.808</td>
<td>52.2</td>
<td>5.680</td>
<td>3.2</td>
</tr>
<tr>
<td>MODERATE</td>
<td>-0.010 0.014</td>
<td>0.795</td>
<td>0.184</td>
<td>2.662</td>
<td>18.8</td>
<td>1.248</td>
<td>1.7</td>
</tr>
<tr>
<td>SEVERE</td>
<td>0.009 0.006</td>
<td>0.709</td>
<td>0.069</td>
<td>2.374</td>
<td>8.9</td>
<td>0.491</td>
<td>1.1</td>
</tr>
</tbody>
</table>
less than \( F_{\text{crit}} \), thus the linear model is acceptable. However, the common linear vector of the mild group only appears to be significant as a model (Sriv-Cart's \( F \) is larger than \( F_{\text{crit}} \)). Moreover, the null linear model of the mild group explains more than half of the entire variation (52.2%), which is a uniquely high proportion. In summary, most of the face shape differences between the asymptomatic group and each OSA subgroup, and the face deformations upon the body position change, seem to be local not global. Even though the linear model is significant, the amount of the common vector change is negligible.

3.1.4 Non-uniform changes

After the linear part of the difference is estimated, the remaining amount of the facial shape difference is assessed against the symptom-free group in each apneic group. The TP spline program maps out each pair of homologous landmark points, interpolates them and creates TP splines. Bending energy is yielded while each transformation is calculated and warped spline planes are displayed. Figure 14 illustrates full splines and the series of principal warps of facial shape changes in each group in the upright position. The full warp of each group depicts that major shape change is observed in the lower part of the face and the neck region. As a whole, the inferior part of the spline spreads out in accordance with the severity of the OSA symptoms. The hyoid bone position moves inferiorly with respect to the Go-Gn baseline. The submentale also reveals a strong downward and forward migration tendency with the severity. The 4th vertebra appears to move posteriorly and accentuates the fanning out feature. The overall bending energy becomes greater in accordance with severity as well. Principal warps of each shape
Figure 14: TP splines of face deformations in accordance with symptom severity and principal warps in the upright position. Fractional numbers represent the amount of bending energy.
difference are also demonstrated. A set of four principal warps are yielded from the deformation decomposition of the symptomatic groups in both body positions. The first principal warps obtained from the deformation of the facial shape of each group in the upright position show that a more prominent submentale and a more upward movement of the hyoid bone seem to be the leading characteristics of the severe group. In overview, the spline surface tends to be stretched diagonally in a forward and downward direction. The series of second principal warps illustrate a simple downward movement of the hyoid bone location. The third and fourth principal warps do not suggest a significant bending; however, the posterior inferior margin of the warping planes of the third principal warps exhibits a tendency to be pushed forward and to construct a concave posterior spline margin as the symptom becomes more severe. In the fourth principal warps, the concave area in the posterior margin of the spline is migrated upward and displays a generally spread out shape of the lower face and neck area.

The overall non-linear face shape differences of each symptomatic group from the face of the asymptomatic group in the supine position are similar to the tendency of the upright position in general, yet the bending energy shows much greater values than in the upright position. Therefore, the shape of the full spline is more contorted (Fig. 15). The 4th vertebra reveals a strong posterior movement in the severe group, yet forward positioning of the submentale is less prominent than the upright. The facial shape difference between the asymptomatic and mild group in the supine position is different from that in the upright. In the supine position, an inferior positioning of the hyoid bone and an inward movement of the submentale are noted. The first principal warps for this deformation emphasize grid changes in the anterior third of the warping plane. Each
Figure 15: TP splines of face deformations in accordance with symptom severity and principal warps in the supine position.
decomposed shape vector of the mild, moderate and severe groups shows a distinct feature. The deformation of the mild group reveals a bulge in the middle anterior margin of the spline and a transient constriction in the lower face. The moderate group shows a minimum bending of the plane. In contrast, the first principal warp of the severe group presents some constriction in the middle anterior area and a transient thickening in the lower face and neck area. The second principal warps are almost identical to those in the upright position except for greater bending energies. The third principal warps describe a change in the posterior part of a warped plane. When the symptom becomes severe, the middle posterior part of the plane appears to be concave. As observed in the upright position, the fourth principal warps describes an anteroposterior change. A constriction appears in the upper one third of the splines and becomes broad in the moderate group. The inferior part of the spline fans out in the neck part in the severe group.

The non-linear deformation of the face after the body position change is depicted by a TP spline interpolation in Figure 16. Each group illustrates a distinct shape of the warped function. Body position changes in the asymptomatic group yields an elevated hyoid bone position. The mild group is recognized by the posterior movement of Submentale. The moderate group depicts a slight elevation of the hyoid bone and a slight forward, downward movement of Submentale with respect to the baseline. Submentale moves slightly downward and backward in the severe group, while Hyoidale moves upward a small amount. The overall bending energy inclines in a gradual fashion when the symptom becomes severe. The first principal warps derived from deformations of the face in each group demonstrate a shape change of the submental region moderately in the mild group and minimally in the moderate group. The second principal
Figure 16: TP spline of face deformation between the upright and the supine position. Principal warps are also displayed with corresponding bending energy.
warps exhibit vertical changes in the anterior part of the warps. The anterior vertical dimensions are decreased most in the asymptomatic group, and less in the mild, moderate and severe groups respectively. The third and fourth principal warps do not demonstrate any distinctive feature and each bending energy is insignificant.

3.1.5 Profile analysis of the shape vector changes

To observe changes of the mean position of each landmark point in accordance with symptom changes, a profile analysis is employed. Mean values of the x and y shape coordinates for C4, H and Subm are displayed in a Cartesian plane (Fig. 17). The numbers in the figures indicate each group: 0 for the asymptomatic group, 1 for the mild, 2 for the moderate and 3 for the severe group. The solid line represents changes of mean coordinates in the upright position and the broken line indicates those in the supine position. The landmark C4 and H demonstrate a similar tendency of vector changes. With symptom severity, both landmarks in both body positions move in a clockwise direction. The mean vector of C4 in the asymptomatic group locates most superiorly. The mild group locates slightly anteriorly and inferiorly. The landmark in the next group moves further down and backward. C4 in the severe group locates most posteriorly and in between the mild and the moderate group superoinferiorly. This clockwise rotation tendency is observed in the profile changes of the hyoid bone as well. In contrast, Submentale in each subgroup exhibits a different profile of the vector change. The landmark Submentale in the asymptomatic group locates most superiorly in both positions. It moves downward and backward in the mild group and then, further inferiorly and anteriorly as symptoms becomes severe.
Figure 17: Profile analyses of the face and tongue landmark variables. The numbers 0, 1, 2, 3 indicate the asymptomatic, mild, moderate, and severe groups respectively. The solid line indicates the upright position, the broken line indicates the supine position.
3.1.6 Symptom severity prediction

The relation of the symptom severity to the vector change of each significant variable is examined by means of simple and multiple regression analyses. RDI is determined to be the dependent variable considered clinically the most reliable index to express the degree of symptom severity. Table 14 summarizes the results of simple and multiple analyses. In general, variables in the supine position exhibit higher correlations with RDI. The vertical position of Submentale with respect to the baseline Go-Gn is found to be the best correlated single variable to RDI (R = 0.487 in the upright position; R = 0.490 in the supine position at P = 0.000). When combined with weight, the multiple correlation becomes 0.571 in the upright, 0.574 in the supine (Fig. 18). Figure 18 demonstrates smoothed 3D trend surfaces on scattered data for both body positions which are equivalent to the non-linear regression line in two-dimensions. They depict a general tendency among three variables. Although there are some irregularities on the surface, these trend surfaces indicate a fairly distinctive, strong correlation between the submentale and weight, and RDI. In both body positions, weight shows a slightly higher correlation with RDI than does BMI. A combination of x, y coordinates of C4, Hyoidale and Submentale explains approximately 30% (Adj R² = 0.293) of RDI variation in the upright position, 34% (Adj R² = 0.337) in the supine position.

3.1.7 Summary

Facial shape differences between the asymptomatic group and the apneic groups, and also between the two different body positions are analyzed. As the
TABLE 14: Regression of RDI on face variables in the upright and the supine body position.
Figure 18: 3D representation of the relationship of RDI to the variable Submy and weight.
symptoms become more severe, the hyoid bone and the landmark submentale move inferiory. The variable C4 moves posteriorly in accordance with symptom severity. This tendency is statistically significant in both positions, but stronger in the supine position. A TP spline analysis confirms this trend. The shape of the face does not change significantly after the body position change. However, the TP spline depicts some minor effects such as the superior movement of the hyoid bone and the posterior movement of the submentale. Each series of principal warps decompose shape changes between the groups and between the body positions. A profile analysis of the variables C4 and H demonstrates a clockwise rotation tendency in the landmark location changes. The point Submentale first move posteriorly inferiorly and then anteriorly inferiorly with the symptom severity. The mean location changes of these landmarks in both body positions are almost parallel. In the regression analysis, the y-coordinate of Submentale is found to be the most strongly correlated variable to RDI. Finally, most of the face shape changes are not global but local.

3.2 Tongue

3.2.1 Determination of baseline

To select a pair of the most invariant landmarks amongst the eight tongue variables, a scattergram of each non-standardized variable is examined. After the best candidate pairs are selected in accordance with the principle of baseline determination, density functions smoothed by the nonparametric kernel density estimator for each chosen variable are obtained. The landmarks E and RGN are employed as the best baseline for the tongue shape study, since the E-RGN baseline may be relatively long and
their distribution appears to be the most stable (Fig. 14).

3.2.2 Overall configuration changes

Amongst the twelve x,y landmark variables, only the anterior posterior relationship of the T1 variable reveals significance in its changes in accordance with symptom severity at a P level of less than 0.05 in the upright body position (Table 15). The T1 variable tends to locate anteriorly as the symptom becomes severe. MANOVA analysis does not find significant tongue shape changes in the upright position. In the supine position, the anterior posterior location of T1 reflects the symptom severity at the P level of 0.003 and the hyoid bone reveals a strong tendency of posterior shift at the P = 0.001 level. However, the overall tongue shape changes due to symptom severity prove to be insignificant in the supine position as well. Tongue deformation upon the body position change is investigated by Hotelling’s $T^2$ test (Table 16). There appears to be a significant deformation of the tongue secondary to the body position change in each group or pooled group (see the most right hand column of Table 16). The vector change of the T1 variable reveals a consistent trend to move posteriorly and superiorly with respect to the baseline E-RGN for all the groups. T2 also manifests a strong tendency to move downward and backward except in the moderate group. The tongue center reveals a significant overall vector change posteriorly and superiorly. The tongue tip and tongue height show significant changes as well, they both move upward. The overall shape of the tongue in the apneic group is not much different from the tongue shape in the asymptomatic group. However, body position change from the upright to the supine causes a significant change in tongue shape.
TABLE 15: MANOVA analysis of tongue shape differences in two different body positions. The P value under each column of variables results from ANOVA analysis.
### TABLE 16: Hotelling's $T^2$ test for tongue deformation upon the body position changes.

The direction of the vectors in the bottom row corresponds to the patient position in Fig. 6.

<table>
<thead>
<tr>
<th></th>
<th>Tongue Tip</th>
<th>T1</th>
<th>Tongue Height</th>
<th>T2</th>
<th>Hyoidale</th>
<th>Tongue Center</th>
<th>Overall Shape</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$x$</td>
<td>$y$</td>
<td>$x$</td>
<td>$y$</td>
<td>$x$</td>
<td>$y$</td>
<td>$x$</td>
</tr>
<tr>
<td>ASYMPTOMATIC</td>
<td>†0.031</td>
<td>†0.007</td>
<td>†0.024</td>
<td>†0.015</td>
<td>†0.033</td>
<td>†0.027</td>
<td>0.030</td>
</tr>
<tr>
<td>MILD</td>
<td>†0.023</td>
<td>†0.014</td>
<td>†0.005</td>
<td>†0.002</td>
<td>†0.012</td>
<td>†0.031</td>
<td>0.000</td>
</tr>
<tr>
<td>MODERATE</td>
<td>†0.039</td>
<td>†0.002</td>
<td>†0.000</td>
<td>†0.000</td>
<td>†0.005</td>
<td>†0.002</td>
<td>0.021</td>
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<tr>
<td>SEVERE</td>
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<td>†0.001</td>
<td>†0.000</td>
<td>†0.000</td>
<td>†0.000</td>
<td>†0.012</td>
<td>0.002</td>
</tr>
<tr>
<td>Pooled</td>
<td>†0.000</td>
<td>†0.000</td>
<td>†0.000</td>
<td>†0.000</td>
<td>†0.000</td>
<td>†0.000</td>
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<tr>
<td>Vector Expression</td>
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<td>▼</td>
<td>▲</td>
<td>▲</td>
<td>▼</td>
<td>▲</td>
<td>▼</td>
</tr>
</tbody>
</table>

Numbers indicate $P$ values.
† indicates increment of the value.
¶ indicates decrement of the value.
3.2.3 Uniform changes

Global differences in the tongue shape between the symptom-free group and the apnoeic group in the upright and supine position as well as shape deformation after body position changes are assessed. Mean shifts of each landmark are fitted by the program PROJECT which utilizes the least-square method. Each common vector amongst the linearly fitted vector shifts of the tongue landmarks for each transformation is calculated and denoted by x, y terms. In general, anisopropies of the common vector from each shape change demonstrate minimal linear deformations. The residuals from each least-square fitting appear to be large (Table 17 & 18). The size of the residual sum of squares indicates that linear modelling of the tongue shape change may not be usable in the current case. When one disregards the large residuals, 9% - 57% of the tongue shape variation seems to be explained by null linear models; however, a large discrepancy between the null models and the models using observed covariance matrix is also observed. Therefore, it is suggested that the tongue shape difference between the asymptomatic subjects and the OSA subjects and the tongue deformations produced by the body position changes may not be modeled in a linear fashion or the shape deformation of the tongue may be not global. The linear shape change model between the symptom-free group and the mild group in the upright position is uniquely revealed as an acceptable null model amongst the total tongue linear models. It reveals 6.3% of significant anisotropy change of the common vector. This model appears to explain almost 50% of the generalized variance. The linear deformation models for the moderate group in upright and the severe group in the supine position explain approximately 56% of the total variation. Their common vector size or anisotropy, is relatively large and significant.
TABLE 17: Uniform shape differences of the tongue in the upright and the supine body position. Tables demonstrate uniform shape differences of the face of each group from the face of the symptomatic group.
<table>
<thead>
<tr>
<th>Difference between Upright &amp; Supine</th>
<th>$\alpha$ Common Factor</th>
<th>Residual ssq</th>
<th>Fitted ssq</th>
<th>Rao's $F$</th>
<th>% of Linear model explains</th>
<th>Sriv-Cart's $F$</th>
<th>Anisotropy %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASYMPTOMATIC</td>
<td>-0.870</td>
<td>5.260</td>
<td>0.835</td>
<td>16.185</td>
<td>13.7</td>
<td>1.875</td>
<td>9.5</td>
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<td>0.498</td>
<td>21.531</td>
<td>9.0</td>
<td>1.658</td>
<td>6.5</td>
</tr>
<tr>
<td>MODERATE</td>
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<td>3.673</td>
<td>1.381</td>
<td>9.082</td>
<td>27.3</td>
<td>3.271</td>
<td>10.1</td>
</tr>
<tr>
<td>SEVERE</td>
<td>-0.085</td>
<td>8.323</td>
<td>1.141</td>
<td>20.580</td>
<td>12.1</td>
<td>1.351</td>
<td>9.5</td>
</tr>
</tbody>
</table>

**TABLE 18**: Uniform deformation of the tongue between the upright and the supine body position.
(Sriv-Cart's $F = 7.716$ in the moderate group; $F = 8.014$ in the severe group); however, Rao's F values indicate that their residual size barely reject the models. Table 18 illustrates that all of the null models for tongue deformation on the body position change are not acceptable and most of the deformations seem to be nonlinear. In summary, the tongue shape difference between OSA subjects and asymptomatic subjects appear to be local regardless of body position. However, the residuals to the linear regression are large enough to accept them as linear models. Most tongue deformations which occur secondary to the body position change seem to be local and their common vector size minimal.

3.2.4 Non-uniform changes

The amount of nonlinear tongue deformation is extricated by the TP spline method. Shape changes of the tongue in the upright body position in accordance with symptom severity are demonstrated in Fig. 19. The tongue shape difference between the mild group and the symptomatic group may be summarized as an entire tongue forward shift. A minimal strain gradient is observed in the anterior third of the tongue. The overall tongue shape shift to the front is mainly generated by the forward shift of the point T1. Most changes occur in the anterior superior part of the tongue. The tongue shape change of the moderate group may be characterized by a downward movement of the hyoid bone and a mild posterior shift of T2. However, the forward moving tendency of the anterior part of the tongue in the mild group remains unchanged. The middle superior and posteroinferior part of the spline appear to be encroached mildly. The tongue tip and T2 moves posteriorly against the forward migration trend of the point tongue height and T1.
Figure 19: TP splines of tongue deformations in accordance with symptom severity and principal warps in the upright position. Fractional numbers represent the amount of bending energy.
A mild elevation of the tongue center is noted as well. The bending E of this deformation records a somewhat high value (0.00804) when compared to the other two. The shape difference of the tongue in the group with the severe symptoms depicts a similar mode to the mild group; however, the entire outline of the tongue seems to be stretched more anteroposteriorly in a diagonal direction so that the spline becomes shorter vertically when compared to the mild group. The upper part of the tongue tilts forward more intensely and this trend is influenced mainly by the alteration of the T1 position to forward. A moderate strain gradient is observed in the anterior superior part of the tongue.

Each tongue shape change is decomposed into five principal warps (Fig. 19). In the first series of principal warps, the spline for the mild group represents nearly no deformation. However, the moderate group demonstrates a tense warping plane as evidenced by a high bending E (0.00552). T2 drags the grid system posteriorly, and Hyoidale pulls the system inferiorly. There appears to be a mild elevation of the tongue center. The general shape of this spline resembles its own full warp. The first principal warp of the severe group exhibits an inward movement of T2, which most contributes to the shape change of the spline grid. The series of the second principal warps illustrates a minor anterior posterior change of each spline. The mild group shows a minimal change in the superior third of the spline. The tongue centre point in the moderate group tends to move to the posterior side of the spline, while T2 moves forward. Minor changes are noticed in the severe group as well. The third principal warps provide almost no information. Small changes in the posterior margin in the moderate and severe group are noted. The fourth principal warps may indicate the severity of OSA symptoms. T2 moves more posteriorly as the symptom becomes severe and develops the most convex
posterior margin in the severe group. A strain gradient in the anterior superior part of the spline appears to be highest and most protruded in the severe group and least in the mild group. The fifth principal warps may illustrate the symptom severity best. The severe group depicts the most wide spread superior spline margin, a constricted middle portion of the spline and a short vertical dimension. This tendency precisely concurs with the symptom severity.

The manner of the shape changes in the supine position appears more predictable (Fig. 20). The mild group displays the most clumped tongue shape change in general. However, the tendency of the tongue shape change to shift to a forward direction still remains, and this generates a tension in the upper anterior part of the tongue. The posterior and inferior most part of the spline exhibits a strong strain gradient as well. The hyoid bone exhibits an obvious downward migration, whereas the posterior shift of T2 is less strong. T1 reveals a distinctive location change upward and forward. Tongue Centre appears to move inferiorly a small amount. The bending E of this deformation shows a high value (0.01621) which indicates a highly strained tongue. The tongue shape change for the moderate group exhausts less bending E than the mild group, yet the general tendency of the shape change is the same as the mild group. The superior one third of the spline retains the tendency to a forward shift. Hyoidale moves inferiorly and T2 moves posteriorly but with less intensity. The anterior third and posterior inferior portion reveal a mild tension. The severe group demonstrates a more anteroposteriorly stretched spline shape than the moderate. This shape is represented by a much less general tension in the tongue shape deformation. The inferior movement of the hyoid bone is minimal, yet T2 moves posteriorly with respect to the baseline somewhat
Figure 20: TP splines of tongue deformations in accordance with symptom severity and principal warps in the supine position.
most strongly than the other two groups.

A series of five principal warps is generated from the tongue deformation in each group in the supine position (Fig. 20). Each collection of the principal warps behaves in a different manner from those in the upright position. Convexity of the posterior margin of the T2 area appears a primary characteristic of the first principal warps assembled. The bending E for the second principal warps decreases as the OSA symptom becomes severe. However, the shape of the splines remains almost identical in pattern. The superior one third of the spline is spread out. This tendency seems to be led by the separation of TH and T1 at the superior margin and the posterior movement of T2 in the posterior middle of the spline. T1 moves superiorly against the location of TH, and it creates a distinctive deflection at the superior margin. A similar decreasing tendency of the bending E is repeated in the third principal warps as well. The mild group exhibits a most clumped shape, while the anterior inferior corner of the spline in the severe group is stretched most despite the least bending E. The tongue center shows a downward shift in all groups. Each of the fourth principal warps illustrates approximately identical shapes, yet the bending E level decreases in accordance with the severity of symptoms. The fifth principal warps do not demonstrate either any particular shape deformation or a difference in bending E change amongst groups.

The non-linear deformation of the tongue secondary to a body position change from the upright to the supine is investigated with the TP spline method. The position change induces a localized tension gradient in the middle superior and posterior inferior area of the splines in the all groups (Fig. 21). The tension gradients in both areas appear greatest in the severe group and least in the moderate group, and so does the bending
Figure 21: TP splines of tongue deformation between the upright and the supine position. Principal warps are also displayed with corresponding bending energy.
E level accordingly. The grid system confirms the result of the overall change that the tongue centre migrates to the posterior and superior direction slightly. In the symptom-free group, the superior half of the tongue is tilted to the posterior and T2 is observed to fall posteriorly. The tongue height and T1 are mutually pulled and create a small lump of elevation of the local grid system at the middle superior area. The middle anterior half of the spline in the asymptomatic group reveals widely spread grids. Along the inferior margin of the spline, a mild tension is shown in the middle compared to the others. The deformation of the spline in the mild group upon the body position change is less intensive than that of the asymptomatic group. The bulge due to T2 on the posterior margin is less prominent. The tension clump in the middle superior area is less intense as well, yet it shifts anteriorly a bit. The mild tension in the middle inferior area of the spline for the asymptomatic group is dissipated, and instead a rigid tension is developed in the posterior inferior corner. The deformation in the moderate group shows the least grade of intensity among the groups. Each landmark in the tongue reveals the identical tendency as the mild group, but less strong. The severe group displays an extreme distortion of the tongue, thus the bending E level records the highest level of 0.04276 amongst the groups. A prominent bulge of the point T2 is observed. An intensive tension gradient in the middle superior margin severely bulges upward and migrates forward. This strong clumping effect leaves a rather dilated area posteriorly and superiorly. The anterior middle and anterior inferior part of the grid system becomes spacious and expanded as well. The posterior inferior corner of the spline depicts the most rigid tension amongst the four subgroups. Generally, the entire shape of the spline in the severe group appears to be anteroposteriorly stretched. The deformations of the tongue in each group are
orthogonally decomposed into five principal warps.

For the first principal warps, T2 is noticed to be an important landmark which discriminates the asymptomatic group from the OSA groups. T2 does not demonstrate any location change in the asymptomatic spline. TH which locates beneath the middle of the superior margin indicates a mild elevation. Hyoidale exhibits a small downward tendency. While the posterior margin of the asymptomatic spline depicts a smooth surface, the rest of the symptomatic group displays a posterior bulge of the T2 area and a mild or moderate tension in the epiglottis and hyoid area. Other than the two points, the general shape of the splines is similar. The second series of the warping planes denote a somewhat distinctive pattern. The asymptomatic group and the moderate groups appear the same, and the mild and the severe display the same pattern of spline shape changes. Not much of the deformation is observed in the asymptomatic group, or in the moderate group. The second warp of the mild group and the severe group both demonstrate a barrel shape of spline deformation, yet the severe group depicts the more rigid general tension in the grid system, therefore showing a higher bending E level. Among the third principal warps, the asymptomatic, mild and moderate groups reveal a minimal deformation or bending E in each of the third principal warps. However, the group of severe subjects depicts a distinct spline of which the middle portion is stretched posteriorly. The tongue centre moves posteriorly with T2 despite TH and T1 shifting forward. This coupled separating force seems to generate a high bending E. The fourth principal warps yield a similar pattern to the group difference as the second principal warps. The spline shape in the asymptomatic and moderate groups displays the same trend. However, T2 in the moderate group generates a stronger inward movement, and
thereby yields a tenser grid system than the asymptomatic. The fourth orthogonally decomposed spline plane for the mild group reveals no bending, yet a mild, general downward change of the grid system is noticed in the severe group. The last principal warps are the most supple among the series. These warps reveal the same pattern of shape changes as observed in the second and fourth principal warps. The asymptomatic group demonstrates a barrel shape of spline with a distinct curvature in the superior margin, where a clumping of the grid system is observed as well. In the spline of the moderate group, however, a bulge on each side (for T2 and TT) becomes less prominent than that of the asymptomatic group. Moreover, the acute curvature in the middle of the superior margin in the asymptomatic group appears to be straightened and the tension between T2 and TT is alleviated. The shape of the spline for the mild and severe groups is almost superimposed except for the intensity. The severe group reveals a tenser grid network system on the posterior side of the warp than does the mild group.

3.2.5 Profile analysis of the shape vector changes

For the tongue profile analysis, the program SYGRAPH generates profiles of mean value changes of each landmark. T1, H and C demonstrate significant tongue shape changes (Fig. 17). The landmark T1 exhibits an independent way of changing the location in each subgroup in the upright and the supine position. The landmark Tongue Centre manifests a similar tendency to that of T1. The landmarks T1 and C in the supine position locate more superiorly and posteriorly with respect to the baseline E-RGN than in the upright position. Interestingly, the profile changes of these landmarks in the same body position appears in the same pattern. Vector changes of the landmarks T1 and C
in the upright position demonstrate a 'Z' shape pattern, whereas those in the supine position exhibit a clockwise pattern. However, the profile starts from the posterior side, then locates in the mild group more superiorly and anteriorly, and then moves downward and backward in the moderate and severe groups. The profile of the hyoid bone position with respect to the baseline depicts the most distinctive phenomenon. The general tendency of the hyoid bone changes looks alike in the upright and supine position. However, the mean vector profile of the hyoid location changes in the supine position clearly discriminates the asymptomatic group from the OSA symptomatic group.

3.2.6 Symptom severity prediction

The relationship between the OSA symptom severity and the vector changes of the tongue landmarks is investigated. The anteroposterior relationship of T1 shows a high correlation (30%) with RDI among the entire x,y variables of the tongue in the upright position (Table 19). A multiple regression analysis of RDI with the location of T1 in the x-, y-coordinate table with respect to the E-RGN baseline denotes a small amount of improvement in the correlation. The multiple regression of RDI on T1x combined with BMI indicates that the T1x and BMI combination may explain approximately 30% of RDI variation. The combination of T1x with weight exhibits slightly lower values (multiple R = 0.542; Adj R² = 0.274) than the combination with BMI. Regression analyses on the OSA symptom are undertaken in the supine position as well. Hx appears to be the variable which reveals the highest correlation with RDI (35%) in the supine body position. BMI is shown to be the most highly correlated with the variable RDI (52%) when combined with Hx.
**TABLE 19: Regression of RDI on tongue variables in two body positions.**

<table>
<thead>
<tr>
<th>UPRIGHT</th>
<th>RDI=constant+</th>
<th>R</th>
<th>Adj R²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1x</td>
<td>0.308</td>
<td>0.083</td>
<td>0.006</td>
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</tr>
<tr>
<td>T1x + T1y</td>
<td>0.326</td>
<td>0.082</td>
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<tr>
<td>T1x + BMI</td>
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</table>

<table>
<thead>
<tr>
<th>SUPINE</th>
<th>RDI=constant+</th>
<th>R</th>
<th>Adj R²</th>
<th>P</th>
</tr>
</thead>
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<tr>
<td>Hx</td>
<td>0.326</td>
<td>0.112</td>
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<tr>
<td>Hx + Hy</td>
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</tr>
<tr>
<td>Hx + BMI</td>
<td>0.523</td>
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</table>
3.2.7 Summary

The baseline E-RGN is determined to be utilized for the tongue shape analysis. The overall tongue shape changes in relation to the symptom are not significant in the upright or the supine position. In contrast, the body position change generates tongue shape deformations. With position changes from the upright to the supine, T1 and the tongue center migrate posteriorly superiorly, and T2 changes the location posteriorly inferiorly. The tongue tip and tongue height are relocated superiorly. These location changes of landmark points could be easily visualized with the TP spline. Since the linear model does not explain much about the shape difference and deformation, the non-linear deformation represented by a TP spline may contain most of the information about shape changes. The TP spline study suggests that the tongue shape changes in the supine position better reflect symptom severity. The tongue shape comparison between the upright and the supine body position may imply the association between the tongue shape changes and the physiologic response of the tongue to the body position change in accordance with symptom severity. Specifically, the middle superior area and the posterior inferior region of the spline appear to provide the information with regard to symptom severity. In the profile analysis, the vector change of Hyoidale in the supine position may deliver an important message. The mean location of the hyoid bone in the supine body position may be clearly segregated from the symptom group. Regression analysis found that the landmark position of T1 is most strongly associated with RDI in the upright position. In the supine position, the hyoid bone appears to be the best landmark to explain the variation of RDI. However, neither of the landmarks explains a significant amount of RDI variation in a clinical sense.
3.3 Pharynx

3.3.1 Overall form changes

The MANOVA analysis is carried out on the 10 interlandmark variables for the pharynx. The results indicate that there are significant differences among the group for the entire set of variables. Table 20 exhibits statistically significant variables in the upright and supine position examined by a univariate F test, and displays the mean vector changes for each group. In the upright position, the total length (LT) and the length of the middle part (LM) demonstrate a tendency to increase with symptom severity at the P level of 0.000, while W1 describes an opposite trend (P = 0.001). When the symptom becomes severe, the pharynx becomes longer and narrower. The variables LT/W1 confirms this, yet the relationship between the two variables was not strong (P = 0.028). A MANOVA table for the supine body position also evidences the significant group difference in shape and size of the pharynx at a P level of 0.000. The variable LT, LM, and LT/W1 illustrate the same trend as in the upright position at the similar significance levels. Mean values of the variables LT and LM in the supine position show a more elongated pharynx than those in the upright position. The univariate F test newly brings three more variables as significant variables (P = 0.025 for e2; P = 0.049 for W2; P = 0.011 for WR). Particularly, the variable W2, which expresses divergency of the pharynx, appeared to be significant. Each of the pharyngeal measurements in the upright and supine position are compared by a paired t-test in the pooled sample size (Table 21). The variables LT, LM, e1, W1, W2, WR, and LT/W1 in the upright position appear to be significantly different from those in the supine position. LT and LM become longer after a change in body position, while the most constricted area W1 becomes narrower. The curvature of the pharynx, e1, becomes more
<table>
<thead>
<tr>
<th></th>
<th>LT</th>
<th>LM</th>
<th>W1</th>
<th>LT/W1</th>
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<td>UPRIGHT</td>
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<td>P</td>
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<td>0.000</td>
<td>0.001</td>
<td>0.028</td>
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<td><strong>Overall Pharynx</strong></td>
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<td><strong>P = 0.000</strong></td>
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<table>
<thead>
<tr>
<th></th>
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<th>LM</th>
<th>Θ2</th>
<th>W2</th>
<th>WR</th>
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<tbody>
<tr>
<td>SUPINE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASYMPTOMATIC</td>
<td>71.75</td>
<td>28.62</td>
<td>13.98</td>
<td>10.40</td>
<td>5.07</td>
<td>37.35</td>
</tr>
<tr>
<td>MILD</td>
<td>93.17</td>
<td>42.59</td>
<td>9.04</td>
<td>11.64</td>
<td>6.60</td>
<td>56.67</td>
</tr>
<tr>
<td>MODERATE</td>
<td>82.44</td>
<td>37.15</td>
<td>11.06</td>
<td>11.41</td>
<td>7.38</td>
<td>56.61</td>
</tr>
<tr>
<td>SEVERE</td>
<td>95.97</td>
<td>43.55</td>
<td>11.50</td>
<td>13.59</td>
<td>10.76</td>
<td>73.97</td>
</tr>
<tr>
<td>P</td>
<td>0.000</td>
<td>0.000</td>
<td>0.025</td>
<td>0.049</td>
<td>0.011</td>
<td>0.036</td>
</tr>
<tr>
<td><strong>Overall Pharynx</strong></td>
<td>Wilk'sΛ = 0.053</td>
<td><strong>F = 7.426</strong></td>
<td><strong>P = 0.000</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 20:** **MANOVA** analysis of pharynx form differences in two different body positions. The P value under each column of variables results from ANOVA analysis.
TABLE 21: Comparison of the pharynx configuration between the upright and the supine position.

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>UPRIGHT</th>
<th>SUPINE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LT</td>
<td>73.24</td>
<td>86.13</td>
<td>0.000</td>
</tr>
<tr>
<td>LM</td>
<td>30.95</td>
<td>38.61</td>
<td>0.000</td>
</tr>
<tr>
<td>Θ1</td>
<td>160.31</td>
<td>155.43</td>
<td>0.001</td>
</tr>
<tr>
<td>W1</td>
<td>3.09</td>
<td>2.38</td>
<td>0.005</td>
</tr>
<tr>
<td>W2</td>
<td>9.56</td>
<td>11.70</td>
<td>0.000</td>
</tr>
<tr>
<td>WR</td>
<td>4.47</td>
<td>7.25</td>
<td>0.000</td>
</tr>
<tr>
<td>LT/W1</td>
<td>34.81</td>
<td>55.51</td>
<td>0.000</td>
</tr>
</tbody>
</table>
bent and $W_2$ becomes wider. Other ratio variables respond accordingly. Hotelling's $T^2$ is also employed to examine an overall shape or size change ($P = 0.000$) upon body position changes (Table 22). The variables found to be significant are separated into length and ratio variables. Furthermore, the difference caused by the body position change in each group is also assessed by the Hotelling's $T^2$. Each reveals the overall statistical differences in their forms ($P = 0.002$ in asymptomatic; $P = 0.000$ in milds; $P = 0.000$ in moderates; $P = 0.011$ in severe). Table 22 elaborates the increment and decrement of each variable. In the asymptomatic group, the ratio variables are more influenced by the body position change. In the symptomatic groups, however, linear measurements are mostly affected by the body position change. While the linear dimension at the most constricted area in the pharynx ($W_1$) decreases when body position is changed from the upright to the supine in the asymptomatic group, none of the changes in the symptomatic groups are significant. The value of $\theta_1$, the curvature of the pharynx, in the asymptomatic group is reduced upon the body position change. The measurement $LT$ is significantly increased in all of the symptomatic groups, yet not in the asymptomatic. The $W_2$ dimension in the mild and severe group appear to be increased, but there is no significant change related to this variable in other groups. The mild group reports an increase of $LM$ measurement and a decrease of the pharyngeal airway divergency.

3.3.2 Symptom severity prediction

Simple and multiple regression analyses are utilized to assess the relationship between each measurement and the severity of OSA. $LT$, the length of the pharynx, is
<table>
<thead>
<tr>
<th></th>
<th>SIZE</th>
<th></th>
<th></th>
<th>SHAPE</th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LT</td>
<td>LM</td>
<td>W1</td>
<td>W2</td>
<td>LT/W1</td>
<td>Θ1</td>
<td>Θ2</td>
<td>Wr</td>
<td>T²</td>
</tr>
<tr>
<td>ASYMPTOMATIC</td>
<td>↑ **</td>
<td>↑ **</td>
<td>↓ *</td>
<td>↑ **</td>
<td>↑ **</td>
<td>↓ **</td>
<td>↑ **</td>
<td></td>
<td>1.208</td>
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<td>MILD</td>
<td>↑ **</td>
<td>↑ **</td>
<td>↑ **</td>
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<td>↑ **</td>
<td>↑ **</td>
<td></td>
<td></td>
<td>30.468</td>
</tr>
<tr>
<td>MODERATE</td>
<td>↑ **</td>
<td>↑ **</td>
<td>↑ **</td>
<td>↑ *</td>
<td>↑ **</td>
<td>↑ **</td>
<td></td>
<td></td>
<td>5.131</td>
</tr>
<tr>
<td>SEVERE</td>
<td>↑ **</td>
<td>↑ **</td>
<td>↑ **</td>
<td>↑ **</td>
<td>↑ **</td>
<td>↑ **</td>
<td></td>
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<td>3.790</td>
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<tr>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Hotelling's T² = 0.722</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>F</td>
<td>13.620</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>P</td>
<td>0.000</td>
</tr>
</tbody>
</table>

* indicates P < 0.05  
** indicates P < 0.01  
↑ indicates increment of the mean value  
↓ indicates decrement of the mean value

**TABLE 22**: Comparison of the pharynx form between two body positions in each group and the total. The P value in the column of the most right side results from ANOVA analysis and the P value in the bottom row is the result from Hotelling's T² analysis.
found to be the most significant variable amongst all the measurements. BMI shows better correlation with RDI than Weight. Table 23 exhibits the results of the analysis. The variable LT alone appears to explain almost 38% of the RDI variation. Moreover, when it is combined with BMI, the combination explains 44% of RDI variation in the upright position. When the position is compared, the upright position displays higher R and Adj R² values than the supine. Two 3D regression surfaces in Figure 22 depict a general tendency of the scattered data. The graphs show that BMI may maintain the proportional relationship with RDI only to its value of approximately 40. A BMI over 40 may not always indicate a severe case. This viewpoint can also be applied to the variable LT in the supine position. A pharyngeal length longer than 100 mm may not suggest a proportional RDI value. Further, the measured values may not be proportional mutually around the "plateau" area or a pit indicated in the figure. However, the shape of the graph implies a strong predictability of RDI.

3.3.3 Summary

Overall, results from pharyngeal form analyses suggest that the pharynx appears longer and narrower as the symptom becomes more severe in the upright position. The same tendency is observed in the supine position as well, yet a few more significant changes are added such as a widening of the hypopharynx area and its related variables. As the body position changes from the upright to the supine, the airway becomes longer, narrower, and more curved and divergent. Comparison of the pharyngeal form between the upright and supine position provides many interesting pieces of information. Body position changes cause a longer pharynx in symptomatic
TABLE 23: Regression of RDI on the pharynx variables in both body positions.

<table>
<thead>
<tr>
<th>RDI=constant +</th>
<th>UPRIGHT</th>
<th>SUPINE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>Adj R²</td>
</tr>
<tr>
<td>LT</td>
<td>0.622</td>
<td>0.379</td>
</tr>
<tr>
<td>LT + BMI</td>
<td>0.675</td>
<td>0.441</td>
</tr>
</tbody>
</table>
Figure 22: 3D representation of the relationship of RDI to the variable $LT$ and BMI.
groups, whereas the airway length did not change in the symptom-free group. Furthermore, the most narrow area, W1, becomes narrower after the body position change in the asymptomatic group, yet the measurement on the same variable in the other group do not show significant changes. Another width measurement of the pharynx, W2, demonstrates an increment of values in the mild and severe groups. Regression analysis and its graphical representation reveal that the pharyngeal length LT may be the strongest variable amongst pharynx measurements to explain RDI variance.

4. PLS Analysis

Analyzed complex data are summarized with the PLS technique. To facilitate comprehension of the results, the PLS analyses are executed in two ways with collected data in a block fashion; first, a two-block analysis, and second, a multi-block analysis (Fig. 4).

4.1 Two-block analysis

The two-block PLS analysis examine the amount of association between the indicator block and the outcome block. For indicator blocks, a demographic variable block, an upright and supine pair of size variable blocks, face variable blocks, tongue variable blocks, and pharynx variable blocks are employed. For the outcome block, an apnea index block is incorporated with AI, RDI and TAT variables. Latent variables for each block are named as follows; DEMO LV for the Demographic Variable block, SIZE UPRIGHT LV and SIZE SUPINE LV for the size block in the upright and supine position, FACE UPRIGHT LV and FACE SUPINE LV for the face blocks, TONGUE UPRIGHT LV
and TONGUE SUPINE LV for the tongue blocks, and PHARYNX UPRIGHT LV and PHARYNX SUPINE LV for the pharynx blocks. A latent variable for the apnea index block is noted as INDEX LV.

4.1.1 Contribution of demographic variables to OSA severity

Age, BMI and WT are chosen as indicators of the Demographic Variable block. Figure 23 represents an overview of the results. The two blocks appear to have 45% of correlation between them (r = 0.45). An rsv value of 3.46 suggests that this two block PLS structure is permissible, for it is greater than a threshold of 2.0. The same salience for BMI and WT (s = 0.52) indicates that these two variables demonstrate parallel profiles of prediction power to the index block score. Age shows the lowest salience with INDEX LV. Amongst variables in the apnea index block, RDI reveals the highest salience value (s = 0.75) i.e. INDEX LV weights RDI most. Al shows approximately half of RDI in its strength of association with the demographic block. However, TAT shows almost no relationship with DEMO LV. 92% of the total summed squared inter-block correlations is explained by the pair of singular vector of LVs.

4.1.2 Contribution of size factor to OSA severity

The two-block PLS analysis investigates the size effect on the apnea severity in the upright and supine position as a separate run (Fig. 24). In a model for the upright position, an rsv value of 2.28 suggests that a linear representation of the inter-block correlation matrix structure is marginally appropriate. The correlation coefficient between the two LVs is 0.32. SIZTONGUE appears to be the strongest variable (s = 0.81) to
Figure 23: Two-block PLS analysis of demographic variables and apnea index variables. s indicates salience. r indicates Pearson’s simple product moment correlation. rsv indicates the ratio between two first singular values.
Figure 24: Two-block PLS analysis of size variables and apnea index variables.
predict INDEX LV which is comprised of three index variables. RDI exhibits the best salience score (0.67) to the block for size. The fraction of the total summed squared inter-block correlations for the two LVs is 84%. The PLS estimation of the relationship between the size block and the apnea index block in the supine position is attempted. Results suggest that an association between the two block variables might have a different structure (Fig. 24). First, the rsv value of 1.94 is lower than the recommended threshold for appropriateness as a model. This implies that a linear combination of the cross-correlation matrix might not be permissible, viz. more than a single dimension of relation may exist between the two blocks. Although 22% of the inter-block correlation of this pair of LVs is still shown, it may not reflect a sufficient or faithful fraction of the correlation. SIZFACE and SIZTONGUE show almost equal values of salience to the index block score (0.54 for SIZFACE; 0.52 for SIZTONGUE). RDI reveals the highest salience value to SIZE SUPINE LV (s = 0.66). The pair of LVs provides 79% of explanation of the summed squared inter-block correlations. However, this model may not be sound.

4.1.3 Prediction of OSA severity by face shape

Figure 25 displays a two-block PLS analysis of the association between face variables and apnea index variables. The rsv value of 4.30 provided for the upright position and 4.26 for the supine position accept the inter-correlation matrix structures of the face shape and apnea index variables in both body positions as sound models (Fig. 25). In the upright model, two LVs reveal a correlation of 44%. A squared correlation of the two LVs accounts for 93% of the total squared correlation of the blocks. Submy (s = -0.41) and Hy (s = -0.34) appear to be important variables to explain the OSA severity.
Figure 25: Two-block PLS analysis of face variables and apnea index variables.
The variable Submx which indicates the anteroposterior location of the landmark point shows a relatively high positive salience value \((s = 0.23)\). Interestingly, C4y \((s = -0.20)\) reveals a higher salience value than C4x \((s = -0.11)\) does. Hx demonstrates a relatively low value yet a positive one \((s = 0.17)\). RDI \((s = 0.55)\) and AI \((s = 0.40)\) appear as variables which share the explanation of FACE LV in the upright position. In the supine position, a correlation between the two LVs \((r = 0.52)\) is higher than that in the upright model. 92% of all possible associations between the blocks may be explained by the LVs. Submy \((s = -0.46)\) and Hy \((s = -0.38)\) are shown to be the most correspondable indicators to the apnea index block. In addition, the position of C4 \((s = -0.32\) for C4x; \(s = -0.26\) for C4y) appears to be important for the OSA severity. RDI \((s = 0.42)\) and AI \((s = 0.54)\) best explain the face shape change in the supine position. The association between the index variable TAT and the LVs for the face is higher \((s = 0.29\) in the upright position; \(s = 0.20\) in the supine position) than its relation to DEMO LV or SIZE LVs.

4.1.4 Prediction of OSA severity by tongue shape

The LVs for tongue shape and OSA severity are correlated at 36% to each other in the upright position and explain 94% of the fraction of the summed squared inter-block correlation (Fig. 26). The appropriateness of the PLS model structure is proven to be sound by an rsv value of 4.60. Cx, T1x and THx which manifest the anteroposterior location of each landmark appear to be the significant variables among the 12 tongue variables \((s = 0.24\) for Cx; \(s = 0.23\) for T1x and THx). Interestingly, the salience for TAT shows high value, and thus appears to be a significant apnea index variable in the two
**Figure 26:** Two-block PLS analysis of tongue variables and apnea index variables.

<table>
<thead>
<tr>
<th>Variable</th>
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<th>SUPINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cx</td>
<td>0.24</td>
<td>0.21</td>
</tr>
<tr>
<td>Cy</td>
<td>-0.09</td>
<td>-0.04</td>
</tr>
<tr>
<td>Hx</td>
<td>0.00</td>
<td>-0.16</td>
</tr>
<tr>
<td>Hy</td>
<td>-0.07</td>
<td>-0.08</td>
</tr>
<tr>
<td>T1x</td>
<td>0.23</td>
<td>0.26</td>
</tr>
<tr>
<td>T1y</td>
<td>-0.08</td>
<td>0.03</td>
</tr>
<tr>
<td>T2x</td>
<td>0.16</td>
<td>0.07</td>
</tr>
<tr>
<td>T2y</td>
<td>0.00</td>
<td>-0.03</td>
</tr>
<tr>
<td>THx</td>
<td>0.23</td>
<td>0.20</td>
</tr>
<tr>
<td>THy</td>
<td>0.06</td>
<td>0.05</td>
</tr>
<tr>
<td>TTx</td>
<td>0.08</td>
<td>0.17</td>
</tr>
<tr>
<td>TTy</td>
<td>-0.14</td>
<td>-0.16</td>
</tr>
<tr>
<td>s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>r</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rsv</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RDI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AI</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
block association. TONGUE UPRIGHT LV weights TAT as much as RDI (s = 0.42). In the supine position, the rsv value for the first two singular vectors of the inter-correlation matrix is notably low (rsv = 2.95); however the r value of 0.32 indicates that still a considerable amount of correlation between the two blocks remains solid. The fraction of the total summed squared inter-block correlations is 86%. Cx, T1x and THx variables in the supine position are denoted to be primarily significant variables among the tongue variables with saliences of 0.21, 0.26 and 0.20 respectively. In addition, Hx (s = -0.16), TTx (s = 0.17) and TTy (s = -0.16) are shown to be secondarily important variables in predicting INDEX LV. TAT exhibits the highest salience value (0.51) among the three index variables. AI shows 0.47 and RDI reveals the lowest value of salience (s = 0.20) to the tongue shape variables in the supine position.

4.1.5 Prediction of OSA severity by pharynx configuration

PHARYNX UPRIGHT LV expresses the strongest inter-block association with the INDEX LV amongst all two-block combinations (Fig. 27). In the upright position, the correlation between the two LVs shows the value of 0.69. An rsv value of 5.89 indicates that the uni-dimensionality of the LVs is highly robust. The first two singular vectors of the matrix explain 96% of the total summed squared inter-block correlations. The LV of the index block weights LT most (s = 0.35). LM, LT/W1 and WR also reveal significantly high values of the salience (LM = 0.26, LT/W1 = 0.26 and WR = 0.22). The most constricted area W1 shows a somewhat low negative number (s = -0.19), yet suggests a significant negative association with the apnea index block. The variable SIZPHARYNX is included in the items of the pharyngeal configuration block to weigh its significance, however its
Figure 27: Two-block PLS analysis of pharynx variables and apnea index variables.
influence is minimal ($s = -0.08$). AI and RDI illustrate almost similar predictabilities for PHARYNX UPRIGHT LV, yet TAT shows approximately half of them in its predictability level ($s = 0.50$ for AI; $s = 0.48$ for RDI; $s = 0.23$ for TAT). The latent variable for the pharyngeal configuration in the supine position reveals 53% of correlation with INDEX LV. The rsr value of 3.13 suggests that the optimized linear relationship between two LVs from the inter-block correlation matrix is acceptable. In this model, the two LVs account for 85% of the summed squared inter-block correlations. Amongst the indicators in the pharynx block, the linear measurements such as LT and LM become more important in the supine position. In addition, a few ratio variables, such as $e1$ ($s = 0.20$) and LR ($s = -0.19$), appear to be significant. W2 means nothing to the index block in the upright position, whereas it becomes a significant variable in the supine position. The weight of the index block for SIZPHARYNX indicates a minimum contribution of the size variable to the model structure ($s = -0.04$). RDI represents a higher salience value ($s = 0.48$) to the pharynx block than the other two ($s = 0.37$ for AI and TAT).

4.1.6 Summary of two-block analyses

Table 24 provides an overview of the two-block analyses. Scrutiny of the two-block saliences of Index variables of the outcome block to the opposing predictor LVs illustrates that AI shows a high value of the salience against TONGUE SUPINE LV ($s = 0.47$) and PHARYNX UPRIGHT LV ($s = 0.50$). RDI exhibits a high association with LVs for the demographic block ($s = 0.75$), size block in the upright ($s = 0.67$) and the supine position ($s = 0.66$). TAT shows a distinct relation with TONGUE UPRIGHT LV ($s = 0.42$) and TONGUE SUPINE LV ($s = 0.51$). The saliences of the index block to the indicator
<table>
<thead>
<tr>
<th>Predictor LVs</th>
<th>Apnea Index Variables</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Al</td>
<td>RDI</td>
<td>TAT</td>
</tr>
<tr>
<td>DEMO</td>
<td>0.36</td>
<td>0.75</td>
<td>-0.01</td>
</tr>
<tr>
<td>SIZE UPRIGHT</td>
<td>0.22</td>
<td>0.67</td>
<td>0.29</td>
</tr>
<tr>
<td>SIZE SUPINE</td>
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<td>0.66</td>
<td>0.16</td>
</tr>
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<td>FACE UPRIGHT</td>
<td>0.40</td>
<td>0.55</td>
<td>0.29</td>
</tr>
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<td>FACE SUPINE</td>
<td>0.42</td>
<td>0.54</td>
<td>0.20</td>
</tr>
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<td>TONGUE UPRIGHT</td>
<td>0.36</td>
<td>0.42</td>
<td>0.42</td>
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<tr>
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<td>0.20</td>
<td>0.51</td>
</tr>
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<td>PHARYNX UPRIGHT</td>
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<td>0.23</td>
</tr>
<tr>
<td>PHARYNX SUPINE</td>
<td>0.37</td>
<td>0.48</td>
<td>0.37</td>
</tr>
</tbody>
</table>

**TABLE 24:** Two-block saliences of apnea index variables to indicator blocks.
block demonstrate a relatively steady consistency in sign and magnitude.

In the analysis for the demographic variable block and the apnea index block, BMI and WT are shown to be the same in their significance to the index block. Demographic variables may have 45% of correlation with the symptom severity. A PLS size analysis suggests that tongue size seems to best reflect symptom severity in the upright position. The model for the supine position is found to be unsound. As summarized in Table 24, the r values for the size LVs demonstrate distinctively low values. In the face block, the landmark C4, Submentale and Hyoidale appear to be significant variables in both body positions. Al and RDI best reflect facial shape changes. Of the landmarks on the tongue, the tongue center, T1 and the tongue height are found to be the most significant variables. These findings generally agree with the finding obtained in the MANOVA study. Association of the tongue shape change with the symptom change is weak in both body positions. This observation also concurs with the finding in the MANOVA analysis. The pharynx PLS analysis suggests that the length of the pharynx and associated ratio variables most correlate to the severity of OSA in both positions. In contrast, the size of the pharynx contributes nothing to the severity prediction. A narrower pharynx may be associated with OSA severity in the upright position, while a more curved pharynx appears to have a strong correlation with OSA severity.

4.2 Multi-block Analysis

A multi-block analysis evaluates the correlation of the morphological characteristics of the face, tongue and pharynx with the Index block (Fig. 28). The correlation coefficient for the face and tongue block with the index block reveal slightly
Figure 28: Multi-block PLS analysis of the upper airway shape related with OSA severity. The r value in a double lined box indicates the overall correlation between three indicator blocks and the index outcome block.
smaller values than the corresponding ones in the two-block analyses. However, the block correlation for PHARYNX UPRIGHT and SUPINE LVs to INDEX LV becomes stronger than the two-block cases. In multi-block analysis, the geometrical location of each LV seems to be rotated somewhat away from where it was in the two-block analysis, where it is in the most optimal least-squared position in the multi-block situation. This results in the attenuation of the LV correlation value. The correlation values in the Pharyngeal blocks are higher than those in the two-block case since several indicators are precluded due to a limitation of the program. The pharynx block in the upright position exhibits a 72% correlation with the index block. The salience for PHARYNX UPRIGHT LV to the index block shows an extremely high value (s = 0.94). The correlation coefficient between the face block and tongue block with the index block are similar (r = 0.42 for the face; r = 0.38 for the tongue). However, the value of salience for the face (s = -0.10) shows less than half of the salience value for the tongue (s = 0.26) in terms of magnitude. Further, it shows a negative number. An overall correlation between the three indicator blocks and the Index block is the salience weighted sum of the three correlations. The overall correlation of the three indicator blocks with the Index block in the upright position is shown to be 0.74. Amongst the index variables, AI and RDI appear to correspond to a two-third of variation of the upper airway morphology (s = 0.43 for AI; s = 0.44 for RDI). Amongst all the indicators in each indicator block, LT shows the highest salience (s = 0.83) against INDEX LV. Submy (s = -0.44) and Hy (s = -0.38) among the face block variables, the variable of Cx (s = 0.34), T1x (s = 0.32) and THx (s = 0.32) in the tongue block, and LT/W1 (s = 0.36) appear to be significant variables in both upright and supine positions. In the supine position, the weight of the tongue block to the index block is very
low (s = 0.05) and the r value reveals the lowest value amongst the three indicator blocks (r = 0.24). The face and pharynx blocks share approximately the same amount of the weight (s = 0.50 for the face block; s = 0.64 for the pharynx block), thereby revealing similar r values (r = 0.50 for the face block; r = 0.54 for the pharynx block). The overall r is somewhat lower (r = 0.60) than the one in the upright position. Amongst the index variables, RDI best reflects the morphological change of the upper airway structure in the supine position (s = 0.51). AI (s = 0.40) shows the next strongest correlation and TAT (s = 0.28) shows the lowest salience value. The total length of the pharynx reveals the highest salience to INDEX LV among all indicators. In the face block, Submy (s = -0.49), Hy (s = -0.43) and C4x (s = -0.33) demonstrate high values of salience. In the tongue block, x-variables for T1 (s = 0.41), C (s = 0.31) and TH (s = 0.30) appear significant in the relationship to OSA severity. In the pharynx block, the ratio variable of the length to the width of the pharynx (s = 0.37) shows a high value of the salience between the variable and the INDEX LV.

4.2.1 Summary of the multi-block analysis

The multi-block structure weighs the pharynx block more (s = 0.94) in the supine position than in the upright. The tongue is next (s = 0.26), and the face block (s = -0.10) shows the least salience. Interestingly, however, the face block (r = 0.42) reveals a higher correlation coefficient than the tongue block (r = 0.38). The overall correlation between the indicator blocks and the index block in the upright body position showed 0.74 which was a higher value than the correlation coefficient (r = 0.60) for the supine position. In the supine position, the face block became stronger in correlation (r = 0.50)
and salience ($s = 0.50$). In contrast, the tongue shape and the pharynx configuration lost strength in their power to predict OSA severity. The low salience value ($s = 0.05$) for the tongue block to the index block indicates the comparatively weak power of the tongue block to predict the severity of the OSA symptom. The association of variables AI and RDI with each of the blocks remains steady.
DISCUSSION

Although the size of the 3D upper airway structure cannot be measured precisely from 2D lateral cephalograms, information about the shape of each structure and the spatial relation among upper airway structures may envision different aspects of OSA pathophysiology. Cephalometric techniques display a midsagittal cross-sectional profile of the orofacial configuration. There may be an obvious limitation in a 2D visualization technique to understand a 3D object. To overcome the inevitable handicap of the cephalometric technique, several efforts have been attempted such as using a concept of stereometry (Baumrind and Korn, 1992; Sarnas et al., 1992) or invoking mathematics (Bookstein et al., 1991). Despite the limitations of traditional cephalometrics, it has been more and more frequently applied to study of the OSA over the last decade, and has now become a routine diagnostic tool for OSA patients in some centers. Cephalometrics is not only a handy visualizing technique but also can yield cogent data depending on how it is analyzed. Judicious analysis of the technically-limited data with a potent tool may facilitate a new explanation of the logical relation between observations and their causal factors. Conventional cephalometric analysis provides discrete linear, angular, and two-dimensional area measurements. To understand the overall relative relation between the measurements, we have to rely on our imagination to a large extent. The new concept and methodology applied to the current project may overcome this weakness of conventional data by supplying geometrical illustrations and more directly interpretable numbers.

Science has been sharing its domain with mathematics ever since its inception. Numerous scientists have tried to explain how the natural phenomena change grounded
on a pattern of data could be summarized by mathematical expressions (Steen, 1988). The philosophy of the Newtonian school upholds the idea that analysis should be based on the crystallization of the logical relations of empirical data in mathematical terms. Statistics, on the other hand, has been an implement for inductive research, mainly focusing on hypothesis testing. However, the major part of scientific conclusion is pretty much left to the intuition of the researchers themselves, and this seems to be true in the field of biology as well. Contemporary biological works have counted heavily on mathematics and statistics, and the present project must be cautious of two pitfalls in this regard. The first pitfall is over-simplification. There has been a tendency towards a stereotypic approach to analysis in biological study. We express biological phenomena in numbers, and symbolize them in formulas or summarize them by means of some variates, and then we return to biology for interpretation. Importantly, the stage of changes in numeric form must sincerely reflect the biological phenomenon without omission and deflection since over-simplification deduces a false conclusion. The second possible pitfall is over-conviction. Modelling of biological phenomena in terms of numbers is a metaphoric conversion of expression. Empirical reality of biological phenomena, however, cannot always be simplified in a numeric representation. Conversely, mathematics does not exist for the validation of biology, and multivariate statistics is not a panacea to solve complex phenomena. It must be a misapplication of mathematics or statistics to conform biology to arithmetical symbols. Moreover, it must be erroneous to distort the biologic observation to fit the analytic tool in order to obtain logical results. The current study attempted to use new mathematical methodologies to draw more plausible findings for OSA from the transformed morphometric data. The current study visualized the change in numbers by
means of geometry to minimize an abuse of the metaphoric expression. To avoid oversimplification and over-conviction in modelling, the analyzed results were summarized with the PLS method.

1. Implications of Findings

Most morphometric studies contain statistically analyzed results, for they contain numbers. To secure the ground for statistical inference tests on collected variables, inspection of distribution on each datum is crucial. The QQ plot conveniently demonstrates if a distribution is Gaussian or not, yet scattergrams may supply the idea more clearly in a small sample size. Sample scatters of landmark coordinates can be utilized for several purposes (Bookstein, 1991); inspection of outliers, finding elliptical evidence of factors, ordination for classification, and observation of overlap of a priori grouping. Particularly, scrutiny of elliptical scatters with great care endorses collecting information about the exogenous factor which influences the distribution. For instance, the scattergram for hyoid bone position in fig. 11 tells much about the relationship between hyoid bone location and the severity of OSA. The shape of the distribution of H on the left side figure is not circular. The scatter plot of H is magnified on the right side. We can notice that the 0 labelled points are scattered above the y-coordinate -0.4. The mean vertical location of all points labelled by 1, 2, 3 may be located around or lower than the y-coordinate criterion. Accordingly, we can say that the vertical hyoid position may discriminate the asymptomatic normal from the group with symptom (Pae et al., 1992). In order to investigate the distribution of non-coordinate data such as pharynx variables or size variables, histograms or any kind of density function may
provide overall intuitions.

1.1 Size and predictability of OSA

1.1.1 Obesity, tongue size and OSA

Obesity has been recognized as the strongest predisposing factor to the OSA severity (Guilleminault et al., 1978; Brownman et al., 1984). The mechanical work of breathing is increased 30% in simple obesity, and is significantly exaggerated in the supine position (Kopelman, 1992). Table 2 and Table 3 demonstrate that BMI and Weight are significantly associated with OSA symptoms. Of the two, BMI has been considered the variable that best reflects obesity. However, the results of the current study for weight variables revealed that BMI did not surpass the variable Weight in its predictability of RDI. A similar result was found in other research as well (Hoffstein et al., 1991). Furthermore, it was found that weight better predicts size of the orofacial structures in the current result (Table 7). It is suggested that weight may be a better demographic variable expressing body size than a synthetic variable BMI. Another interesting observation in this study was that the face size is more associated with weight than is tongue size (Table 4). Therefore, we consider that an obese person may have a larger face in clinical terms. However, the tongue size in the upright position showed a higher correlation with RDI than the face did (Table 8), and tongue size shows a uniquely strong tie with symptoms in both body positions (Table 5). Further, the tongue size is more associated with RDI than the face size is. This finding may be true in both body positions, since body position changes did not cause any size change of the upper airway structures (Table 6). The ANOVA table generalizes a conclusion that the more severe symptoms the OSA patient shows, the
larger the tongue size (Table 5). To recap, the tongue size is strongly associated with the face size. An obese person has a large face. However, a large face does not predict symptom severity. This may suggest that an individual with a large face tends to be heavy in weight. Nevertheless, this person does not necessarily have a large tongue. And, it is the tongue size that predicts OSA severity. A large tongue in accordance with increased severity may explain corresponding GG EMG activity seen in awake OSA subjects (Mezzanotte et al., 1992).

Strong evidence of a significant relationship between a thick neck and OSA were reported by several groups (Davies and Stradling, 1990; Katz et al., 1990). Predictability by neck circumference for severity of OSA is various and controversial (Partinen, 1991; Bliwise, 1991), yet it seems to be considerably high (Adj R² = 29 - 40). A retrospective and prospective study by Davies et al. (1991) emphasized the importance of the neck measurement by representing an extremely high correlation in low probability of committing type I error between BMI and Neck circumference (r = 0.86, P < 0.0001). These studies suggested a high association of obesity with the disease, yet did not directly prove the etiologic mechanism of the thick neck on the airway obstruction. Horner et al. (1989) investigated the distribution of fat around the pharynx by MRI (Magnetic Resonance Imaging). They observed significant fat deposit in the region of oropharynx and soft palate. However, they could not establish a significant association between the degree of obesity and the size of the fat deposit. Kopelman’s review (1992) suggested a general role of the mass loading effect of fat on the respiratory muscle function. Likewise, Horner et al. (1989) presumed that fat deposits may predispose the upper airway to collapse during sleep by compromising upper airway muscle function and directly or
indirectly making a narrow airway space. The inferiorly and anteriorly positioned Submentale currently observed may underpin the finding and related inferences about a thick neck (Table 14 and Fig. 14 & 15).

1.1.2 Allometry in measurements on OSA subjects

As explained in the literature review, the inter-correlation between the shape coordinates and the size of the face and tongue may be a "pseudo-allometry" as the one we can observe in growth and development data. If one insists on calling it allometry, then it may be a static allometry (Cheverud, 1982), however, the static allometry cased here may be not allometry but something else. The current data reveal a strong correlation between the size of upper airway structures and the shape variables, primarily in the supine position for the face and pharynx, and in the upright position for the tongue (see Table 9). It may be speculated that this static phenotypic allometry may infer shape changes by an adaptive process rather than just growth related variations, because shape variables which were originally obtained from a non-growing population are already size eliminated. Or it may be that there is a genotypic characteristic which has been hidden until a certain "trigger-like" condition reaches a particular threshold. An existence of allometry indicates that there is a size change accompanied with a shape change reversely speaking. I assert here that there may be a shape change before size change has occurred, viz. a shape difference may already be there, because the shape of the orofacial structure including muscle and bone is strongly influenced by genetic factors (Lauweryns et al, 1993; Markovic, 1992). Slight weight change may add difficulty on the airway, and in turn, size change occurs. I argue that the shape of the structure may be
a primary predisposing factor and that weight or size changes follow as secondary factors.

1.2 Shape changes in the face and tongue

The present study employed landmark data. Landmark data may not only constitute study material, but may also be employed as a tool to provide a prospective view of the data change. Landmark data should be observed and interpreted in the notion of geometry.

1.2.1 Overall shape changes

Shape changes of the face in accordance with the symptom severity existed in the lower face at the $P = 0.038$ level (Table 10). This general face shape change is dominated by inferior migration of the hyoid bone and the point submentale, and additionally by posterior movement of the 4th vertebra. These changes are exaggerated in the supine position. This may indicate that a large neck circumference is not caused by obesity or fat deposition but by the effort of the upper airway structure to compensate for narrowing of the airway. If the thick neck is simply a characteristic of OSA patients and caused mainly by fat deposition, then the neck circumference in the same patient in the supine position should be smaller or at least the same as that in the upright position, because deposited fat may react to gravity when one lies down. The TP splines on the supine cephalogram clearly visualize a "fan type" spread of the lower face and neck configuration. Therefore, it is speculated that the thick neck is not the result of fat deposition but of the spatial change or the difference of the upper airway structure.
Therefore, the assertion that the OSA patient has a thick neck may not be always true. The reason for the high correlation coefficient between the thick neck and the severity may be not that OSA patients have fat necks but that the subjects collected were OSA patients who had thick necks. Now, the current pure shape data analysis may answer the reasons for the existence of many non-obese patients and obese non-patients.

In contrast, the overall tongue shape does not change much in accordance with the symptom change (Table 15) in either body positions. The anterior shift of the landmark T1 may be noticed in the upright position and the forward movement of the hyoid bone accompanying the same directional movement of T1 is observed in the supine position. The anterior shift of the hyoid bone location in the OSA patient was observed in other cephalometric studies as well (Lowe et al., 1986; Pae et al., 1993) and also denied by others (Tsuchiya et al., 1992). Interestingly, the anterior hyoid position change in accordance with the symptom change was not seen in the current face shape study in either upright or supine positions, but it did show in the tongue shape study in the supine position (Table 10 & 15). This is clearly contradictory to the result of the previous study by Pae (1989) and Pae and associates (1993), which could not pick up the anterior shift of the hyoid bone. Precisely speaking, they could not observe the difference of the linear measurement H-RGN (the length between the hyoid bone and the retrognathion) between normal asymptomatic and OSA patients in the supine position. The reason for the diversity in the results of the two studies may be explained as follows. The previous study measured a linear distance between the hyoid bone and the retrognathion. The current study measured the position change of the landmark Hyoidale and further, it was size standardized. Therefore, for appropriate comparison, the linear measurement H-RGN
should be decomposed in terms of x- and y-coordinates and size should be eliminated as well. Next, the contradicting results on the same data in the same study may be embarrassing. However, an argument is proposed as follows. Two different baselines utilized for two structures may result in quite different numbers. Bookstein (1991) assumed and mathematically proved that change of a baseline does not effect the measurements of the vector change. But, that may be the case only when the baseline is changed in a same object. Bookstein also demonstrated that the effect of a baseline change yields infinitesimal non-linear changes when the adopted baseline length is long enough. Comparing the distance of the hyoid bone from the two baselines, Go-RGN and E-RGN, the hyoid bone changes in relation to the baseline Go-RGN are smaller than those to the E-RGN. Since the change with respect to the E-RGN is much greater and more direct, it was easier to observe its change. However, it may be somewhat dangerous to conclude that the result from the tongue analysis is more accurate based on this explanation. Another analysis which includes two structures in one can answer this question.

Body position changes from upright to supine generated a significant shape and orientation change on the tongue at a P level of 0.000 (Table 15) accompanied by an insignificant decrease of its size (Table 6), yet no change was observed in the face (Table 11). This result indicates that the position change may not effect the face but may create a significant impact on the tongue. In other words, the actual airway occlusion may not be directly related to the face shape, but may be tightly associated with the tongue shape in the supine position. It was observed that while the landmarks T1 and C in the tongue move superiorly and posteriorly, the point T2 moves downward and backward. This finding may suggest that the tongue tries to keep the airway open but has difficulty
overcoming gravity. This concept is developed further in section 1.2.3.

1.2.2 Uniform shape changes

Uniform shape changes reveal a trend of a general shape change. It is a common or widespread change which occurs at every landmark point. Therefore, we call it a global shape change. Most of the shape changes in the face or tongue that correspond to the symptom changes and to the body position changes occur locally, not globally (Table 12 & 13; Table 17 & 18). A Common factor $\alpha$ (Fig. 3) was calculated by a least square method in the data matrix. Each value in the column for common factor and anisotropy change is of relative value to the baseline length i.e. Go-Gn for the face and E-RGN for the tongue. Hence, obtained values of each $x$-, $y$-coordinate of the common factor ranged from approximately a fraction of 1 mm to 4 mm at the most. A 1% change in anisotropy may be equivalent to a 1 mm change approximately. Rao’s F value determined whether a model is sound or not by measuring the amount of fitted variation to the model. The amount of overall variation explained by a linear model was represented by percentage. The percentage was obtained from the ratio of the fitted sum of squares to the residual sum of squares. Sriv-Cart’s F decides whether the computed common factor $\alpha$ is significant or not. The results of this study indicate that most uniform shape differences or changes modelled in a linear fashion were not appropriate. The exception was the model of the mild group, shown in Table 13. However, its anisotropy corresponds to only 3.2% of the baseline length which may be equivalent to approximately 3.2 mm. Some of the tongue models at times explained a high percentage of the total variation. One showed almost 15% of anisotropy change which may be equivalent to 15 mm.
However, the model for the mild group uniquely appeared to be a significant model, but unfortunately, the anisotropy of the uniform change was little (6.3\% i.e. approximately 6.3 mm). In summary, it was deduced that most of the shape differences in the face and tongue between the asymptomatic group and other symptom groups were not global. Therefore, a linear model construction for those changes was not possible. A deformation of the face and tongue after body position change could not be modelled in a linear fashion either. No graphical presentation was attempted, since vector changes in a common factor in a significant model were very small.

1.2.3 Non-uniform shape changes

The biomechanics of the hyoid apparatus can be explained in terms of vectors (Van Lunteren et al., 1987ab). Several researchers describe the effects of shape changes by tensors (Diewert and Lozanoff, 1988). Likewise, I suggest that the pattern of meshes in the TP spline may be interpreted as a "strain gradient" which represents tension on a biological structure. The facial shape changes in accordance with symptom severity are characterized by a "fanning out" deformation of the inferior part of the face including the submental region (Fig. 14 & 15). This tendency is observed equally in the upright and supine position. This local facial configuration change may indicate that the patients with more severe symptoms try to keep their airway wide and straight. The pattern of the tongue shape change in accordance with the symptom in the upright position is different from those in the supine (Fig. 19 & 20). Although no spline demonstrates significance in their shape changes, each subgroup reveals its own physiological tongue response matching its symptom severity specifically in the supine position. The mild group exhibits
a strong tongue muscle response to the body position change. On the contrary, the moderate and severe groups show a much weaker tongue reaction. However, the severe group appears to try to keep their tongue in a more forward position in the supine position to keep the airway open. This may be evidenced by a mild tension in the anterior superior region of the spline.

Non-uniform shape changes of the face and tongue upon the body position changes demonstrate physiologically significant responses (Fig. 16 & 21). The facial deformations upon the position change are all different from subgroup to subgroup. However, the magnitude of the bending E reveals a crucial meaning. The asymptomatic group represents the highest value, and the severe group shows the lowest one. Each shape change is not statistically significant (Table 11); however the new shape descriptor bending E demonstrates a very linear consistency. The amount of bending E may reflect the amount of tissue response to the body position change. The upper airway muscle may respond to the positional change most strongly in the asymptomatic group and least strongly in the severe group. Scrutiny of the TP splines for the tongue shape changes upon the body position change suggests exciting interpretations (Fig. 21). Each TP spline for each group presents a tension gradient in the middle superior area of the spline. The relative location of this lump along the superior margin of the spline may provide information about symptom severity. The more the middle superior clump locates to the anterior part of the spline with respect to the entire length of the superior margin, the more severe the symptom. Another distinct characteristic of the deformation is that the asymptomatic group alone does not reveal a tension gradient at the posterior inferior corner of the spline. Each series of the principal warps of the face and tongue shape
changes demonstrates decomposed characteristics of each deformation. Principal warps are a set of numbers extracted from a matrix that is comprised of landmark data. Each cloud of measurements around the mean coordinate of each landmark point residing in the hyper-plane of the matrix system can be cross-cut by a "two-dimensional plane-like knife." In this way it can be decomposed into several planes in the order of the overall variation. The overall variation is thereby explained by the set of perturbation at each landmark on the plane cross-cut by the knife. The series of cross-cut planes are the principal warps. Therefore, careful consideration is required for proper interpretation of the principal analysis. Careful description of each principal warp was attempted in the present study. However, the interpretation of principal warps has not been made clear by anyone to date. Therefore, discussion on this material must be reserved for a future study.

1.3 Form changes in the pharynx

Unfortunately, SIZPHARYNX variable did not contribute much to the current study. However, Table 4 may suggest some plausible implication. The correlation coefficient between the tongue size and the pharynx size revealed a lower value than that between the face size and the pharynx size. This finding may indicate that an OSA patient with a large face may have a large pharynx as well. However, theoretically, an OSA patient with a large tongue ought to have a smaller pharynx in the supine position than in the upright when one considers the physiology of the tongue muscle reaction to gravity. However, the result reported a positively increased correlation coefficient value in the supine position. This finding suggests three postulates. First, the area of the pharynx may increase after a body position change mainly by an elongation of the structure (Table 21).
Second, the tongue size does not change significantly as illustrated in Table 6. This finding agrees with the result obtained by Lybergs et al. (1989). However, the mean value of the tongue size decreased slightly. Therefore, the value for SIZPHARYNX was not necessarily reduced. Third, the variable SIZPHARYNX may not reflect the real size of the pharynx. The shape and size of the pharynx may be tightly related to those of the tongue, thus it may not be easy to measure its actual size using two-dimensional data. In order to quantify the size of the pharynx a three-dimensional technique may be more accurate (Lowe and Fleetham, 1991).

As a convoluted and flaccid channel, the upper airway is considered to account for a significant percentage of the total airway resistance during breathing when a person is at rest in the awake state (Cherniack and Hudgel, 1987). The airway size keeps fluctuating due to the rhythmic activation of the respiratory muscles and therefore the airflow fluctuates as well (Pedley and Drazen, 1986). Previous studies suggest that the behavior of the upper airway dilating muscles, tissue compliance and air flow through the airway conduit may all play a crucial role at the final moment of airway occlusion in pathogenesis of OSA (Remmers et al, 1978; Gleadhill et al., 1991). A high resistance in the rostral part of the airway results in an increase of the intraluminal downstream pressure during inspiration (Issa and Sullivan, 1984). This transmural pressure may act on the compliant pharyngeal airway mucosa and muscle and decrease the size of the airway. Airflow velocity is determined by the calibre of the upper airway and by inspiratory effort. Along the airway of which the cross-sectional area varies, the mass of the air flowing in one cross-sectional area $A_1$ at a time $dt$ must equal that leaving $A_2$ at the same time. Hence $\mu A_1 V_1 dt = \mu A_2 V_2 dt$, where $\mu =$ viscosity of the air, $V =$ volume of the air, hence
\( A_1 V_1 = A_2 V_2 \). This continuity equation of fluid obviously implies that as the airway narrows, the linear velocity of the fluid through it increases. When an incompressible fluid flows along a tube of varying cross-section its velocity changes. It must therefore be acted on by a resultant force, and this indicates that pressure should vary along the tube. Bernoulli’s equation, in most biological situations, becomes \( P + \frac{1}{2} \nu v^2 = \text{constant} \), where \( \nu \) = viscosity. As the velocity increases with the decreasing cross-sectional area, the equation denotes that the pressure in a tube decreases at a point of constriction. As an airflow stream passes through a constricted area in the upper airway, the velocity of the stream becomes more rapid, thereupon a negative pressure will be developed at that point. If the airway structure of that portion is compliant enough or the underlining muscle sustaining the structure is hypotonic enough, then an obstruction occurs (Lambert and Wilson, 1972; Shapiro, 1977). Curiously enough, a description of the collapsing process of a collapsible tube by Lambert and Wilson was remarkably similar to the one that happens during sleep in OSA subjects. A strong vibration is always anteceded by occlusion of the tube. And, once a critical negative pressure has been developed, a self-perpetuating progressive narrowing of the collapsible segment may rapidly obstruct airflow (Oliven et al., 1989). Remmers and his associates (1990) examined collapsibility of the pharynx in OSA patients under the condition of no muscle functioning. They speculated that the collapsing segment in the absence of the pharyngeal muscle contraction may not correspond to the pharyngeal segment which occludes in the spontaneous ventilation. This is due to the fact that the degree of pharyngeal muscle contraction and trans-pharyngeal pressure could interact to modify the shape of the airway. However, occlusion of the airway may occur when upper airway muscles are least active. Without muscle
activation, the airway passage should more rely on the passive properties of the tissue proper such as contractility, or geometrical orientation of the anatomical structures which determine the shape of the pharyngeal conduit. If the muscle contractility and the strategic orientation of structures cannot overcome the intraluminal force developed by an aerodynamics, the airway may close.

Overall form changes of the pharynx in accordance with the symptom severity in the upright position are noticed by the elongation of the pharynx and the narrowing of the most constricted area (Table 20). The result indicates that the longer the pharynx one has, the more severe the symptoms one shows. The current finding about the minimum cross-sectional area largely coincides with the results of Shepard et al.’s (1990) study. However, the supine position draws some other findings in the pharyngeal form (Table 20). Of interest, W2 becomes wider as the symptom develops, hence Wr becomes bigger accordingly. This observation agrees with Polo et al. (1991, 1992) and the previous observation by Pae in 1989. Pae observed the increase of the area measurement on the hypopharynx after the body position change from the upright to the supine, but could not explain it. However, Polo et al. remarked that airway collapse is favoured by a narrow velopharynx associated with a large hypopharynx. A large hypopharynx is the necessary condition for the airway collapse of heavy snorers. When OSA patients change body position from the upright to the supine, the airway deforms significantly (Table 21 & 22). The pharynx becomes longer (however, notice that this change was not significant in the asymptomatic group in Table 22), it bends and becomes more divergent in its shape (Table 21). The narrowest point in the pharynx becomes narrower, and the widest part below the constricted area i.e. W2 becomes wider (Table 22). Further, the angle e2, which
indicates divergence of the pharynx becomes smaller in the symptomatic groups but larger in the asymptomatic group. Interestingly, the main reason for this result may be that the most constricted area, $W_1$, decreased not in the apneic group but in the symptom-free group. This implies that the variable which decides the severity of OSA may not be the most constricted area, $W_1$, but the total pharynx length and the pharynx width below the constricted point, i.e. $W_2$. Various form changes to the pharynx, elicited when one lies down, impede patent air flow. The much longer pharynx in the supine position, as compared to the upright, in OSA subjects may be more vulnerable to airway collapse. Contrarily, no significant pharynx length change was observed in the symptom-free group upon the body position change. This may indicate a better compensational reflex for the patent airway in normal subjects. The airflow through the upper airway during spontaneous breathing may be laminar to transient (Campbell et al., 1988). Several studies suggest that strong forward accelerations such as in a deep inspiratory flow tend to abolish turbulence at the peak of an oscillatory flow cycle (Hino et al, 1976). Therefore, quasisteady flow in the pharyngeal airway can be assumed specifically in a longer pipe. In Poiseuille flow, the flow rate is directly proportional to the pressure gradient driving the flow and we can assume Bernoulli’s equation. Further, the reduced minimum airway point should contribute to that as well. For explanation of the wider hypopharynx of OSA subjects as opposed to non-apneic heavy snorers, Polo et al. (1991) speculated that the additional suction energy in the simple snorer may be damped down at the lower part of the upper airway. It may be that an abruptly widened collapsible airway in OSA patients cannot have a chance to damp out the vibration wave coming from the upper stream and may therefore collapse. The current study could not endorse this postulate. However, at
least the result from the current study may be exactly superimposed on the result of the previous area measurement study (Pae, 1989) and the result from Polo et al. (1991). The present study failed to find variables for the pharynx which appropriately describe shape and size separately. It is suggested here that a curve function of the anterior wall of the pharynx may provide a better explanation of the logical relation between size or shape of the pharynx and the fluid mechanics that occur inside it.

1.4 Profile analysis for the mean vector changes

Profile analysis is a convenient technique to represent mean vector changes of two- or three-dimensional landmark data. For the present study the profile analysis was employed simply in order to demonstrate landmark point changes. Mean values of the landmarks C4 and H, and Subm in the face, exhibit a consistent trend in both body positions (Fig. 17). The landmarks C4 and H show a pattern of asymptomatic, mild, severe, and moderate, whereas Subm reveals the order of asymptomatic, mild, moderate, and severe. Among the mean vector changes of the landmarks for the tongue, H exposes a crucial piece of information. The profile of the hyoid bone location change with respect to the baseline E-RGN may be utilized for discrimination of the OSA subjects from the normal. The interesting finding about the hyoid bone landmark was heavily discussed in the previous section. However, the fact of the matter is that landmark location differences of the hyoid bone in different groups may be subtle even though they look large in the profile analysis. The actual value of the hyoid bone position difference in the tongue measurements between the asymptomatic and mild groups displayed in the middle of the right column of Fig. 17, is a fraction of a centimetre, approximately 5mm. However, the
statistical inference test evidences its significance (Table 15) and the profile analysis demonstrates its difference (Fig. 17).

1.5 Severity prediction and PLS summary

1.5.1 Correlation and prediction

As Newton's Laws do not cause the planets to choose the orbits they take (Bookstein, 1990), regression coefficients do not explain the causality of OSA. An interesting report by Neyman titled "Do storks bring babies?" (Scott, 1979) warns against spurious correlation. When employing a nuisance variable for standardization of variables, one should be cautious of a suggestion of causality based on regression coefficients. Moreover, if one wants to see the association between antecedents and consequences, one has to fit all the related variables into one equation, which is obviously impossible. However, the regressions are still based on a presumption of causality and are supposed to be interpreted in terms of mechanisms, not coefficients. Therefore, only a meticulous interpretation of the coefficients can lead us to a better comprehension of the mechanism. Another point that needs to be clarified in correlation study is multicollinearity in a multiple regression equation. By assumption, each regressant must be independent; however, multicollinearity is inevitable in most cases in biology. Therefore, violation of this assumption must be considered when interpreting results. The relationship between neck circumference and OSA was discussed in a previous section. The neck circumference may be a useful variable in predicting the severity of the symptom in OSA determined patients. Furthermore, as was statistically proven in the work carried out by Davies et al. (1992), the neck circumference may show high specificity and sensitivity in detecting OSA.
However, as argued in a previous section, the measurement may not be directly associated with the pathophysiology of OSA. In other words, a thick neck does not bring OSA symptoms as a stork does not bring babies.

1.5.2 Summary of the PLS study

Salience may be the most important statistic used to evaluate the significance of a variable. An interesting but important point in the landmark data analysis by PLS is that one must decide the sign of the salience *a priori*. The indicator variable contains an extrameaning that is directions, for they are vectors, not scalars. Therefore, signs are critical for interpretation of their coefficients. Saliences are coefficients for the indicator variables in a linear equation. However, they are a kind of weight at the same time. Therefore, they compete with each other in an equation for the best optimality. Salience is not a score which can be compared to the absolute standard such as 0; however, it can be weighed relatively in terms of percentage.

For the regression analysis of the severity of OSA in the current study, RDI is employed. RDI has been considered a variable which best describes the symptom severity in a clinical sense. However, the current PLS summary suggests that RDI may not always be the best indicator to explain morphometric abnormalities in the OSA patients. Table 24 provides some interesting arguments in terms of this issue. Particularly, TAT is not a mediocre indicator which explains the block for tongue shape in both body positions. This indicates that the tongue shape may predict TAT and vice versa. Further, Al is superior to RDI for the interpretation of the associations between the blocks for tongue shape in the supine and for the pharynx in the upright position. As noted in the table, RDI is tightly
associated with the demographic variables and size variables. This indicates that these variables, whatever their measurements are, are correlated to each other. Therefore, it is suggested that one should use any index variables, other than RDI or unassorted demographic variables, with any size measurement, to see what happens to RDI. PLS confirmed that size of the upper airway structure may not explain much about OSA severity (Fig. 24). Even though SIZETONGUE demonstrates a considerably high value of salience (0.81), the inter-block correlation level stays around 0.32. Furthermore, the linear model for the supine position appears not to be an acceptable model. Saliences of the face shape variables confirm the significance and direction of each landmark movement. Signs on the value of salience reveal a direction of the landmark which confirms the explanation of the TP spline. For instance, the salience value of -0.11 and -0.20 for C4x and C4y indicate association between each shape variable and INDEX LV. Therefore, 0.11 explains the amount of association between C4x and the severity of OSA, and the negative sign indicates the direction of the landmark data movement. To recap, as OSA symptom becomes more severe, the point C4 moves posteriorly and inferiorly. Likewise, Submentale and Hyoidale move anteriorly and inferiorly. The model for the tongue shape can be explained in the same way as the face model (Fig. 25). Most significant changes occurred in the x-direction. The tongue center, T1 and tongue height show an association with the symptom severity in their anterior movement. The pharynx model should be explained differently, because of its inter-landmark measurements (Fig. 27). The sign in this model does not indicate the direction of a vector, but simply indicates the direction of the association in an inter-landmark data. PLS models for the pharynx show that the pharynx length may be positively associated with OSA symptoms, particularly in the
supine position.

In order to obtain a more comprehensible result, it may be desirable to include significant blocks only in the multiple block PLS analysis. Table 24 is useful in determining which block should be excluded. The $r$ and $rsv$ values for the size block denote low values. Further, it may be preferable to study the shape of the upper airway structure only. Saliences for each LVs are averaged correlation coefficients (see Fig. 28). Overall correlation between the three predictor LVs and the index block LV is derived from the salience weighted sum of the three $r$ values on each block. Amongst three anatomical structures, the pharynx configuration reveals the strongest association with the index block in the upright ($s = 0.94$) and supine positions ($s = 0.64$). The salience for the pharynx block in the upright position shows an exclusively high value, which indicates a high association. On the contrary, the salience for the tongue block in the supine position is extremely low ($s = 0.05$). As discussed above, one cannot interpret these raw values as they are, since they compete mutually and express a relative significance. Therefore, a strong block or indicator is weighted more, and reversely a weak one is weighted less by the opposing block score. Salience on each indicator of each indicator block reveals almost the same ratio of significance as the OSA index block, with the exception of the pharynx block. The variable LT appears to prove the result of the regression study. Its relative significance compared to other variables in its own block is extremly high, particularly in the upright position. This may significantly affect the block salience, and in turn, the overall correlation. The values for the overall correlation may indicate that configuration of the upper airway in the upright position ($r = 0.74$) predicts the OSA severity better than the one ($s = 0.60$) in the supine body position. AI ($s = 0.43$) and RDI
1.6 Clinical inferences

Of the various anatomical abnormalities of OSA patients, the inferiorly displaced hyoid bone may be the most prominent feature. This point is very well documented by numerous scholars (Pepin et al., 1992ab; Maltais et al., 1991). Owing to a lack of longitudinal data, however, whether this is an antecedent predisposing factor or a compensational response of the airway structure to the OSA symptoms (Davies and Stradling, 1990, 1991) is still not clear. Numerous studies have reported the relationship between airway size, hyoid bone location and age. White et al. (1985) documented that age is correlated closely with pharyngeal resistance in men. Correlation between hyoid bone position and age was also investigated by others (Tallgren and Solow, 1987; Windberg, 1987, 1989) who suggested the anterior inferior migration of the hyoid bone with age. Without strong evidence, the relationship between the hyoid bone location and the upper airway size has been questioned. Recently, Athanasios et al. (1991) postulated that the secondary adaptation to surgery for correction of mandibular prognathism may cause inferior migration of the hyoid bone. However, this deduction cannot authenticate the reason for the inferiorly positioned hyoid bone in OSA patients, since we do not know the original location of the bone in OSA subjects. Another factor that makes the interpretation difficult is age, which is a strong confounding factor of hyoid location. The results of this study revealed that age may not be correlated with OSA symptoms (Table 3). However, Table 2 indicates that age may be a weak confounding factor at the P value.
of less than 5%. Age might be proportionally related to airway resistance. In this case, the
hyoid bone migrates down accordingly. Therefore, one can argue that the inferiorly
positioned hyoid bone per se may not indicate the symptom severity proportionally.
However, a lot of questions still remain. As mentioned previously, we do not know from
where the hyoid bone started its migration. The hyoid bone in OSA patients could be
located at a more inferior position than that in the matching age group. Guilleminault and
his colleague (1990ab) reported craniofacial morphologic abnormalities in children with
OSA. Further, a more recent long term prospective study in young children (1992) by the
same group inferred a strong association between SIDS (Sudden Infant Death Syndrome)
and OSA. The result of their cephalometric study did not present any observation on the
hyoid bone position, yet they reported a significantly narrow posterior airway space. A
more interesting observation by them was that their censored cases more frequently had
a positive family history of OSA. Although the evidence for the inheritance of OSA is not
strong, there have been a number of reports on the genetic study of OSA (Redline et al.,
1992; Bayadi et al., 1990; Strohl et al., 1978). A recent odds ratio study based on 50
families by Redline et al. (1992) strongly suggests a significant familial aggregation of OSA
which appears to be independent of obesity. Another study by Bayadi and associates
(1990) found that an interiorly positioned hyoid bone and a small posterior airway space
are associated with a familial tendency of sleep apnea. The hyoid bone position shows
a close association with the position of the epiglottis, since these two structures are fairly
tightly connected via the Ligamentum hyoepiglotticum (Proctor, 1986). The hyoid bone
forms the tongue base as a lingual bone of which mechanical dynamics dictates a
stationary set of anatomical relationships (Thexton, 1984). The function of the epiglottis
in humans may be to allow deglutition without disturbing the lower airway patency. The differences in the morphology and function of the oropharyngeal region in humans versus other mammals are extensive (Smith, 1992). Interestingly enough, configuration of the epiglottis and its relationship to the structures around it in human newborns approximates those of adult nonhuman primates (Smith, 1992; Sasaki et al., 1977). However, the ontogenetical descent of the epiglottis occurs only in humans (Smith, 1992; Petcu and Sasaki, 1991). Sasaki et al. (1977) has already noticed the significant association of the epiglottis position with SIDS. Hence, it is not surprising that Strohl et al. (1978) speculated some relations between SIDS and OSA. The significance of morphologic changes has already been exhaustively demonstrated in the context of expression of function in this dissertation. Gould (1977) attested that changes in shape unrelated to size are attributed to independent adaptive processes. Wimberger (1991) remarked that plasticity may contribute to the morphological diversity. Further, Lovtrup (1988) asserted that ontogenetic development will constitute a recapitulation of the course of phylogenetic evolution. If one considers changes in morphological characteristics as an expression of an epigenetic mechanism, one possibly agrees that not only a chemical substance, but also internal processes and environmental factors can act as a morphogen which may create a vulnerable craniofacial morphology to OSA. The inferiorly positioned hyoid bone reported in this project may lead to the expression of genotypic characteristics of OSA in genetically predisposed individuals. By scrutinizing two structure shapes obtained from the members of a family showing OSA symptoms, e.g. a father and son with OSA, one might decode an encoded potential of genotypic errors.
To investigate the hyoid bone position with respect to other upper airway structures, cephalometrics may be the method of choice. Cephalometric analysis has long been used for the investigation of facial growth and development in the field of orthodontics and also been applied in soft-tissue analysis beginning with Linder Arronson's work in 1960. The cephalometric technique has more recently become an auxiliary diagnostic tool to evaluate the size of the tongue and airway, for it is easily accessible, less invasive, and less expensive. The 2D characteristics of the upper airway structure in OSA subjects are well documented in numerous cephalometric studies and most of them were carried out in the conventional upright position. As a convenient diagnostic method for examining the upper airway, upright cephalometric analysis provides several advantages. Different from other visualization techniques, cephalometric measurements are readily comparable, for the process of obtaining data is stringently standardized and therefore easily convertable from study to study by simple mathematics. Since it has a relatively long history as a diagnostic technique for OSA study, abundant comparable data are available. The results of this PLS study denotes that upright cephalograms may predict OSA indices better. Particularly, information about the tongue shape and size may be better obtained from upright cephalograms. The supine cephalometric technique upholds several good reasons for further development for better OSA studies. As pointed out by Yildirim et al. (1991), the supine cephalometric technique may be the best alternative for the more time and money cost technique such as CT or MRI. Moreover, the current study confirms that supine cephalograms may provide physiologic information. General physiologic response of the upper airway to keep the airway open in the supine position was observed in supine cephalograms. The hyoid bone
location in a supine cephalogram with respect to the mandibular plane might provide a clue in order to distinguish OSA subjects from normals. Moreover, when a upright cephalogram is compared with a supine cephalogram on the same subject, the tongue shape change may deliver crucial information for symptom severity. In this regard, obtaining a supine cephalogram in addition to a conventional upright cephalogram should be for more than an adjunctive purpose.

2. Morphometrics and Statistics

A morphometric study which does not present the statistical evidence may lose its power of persuasion even though it is logically perfect and mathematically correct (Coombes et al., 1991). Morphometrics measures forms and their variations. In the case of a phylogenetic study, morphometrics examines mainly inter-species variations. If it is an ontogenetic study, morphometrics focuses on intra-species variations amongst measured values. The current study was undertaken in the notion of phylogenetic study, since the data is a set of cross-sectional data. Bookstein (1991) defined that morphometrics is the statistical study of the covariance of two different shapes. Variation provides information about measurements in a group, while covariation reveals relationship among measurements between groups. Covariation of the shape change between groups is represented by covariation of the homologous landmark locations between two groups. Hence, shape inter-relation between two groups may be expressed by the covariance between them. If these two shape groups are related systematically or ontogenically, the analysis of their covariance can be construed in the context of deformation analysis from one group to another. On the other hand, from the viewpoint
of spatial statistics, morphometrics may be a study of shape patterns and changes. More specifically, morphometrics may be the study of landmark patterns which vary in a systematic way. Therefore, the biological pattern we pursue in a morphometric study may be a heterogeneity amongst homogenous data.

2.1 Statistical modelling in morphometrics

Whether statistical models in morphometrics are feasible or not has been a recent controversial topic in the field of morphometrics. Like any other delicate argument, this controversy generates heat rather than light. Theoretical advocacy or critique may be beyond the scope of this dissertation, nonetheless I will discuss some of the literature here and present my assertion, because the current study was undertaken based on the same assumption that critics have focused on. Lele and Richardsmeier (1990) exposed some questions about Bookstein’s (1984) basic assumption of the Gaussian perturbation model grounded in their empirical data analysis. They concluded that the assumption of homoscedasticity, which means a characteristic having equal variance for all variables, is not necessarily realistic. However, their elegant argument lost its strength of logic due to several flaws in their data preparation and to the process of development of its reasoning. First, a too small sample size was employed to prove the inadequacy of the circular normal model. It is always easy to statistically prove difference. Second, to check the assumption of homoscedasticity, variance size was examined such as in a case of regression analyses. However, small variances for the small distanced points and large variances for the large spaced points may be associated with spatial autocorrelations. Therefore, an important point to note is not the size of the variation but the shape of
perturbation. Further, the landmarks employed for the current project are separated enough that one need not worry about the size of $\varepsilon$. The investigation by Mardia and Dryden (1989ab) on Bookstein's assumption of isotropic bivariate normal distribution with two means yet a common covariance matrix may close the controversy. They found that the exact maximum likelihood estimation of the parameter $\varepsilon$ and $\tau$ for the Bookstein shape distribution $\beta_{2k-4}(\varepsilon,\tau^1)$ with $n = 25$ was very similar to those of the normal approximation, and so is the standard error obtained from simulation studies. Furthermore, the likelihood ratio statistic $\Lambda$ was asymptotically distributed as $X^2_{12}$ distribution. $X^2$ distribution approximates the sample distribution of the multivariate normal assumed when every mean vector is approximately normal distributed. Therefore, if each sample mean vector is distributed in normal and if the distribution of the $x$-, $y$-variables show $X^2$ distribution, then we may safely apply the central limit theorem in reverse direction to assume the multivariate normal. This supports that the two shape coordinates are independent under the normal approximation. They found that the likelihood ratio statistic for Bookstein's uniform shape change also revealed $X^2_{2k-6}$ distribution asymptotically. The choice of $\tau = \sigma/\delta_{12}$ is dependent on the labelling of the configuration. An intuitive choice of $\tau$, of course, could be the maximum diameter of the baseline. General shape distribution of Bookstein shape variables on $\mathbb{R}^{2(K-2)}$ space was also discussed by Dryden and Mardia (1991). The statistical inference test of the current results was carried out based on the findings of Dryden and Mardia.
2.2 Morphometric tools and statistical models

2.2.1 TP spline and other morphometric tools

Thompson’s masterpiece transformation grid (1917) motivated several methodological propositions in the field of morphometrics. Procrustes methods, finite element methods, and Bookstein’s statistical models with TP splines may be three main passageways leading to the final biological inferences. In his early studies, Bookstein (1978) invented the biorthogonal grids rooted in D’Arcy Thompson’s transformation grids. Bookstein’s biorthogonal coordinate system eliminated the mathematical ambiguity in Thompson’s philosophy. The biorthogonal grid method is neither a kind of FE scaling method (Cheverud et al., 1983) nor a cousin of the Procrustes technique (Rohlf and Slice, 1990). It utilizes a grid system and tensor but it is not based on finite elements nor is it homogeneous. Therefore it does not belong to FE scaling methods. It conceptually coincides with Procrustes methods since it superimposes boundaries of two different outline forms. Yet it distorts the inside of the one image into pointwise homologous correspondence with the inside of the other image analogous to the tensor technique. Thus it is hard to categorize it into a technique of Procrustes methods. However, the biorthogonal method was not a popular morphometrical technique due to its analytical difficulty (Cheverud et al., 1983), and this technique exposes two more flaws. First, it does not yet decompose size and shape, instead it explains shape changes in terms of differential changes in size. Second, it depicts only homogeneous changes, thus it may not demonstrate local changes appropriately. Bookstein’s tools for morphometric analyses of the next generation not only overcome these problems but also surpass two other methods. Shape coordinates neatly quotient out size which is utterly independent from the
shape coordinates. Therefore, allometry can be studied without ambiguity and with ease. Kendall's shape sphere demonstrated a home space of triangles in an elegant manner (1984); however, his space nullifies distance between landmarks in the tangent plane and thereby the Procrustes metric cos\(\rho\) becomes isotropic. Therefore, it may be practically hard to apply his highly mathematical philosophy to somewhat routine biological situations. Otherwise, it may be a different problem from what we are concerned with here as pointed out by Bookstein (1991). Further, Bookstein's multivariate version of anisotropy can partial out a uniform portion of the whole deformation by means of least sums of squares. The remaining part of the entire transformation i.e. the non-linear part can be represented and analyzed by the TP spline method. Lele (1991) criticized the arbitrariness of the superimposition methods, the result of which may vacillate according to the superimposed configurations. However, this may not be a significant handicap for Bookstein’s shape coordinate method. Since, when one selects a baseline, not only the statistical but also the biological appropriateness for the baseline should be considered carefully in advance.

The TP spline technique exhibits several supremacies over other grid techniques. First, it is simple. Although the TP spline method is theoretically supported by sophisticated differential geometry and continuum mechanics, it simplifies them by the straightforward concept of spline interpolation which takes a mean form by computing the average x,y-coordinates for each point (Straus and Bookstein, 1982; Cheverud et al., 1983). Further, this simple mean shape distortion is on one hand philosophically grounded in a simple but fundamental assumption of Gaussian distribution, and on the other hand, it is technically underpinned by spline techniques and advanced computer technologies.
Second, it is biologic. The grid in TP splines is defined by the shape of the biology itself rather than being arbitrarily determined. Biological entities keep moving or changing, which may be an expression of internal physiologic changes. Kinematic changes in configuration of biological objects are always continuous and non-linear thus they can be depicted by a smooth mapping. The TP spline explicitly illustrates nonhomogeneous shape changes. Shape changes in biology are comprised of homogeneous and nonhomogeneous components. Each point within the biological object may have its own local deformation. The TP spline distinctly extracts the local nonhomogeneous portion and displays it. Rohlf and Slice (1990) criticized the ambiguity of in-between landmarks; however, this is not a weak point but may be part of the advantages that describe an unknown betweenness of continuous changes. By reading of the betweenness of ontogenetic and phylogenetic changes one can better comprehend the property of the changes. Recently, as Lele and Richtsmeier (1990) criticized Gaussian perturbation models, they (1991) suggested the Euclidian distance matrix analysis (EDMA) as an alternative, which is coordinate free and scale invariant. They calculated all possible distances between pairs of landmarks and named this matrix 'maximal invariant space' which corresponds to Kendall's shape space (Kendall, 1989). Here, the rank of the matrix is determined \textit{a priori} which is the same as the dimension of the space the landmarks lie on. Thereby, it constitutes a maximal invariant, coordinate free analysis. This technique may be mathematically flawless; however, it trades off predetermined inconveniences instead. First, the arbitrariness of the size measure, second, the form difference cannot be demonstrated, and third, a biologist is interested in localizing shape difference. The EDMA method, however, does not provide the third critical information.
2.2.2 PLS and other modelling methods

PLS analysis was chosen for the current work for the following reasons: first, PLS summarizes intercorrelations among variables, which makes it convenient to analyze a multifaceted structure. OSA is an entity which reveals intricate aspects of pathological characteristics including a morphological anomaly, a functional aberration and an abnormal pathophysiology. In order to analyze possible multiple pathways between antecedents and consequents, the PLS analysis method was incorporated. Second, the PLS method is unusually insensitive to sample size. Owing to the nature of the disease, many measurements compared to sample size should inevitably be employed. Furthermore, the sample size expended for the current project does not allow the pursuit of any rigid parametric estimation. The PLS method may provide supplementary evidence to support a robustness of the previous analyses already carried out. Third, the PLS method is reasonably flexible to its block construction. Thus it permits the unveiling of a possible new link among the block structures normally hidden due to complexity of the disease.

Bookstein's version of PLS differs from Wold's original one in several aspects. The Wold's version stressed a causal-predictive analysis (Wold, 1974), hence the direction of the arrows in the arrow schemes are considered to be important. Moreover, he might have concentrated on condensing a foundation of the soft-structural modelling based on Neyman's philosophy versus the ML technique dominating contemporary statistics. For the LS predictive test, he implemented the Stone-Geisser test for reflective models. For assessment of standard errors, Tukey's jackknife was employed (Wold, 1985). Since both tools are distribution-free, one can apply an irrespectively small number of observations.
As remarked previously however, Bookstein's objectives of PLS analysis are not a testing of models but a summary of intricate relations (Ketterlinus et al., 1989). This new version provides several statistics such as salience, rsv, and correlation coefficient which are readily interpretable. Thus it guides straightforward decisions based on these. In multi-block PLS analysis, instead of using ordinary multiple regression and non-linear operators, Bookstein employs a sum of coefficients from the several simple regressions.

When a matrix system has a complex structure, viz. comprises heterogeneous variables, it is difficult to interpret them as a single system. Because of the complexity, when one tries to analyze the result by common factor analysis or principal component analysis, one mostly cannot avoid spurious interpretation of the floating artifact whatever it is. Bookstein (1989b, 1990d) disclosed a problem common to both component analysis and common factor analysis, which is the emergence of bipolar components or factors after the first component extracted even when path coefficients are expected to be positive. Then one is forced to interpret these bipolar terms as contrasts. Wright's (1932) remedy to protect the results from such a contamination was omission of any cell which belongs to lists of variables sharing a priori or a posteriori group factors. Least-squares computations separate the off-diagonal submatrices block by block. This procedure exactly coincides with Bookstein's PLS algorithm (Bookstein, 1980b, 1987b). PLS examines inter-block associations and block-variable relationships, but ignores intra-block correlations. By ignoring correlations among the intra-block variables, one can escape from the curse of multicollinearity (Bliwise, 1991). Without losing a viewpoint for observing the entire structure, PLS does not overshoot details either. PLS may be an appropriate modelling technique for summary of intricate data structure (Lowe et al., 1992).
3. Applications

Lele and Richtsmeier (1991) pointed out that the mathematical properties of the TP spline may be subjective to express a biological model. However, expression of a biological observation is one aspect of biological science, and the analysis of observed data is another. In Bookstein's shape space, $\beta_{2k-4}(e,m)$, geometry and statistics share their domains via landmark data. In other words, landmark data not only express shape configuration in Euclidean space, but also allow statistical analyses in the same space. Covariance includes information about the relation between two set of landmark data which represent the shape of objects in terms of numbers. By using landmarks as media, TP splines span the geometric Euclidean space and statistical covariance space without constraint or alteration. Therefore, even though TP splines may be subjective mathematically, as long as they are underpinned by statistics, we can trade the unreality of representation for the convenience of the technique. In light of this advantage, the TP spline method can be utilized for diverse purposes in the study of OSA. For instance, an individual facial shape or tongue shape can be compared with a mean shape of each subgroup population by means of a TP spline. Recently, upright and supine cephalometric analyses have begun to be considered as a routine diagnostic procedure (Yildirim et al., 1991; Lowe et al., 1992). The TP spline method can be applied to the obtained cephalogram from a new patient by superimposing the mean shape of the upper airway structure obtained from each subgroup population. The shape of the warped TP spline plane, characteristics of each principal warp, and the amount of warping energy can provide clues as to which group the patient may belong to. Furthermore, the TP spline technique may be applicable not only to a cross-sectional study, but also to a longitudinal
or a kind of longitudinal study. We have already observed second generation OSA patients. A comparison study between the first generation patients and patients of the next generation may provide evidence for the hypothesis about the association between SIDS and OSA discussed earlier. The TP spline can play a crucial role in facial asymmetry study, for instance, quantification of the severity of hemifacial microsomia (Vargervik and Miller, 1984; Grayson et al., 1983). In the reconstructive facial surgery field, a surgeon wants to know the relation between the amount of tissue removed and the amount of face deformed (Schepers et al., 1992). The TP spline method can visualize the effect of orthognatic surgery for OSA patients (Waite et al., 1989; Riely et al., 1989). When we develop this static tool into a more dynamic device by combining it with a powerful computer animation workstation and supportive software, the outcome will be more versatile. When one drags a landmark around, the organism on the screen deforms in accordance with the amount, direction and pace of the landmark movement. We can easily expand the applicability of this technique to growth and development studies. The growth gradient may easily quotient out as the size effect, and the component of pure shape change can be quantified.

While a TP spline analysis provides an intuitive look at the logical relation between observed phenomena and causality by visualizing shape changes, PLS furnishes a significance for the logical relation in terms of numbers. They are mutually supportive. Other structural modelling techniques try to uncover probable underlying factors in terms of latent variables which are linear combinations of observed variables. PLS, on the other hand, starts with latent variables decided a priori and simplifies the structure by means of weighting it in accordance with the importance of each block. If LISREL is said to be
the most general modelling technique in psychometrics, PLS must be the most appropriate one for the summary of any complex biological phenomenon, because biology does not rely on intangible measurements or the 'Ah-ha! principle' as frequently as psychology does. Since the latent variable in the PLS method is determined by an investigator, it allows the researcher more freedom. Landmark variables were employed for the current study. For direct comparison of the predictability between the variable obtained from inter-landmark data and landmark data, PLS two-block analysis can be applied. Furthermore, due to its less stringent assumption, PLS analysis can contribute to OSA study in another sense as well. A PLS assumption allows the use of almost any type of variable in a small size of samples. The variables used for this OSA study are diverse in kind and number. The block design in the PLS method eases handling of variables of different shapes. For instance, one may be able to handle the tongue EMG data obtained from the patient with an intraoral appliance, and the data from cephalometric measurements.

Thompson (1917) already remarked that in theory there may be no difficulty whatsoever in a 3D extension of his coordinate transformation. But, after some trial he seemed to reserve it for other times. Bookstein (1991) suggested eight coordinates per tetrahedron for the purpose of visualizing covariances of 3D shape; however, he also kept this challenging topic for future studies. McCance and his associates (1992) introduced a completely independent technique in their serial works. They obtained 3D coordinates for analysis of the facial surface changes by a laser scanning device. Unfortunately, however, their work was undertaken with insufficient morphometrical consideration in spite of abundant available data and advanced technology. A suggestion might be for them to
invoke Bookstein’s philosophy and shape coordinate methods. The colour mapping they employed may usefully fix one more degree of freedom in 3D coordinate data, and in this manner Bookstein’s 2D TP spline method can probably be extended to 3D data.

In summary, there may be only a few examples of studies in human biology which analyzed an object in a decomposed notion of form, size and shape. The decomposition of a form allowed several advantages for the current analysis. The relationship between the obesity and the size of the structure was assessed. It was speculated that the size factor may not play the most significant role in the pathophysiology of OSA. Particularly, it was asserted that a thick neck may not only be a result of a fat deposition in the airway, but may be more directly associated with the compensatory effort of the upper airway structure to keep the airway patent. This study suggested that the size and shape of the tongue may significantly contribute to symptom severity. An observation of the tongue shape change upon the body position change by TP splines may suggest a new concept for the association between the pathogenesis of OSA and the "differential tongue reaction" to gravity. Pharyngeal form differences among the subgroups and between the two body positions also suggest a new interpretation of the pathogenesis. The pharyngeal length and the pharyngeal width below the most constricted area may be more important in understanding symptom severity than the width of the most constricted area. The current results confirmed an inferiorly positioned hyoid bone in OSA subjects. Moreover, the present study speculated a genetic linkage between the inferiorly positioned hyoid bone and OSA. Future diverse applicability of the analysis tools employed was also discussed.
CONCLUSIONS

The current study attempts to look at the anatomical characteristics of OSA subjects from a new perspective. Although it may be a somewhat theoretical point of view, upper airway structures are decomposed into two aspects: size and shape. This concept and its mathematical manoeuvre provides two advantages. First, one need not be concerned with size matching. In the shape analysis, the difference one observes is a pure shape difference. In order for comparison between two size heterogeneous groups, one need not collect exact size matching subjects. Second, one eliminates size-related noise from the measurement, thus escaping the curse of multicollinearity which is a common problem in multivariate morphometric studies. The first question given for the current project is whether size and shape of the upper airway contribute to OSA severity. The result of the investigation on size is affirmative. However, the tongue is found to be a unique structure which reflects OSA symptoms significantly, yet still provides only a small fraction (11% of RDI variation) of the explanation with regard to OSA symptoms. Thus, it is concluded that size of the upper airway may not be a main predisposing factor which contributes to OSA severity. In contrast, the shape of the structure presents more significant information. The shape of the upper airway configuration explains a higher proportion of RDI variation. Shape change due to OSA severity appears mainly in the lower part of the upper airway structure. Anatomical structures in the hypopharyngeal area reveal a strong tendency to expand the airway to facilitate breathing as symptoms become more severe. The tongue, however, does not seem to respond to the symptom severity with shape changes. The pharyngeal configuration reflects symptoms best. This may be because it is in the pharynx that the actual airway occlusion happens.
Interestingly, however, the length of the pharynx is the factor most strongly associated with OSA symptoms.

The second question is whether body position changes elicit size and shape differences in the upper airway. The statistical inference test on size fails to prove the existence of size changes when the body position changes. Therefore, it is concluded that the size of the upper airway structures does not respond to the body position change from the upright to the supine. The result of the shape study, however, provides several significant findings and implications. The shape of the face does not seem to change in any group in response to the body position change. In contrast, the tongue and the pharynx reveal significant changes. Particularly, the mean location of the hyoid bone in the supine position clearly distinguishes apneic groups from the symptom-free group. This suggests that the hyoid bone position in the supine body position may be used as a criterion for diagnosis of OSA. Furthermore, a TP spline presentation of the tongue shape change secondary to the body position change from the upright to the supine illustrates a gradual shape change of the tongue in accordance with symptom severity. This finding implies that cephalograms taken in the supine position may suggest a physiological response of the tongue to OSA severity. Of the findings obtained in the supine body position, related to the pharynx, the width measurement \( W_2 \) appeared to be an important variable for interpretation of pathophysiology of OSA.

The third question is whether these morphometrical tools are versatile or not. When Thompson (1917) compared the pelvis of Archaeopterynx and of Apatornis, he suggested three transitional figures interpolated between them. A common English expression, "read between the lines", means that a substantial message may be hidden
beneath the surface. Thompson's concept of shape difference measurement may be a scientific version of this connotation. Thompson's Cartesian transformation is an interpolation which may be like stretching out a part of dental rubber dam sheet on which a biological structure is outlined with grids. Using this gridded rubber sheet, the distortion from a normal subject to the subject with severe symptoms differs only from the normal to the mild in an increased intensity or degree of deformation. The background theory of TP spline may appear to be complex; however, it may be a unique morphometrical technique which inherits Thompsonian philosophy without distortion. We observe changing configurations of the face and tongue in accordance with symptom severity and body position changes which are significant according to a statistical inference test. Furthermore, the TP spline analysis visualizes small changes whose significance cannot be proven in terms of statistics. For instance, the TP spline denotes shape changes in the face upon the body position change which could not be demonstrated by statistical means. The main concern of the current project is the shape of the structure. However, the pathogenesis of OSA is extremely complex. It appears to be driven by multiple predisposing and influencing factors. We do not know yet if OSA starts with a genetic defect, and in turn, may be influenced by several developmental factors later, or whether it is a pure developmental disease. Whichever is the case, the integrated outcome including neural inputs, anatomical geometries, and muscular functions must overcome the forces of occlusion in the airway. PLS is a statistical modelling technique which conveniently deals with the intricate relationships of "multiple inequality" amongst multiple data without the influence of multicollinearity. Therefore, we need not be concerned about over-simplification of the model. Optimality in modelling is based on the trade off between
accuracy of demonstration of real phenomena and usability or amenity in analysis. Unlike any other parametric model based on ML assumptions, PLS may not be able to provide an elaborate forecasting ability. It is not a pretentious model. However, it is an appropriate one with which to approach complex biological problems.

The current study has some obvious shortcomings. As discussed previously, the variable SIZPHARYNX may not have faithfully reflected pharynx size. Moreover, the current study fails to suggest proper landmarks for the pharynx. More careful consideration is required to improve comprehension of the structure. Even though there is a software limitation to the program and a limitation of sample size, it could have provided an overall prospective shape change if landmark changes for the face, tongue and pharynx had been measured on one plane simultaneously. This concern is particularly relevant to the two hyoid bone measurements. However, to make such a project possible, one must first find a faithful homologous landmark set on the pharynx.
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Appendix I  Algebraic crux of the TP spline method

Let there be K points

\[ Z_1 = (x_1, y_1), Z_2 = (x_2, y_2), \ldots, Z_K = (x_K, y_K) \]

in the Euclidean plane.

Let \( r_{ij} = |Z_i - Z_j| \) for the distance between points i and j.

Define matrices

\[
P_K = \begin{bmatrix}
0 & U(r_{12}) & \cdots & U(r_{1K}) \\
U(r_{21}) & 0 & \cdots & U(r_{2K}) \\
\vdots & \vdots & \ddots & \vdots \\
U(r_{K1}) & U(r_{K2}) & \cdots & 0
\end{bmatrix}, \quad K \times K,
\]

\[
Q = \begin{bmatrix}
1 & x_1 & y_1 \\
1 & x_2 & y_2 \\
\vdots & \vdots & \vdots \\
1 & x_K & y_K
\end{bmatrix}, \quad K \times 3,
\]

and

\[
L = \begin{bmatrix}
P_K \\ Q^T \\ 0
\end{bmatrix}, \quad (K + 3) \times (K + 3),
\]

where 0 is a 3 x 3 matrix of zeros to match to the number of columns of Q. The matrix \( P_K \) represents a surface spline \( z(x,y) \) which includes a subspace Q. In order to simplify the calculation, the partitioned matrix L, which is the linear combination of the whole image, is constituted.

Let \( V = (v_1, \ldots, v_K) \) be any K vector, and write \( Y = (V \mid 0 \ 0 \ 0)^T \), a column vector of length \( K + 3 \). Three zeros are augmented to match the matrices.

Define the vector \( W = (w_1, \ldots, w_K) \) and the coefficient \( a_1, a_x, a_y \) by the equation

\[
L^{-1}Y = (W \mid a_1 \ a_x \ a_y)^T.
\]

Let the elements of \( L^{-1}Y \) define a function \( f(x,y) \) which describes the spline sheet itself:

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\[ f(x,y) = a_t + a_x x + a_y y + \sum_{i=1}^{K} w_i U(iZ_i - (x,y)) , \]

where the coefficients \( w_i \) sum to zero and their cross-products with the \( x \)- and \( y \)-coordinates of the points \( Z_i \) are zero as well. The function \( f \) represents a thin metal plate originally flat and level, yet now deformed in order to pass through all the points in space. \( f \) is composed of two parts; a uniform part and a non-linear part, sum of function \( U(r) \).

Following are three propositions in this algebra.

1. \( f(x_i,y_i) = v_i, \) all \( i \). This expression indicates that the function \( f \) interpolates the correspondence \( (x_i,y_i) \to v_i ; \) that is, if we imagine the \( (x_i,y_i,v_i) \) as points in three dimensions, the surface \( (x,y,f(x,y)) \) is called the TP plate spline on the nodes \( (x_i,y_i,v_i) \).

2. The function minimizes the non-negative quantity

\[ I_f = \sum_{R=1}^{R} \left( \left( \frac{\partial^2 f}{\partial x^2} \right)^2 + 2\left( \frac{\partial^2 f}{\partial x \partial y} \right)^2 + \left( \frac{\partial^2 f}{\partial y^2} \right)^2 \right) \]

Define this as the bending energy. This integral is zero only when all the components of \( W \) are zero, when the computed spline is \( f(x,y) = a_t + a_x x + a_y y, \) a flat surface.

3. The value of \( I_f \) is proportional to \( WP_K W^T = V(L_K^{-1} P_K L_K^{-1})V^T = VL_K^{-1}V^T \) which is the squared length of the projection of \( L_K^{-1} \) to the subspace \( V \), where \( L_K^{-1} \) is the upper left \( K \times K \) sub-block of \( L^{-1} \).

This sub-block is a function of the points \( (x_i,y_i) \) applied to a vector \( V = (v_i) \) of displacements which yields a scalar of the bending \( E \), where \( V \) is the \( K \times 2 \) matrix

\[ V = \begin{bmatrix} x_1', x_2', \ldots, x_K' \\ y_1', y_2', \ldots, y_K' \end{bmatrix}, \]

where each \( (x_i',y_i') \) is a matching point to \( (x_i,y_i) \). The application of \( L^{-1} \) to the first row of \( V \) determines the coefficients of the function equation of \( f_x(x,y) \), the \( x \)-coordinate of the image of \( (x,y) \). The projection of \( L^{-1} \) to the subspace for the second row of \( V \) does the
same work for the $f_y(x,y)$, the y-coordinate of the image of $(x,y)$. The result function becomes vector valued.

$$f(x,y) = (f_x(x,y), f_y(x,y))$$

This result function $f(x,y)$ maps each point $(x_i, y_i)$ to its corresponding point $(x'_i, y'_i)$. We call this TP spline mappings. Only if the pair of points is mutually homologous, the function $f$ models the difference of two shapes as a deformation. We can compare the mean configuration of one group to another in the context of deformation. The statistical properties of the function $f$ are equivalent to the statistics of the set of data matrix. The total bending $E$ of the full spline is the sum of the bending $E$s of the $x$- and $y$-coordinate separately. The whole procedure is invariant under translations or rotations of either set of landmarks.
Appendix II  Computation for the Two-Block PLS

Two-block PLS is an analysis of the cross-correlation matrix between two blocks of indicator variables which may be denoted as \(X_1,...,X_m\) and \(Y_1,...,Y_n\). All variables are assumed to have a mean value of 0 and a variance of 1. Let the correlations of the \(X_s\) and \(Y_s\) upon each other be as

\[ r_{ij} = \text{cor} \ (X_i, Y_j) \quad i = 1, ..., m \quad \text{and} \quad j = 1, ..., n \]

Let a matrix \(R = (r_{ij})\) be an off-diagonal part of \(m \times n\) nonsymmetric correlation matrix (Ketterlinus et al., 1989). Then, the general rule of SVD (Singular Value Decomposition) allows factorization of the matrix \(R\) such as,

\[ S = U^T D V \]

, where

- \(U\): an orthonormal matrix of left singular vectors
- \(V\): another orthonormal matrix of right singular vectors
- \(D\): a diagonal matrix of singular values which is usually ordered in a descending way, where first \(\min(m,n)\) can be non-zero.

If \(R\) is a data matrix of normalized (z-scored) variables, and \(R\) can be expanded as \(S = U^T D V\), then

1. The rows of matrix \(V\) contain the ordinary principal component loadings of these variables.
2. The columns of \(U^T D\) are the usual principal component scores on each component.

Let the ordinary first principal component \(A = (a_1, ..., a_n)\) of the correlation matrix \(R = (r_{ij})\) for a set of \(n\) variables \(X_1,...,X_n\) be the linear combination of the \(X_s\)'s. Its coefficients show the greatest variance and their squares sum to 1. Then, \(A\) can be considered as having
a least-squares property. When one tries to find a vector for which $A^T A = (a_j a_j)$, 
rank-1 matrix, comes closest to the observed covariance $R$ as measured by the summed-
squared differences $(r_{ij} - a_j a_k)$. Now, the sum of squares of the $a_j$'s is no longer a unity, 
but the eigenvalue of $A$. Since any matrix is the sum of $r$ matrices of rank one, the least-
squares fit to the correlation matrix $R$ is equivalent to a least-squares fit to each of its 
columns $(r_{ik})_{i=1}^n$. In order for the fit to be optimal, $a_j a_k$ must be a least-squares fit to $r_{ik}$ 
as $k$ varies (see Bookstein, 1990, 1991). Thus, the least squares fit of any rank-one matrix 
to $R$ should be

$$R_1 = d_j a_j^T a_k$$

- $d_j$: first singular value
- $a_j$: first row of $A$
- $a_k$: first column of $A$

To simplify the Wold's original version of PLS, ignoring centering the data for norm 1 
scaling, the equation $r_{ik} = a_j a_k$ could be considered as a simple regression equation with 
no intercept. The entries of $a_j$ can be estimated by means of the ordinary regression of 
$r_{ik} = a_j a_k$. To recapitulate, in order to $a_j a_k$ is least squares fitted to an $k$th column of $R$, 
$\sigma_k (r_{ik} - a_j a_k)$ should be minimum

so that

$$a_j = \frac{\sum_{k=1}^n r_{ik} a_k}{\sum_{k=1}^n a_k}$$

where the numerator term $\sum_{k=1}^n r_{ik} a_k$ indicates the sum of the ordinary cross-product 
of the dependent variable in the regression i.e. column $r_{ik}$ by the dependent i.e. the 
column $A$ of coefficients. But, from the other viewpoint, it carries another meaning: 
ordinary covariance $\sigma_i (c_{cases}^T X_i) X_i$ of the $i$th original variable ($X_i$) with the score of the 
LV of the other block $Y$ (Bookstein, 1990). The same rule can be applied on the element
a_k of the first right singular vector. Hence, a_k is proportional to the correlation of the Y variables with the LV of X’s \((m_{i=1}a_iX_i)\). In the least-squares fit to the cross-correlation matrix of the X’s against Y’s, one set of coefficients \((a_i’s)\) are supposed to be already known. Hence, the least-squares approximation of suitable coefficients for the opposite \((b’s)\) only will remain. The coefficient b_j will be derived by minimization of \(zn^T(r_{ij} - a_ib_j)^T\).

After all, the least squares fit to the correlation matrix may be a computation of the coefficients a_i and b_k which are termed as saliences, each are proportional to the covariance of its own indicators with the latent variable of the opposing block. To recap, the least squares fit is an ordinary product of the row salience and column salience to simplify an inter-block correlation matrix. Saliences are path coefficients for regression of the observed variables upon factor scores i.e. the first principal component score.
APPENDIX III  Some Fundamentals in Multivariate Data Management

Multivariate data is a collection of a number of variables from multiple subjects. The values on these variables are measured for each individual items. The n measurements on p variables can be displayed as an array n x p. This rectangular array is called a matrix. An array x of n real numbers x1, x2, ..., xn is called a vector. A matrix is composed of a number of columns and rows which are equivalent to a number of vectors in geometry. A solution of the vectors is a linear combination of the variables. When columns of a matrix are taken directly from the rows of A, the matrix is called as a transposed matrix of A and denoted by AT or A'. If a matrix is transposable, then it is a symmetric matrix. The matrix A is invertible if there exists a matrix B such that BA=1 or AB=1. B is called the inverse matrix A and denoted by A-1. A square matrix is invertible if and only if it is nonsingular. If the system A'x= b has no solution, there is always the unique solution for x= A-1b.

1. Vector space and dimension (Strang, 1988; Johnson and Wichern, 1988)

A vector space \( \mathbb{R}^n \) consists of all column vectors with n components. Matrices can also be vectors. A subspace of a vector space is a non-empty subset that satisfies next two requirements; first, even if any vector is added in the subspace, the sum is still in the subspace. Second, if any scalar is multiplied by any vector, the multiple is still in the subspace. If a vector space \( \mathbb{R} \) consists of all linear combinations of the particular vectors \( w_1, ..., w_p \), then these vectors span the space. In other words, any vector \( v \) in \( \mathbb{R} \) can be expressed as some combination of the w's such that

\[
v = c_1w_1 + ... + c_rw_r \text{ for some coefficients } c_i.
\]
The dimension of the space $\mathbb{R}^n$ is $n$. If there are two column vectors in the space $\mathbb{R}^3$, then we say it is a two-dimensional subspace of $\mathbb{R}^3$. The set of solutions to $Ax = 0$ is defined as the nullspace of $A$. Reversely, the null space of a matrix consists of all vectors $x$ such that $Ax = 0$. Suppose we start with a matrix that has more columns than rows $(m > r)$. Then, there must be at least $m - r$ free variables. To rephrase, if a homogenous system $Ax = 0$ has more unknowns than equations $(m > r)$, it has $n - r$ dimension of the null space which counts for the degrees of freedom and the rank of the matrix. The simplest pieces of matrices are matrices of rank one. Every matrix of rank one can be transformed as the product of a column vector and a row vector such as, $A = uv^T$.

2. Projection and least Squares (Strang, 1988; Johnson and Wichern, 1988)

Suppose $x$ is an $n$-dimensional vector. When $A$ multiplies $x$, we consider it as a transformation of the vector $x$ into a new vector $Ax$. When it happens at every point $x$ of the $\mathbb{R}^n$, we say that the whole space is transformed or mapped into itself. Every transformation which meets the following three conditions is considered as a linear transformation.

1. It is impossible to move the origin.
2. $cx$ must go to $cx'$, for $A(cx) = c(Ax)$.
3. If the vectors $x$ and $y$ go to $x'$ and $y'$, then their sum $x + y$ must go to $x' + y$, for $A(x + y) = Ax + Ay$.

A projection is analogous to a linear transformation. A projection matrix takes the whole space, therefore, fails to be invertible. Suppose a projection onto the $e$-line. The length of the projection will be $c = \cos e$ and the projection matrix will be $c (c, s)^T$, where $s = \ldots$
The length $|x|$ of a vector in $\mathbb{R}_n$ is the positive square root of such that

$$|x| = x_1^2 + x_2^2 + \cdots + x_n^2 = x^T x$$

If vectors $x$ and $y$ are orthogonal, then their inner product $x \cdot y$ ($x^T y$) is zero. The inner product $x^T y$ determines the angle between them, e.g. perpendicular vectors have $\cos \theta = 0$. If the non-zero vectors are mutually orthogonal, then they are linearly independent.

The cosine of the angle between any two vectors $a$ and $b$ is $\cos \theta = a^T b/|a||b|$. To project $b$ onto $a$, $b$ is multiplied by the projection matrix $P$, where $P = aa^T/|a|a^T a$ which is a column times a row divided by the number $a^T a$ and actually is $|a| a$. The least squares solution to a problem $ax = b$ in one unknown is $x_\sim = a^T b/a^T a$. A singular case in matrix calculation is when a case does not have a solution or it has many solutions. In most of the cases dealt with in statistics there are too many solutions. Let's consider least squares problems with several unknowns. Let $A$ be an $m \times n$ matrix, where the number of observations $m$ is larger than the number of unknowns $n$. It must be expected that $Ax = b$ will be inconsistent. The vector $b$ will not be a simple combination of the columns of $A$. Therefore, minimization of the error is required in the least squares sense. The error can be denoted as $|Ax - b|$. We are looking for the least squares solution $x_\sim$ which minimizes $|Ax - b|$. This is the same as locating the point $p (=Ax_\sim)$ that is closest to $b$ in the column space. In other words, the error vector must be perpendicular to the subspace. The least squares solution must satisfy the normal equations such that

$$A^T Ax_\sim = A^T b$$

If the columns of $A$ are linearly independent, then $A^T A$ is square, symmetric and invertible, thus $x_\sim = (A^T A)^{-1}A^T b$. The projection of $b$ onto the column space is therefore $P = Ax_\sim$. 

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= A(A^T A)^{-1} A^T b.

3. Characteristic function and spectral decomposition (Johnson and Wichern, 1988; Srivastava and Carter, 1983)

Let the matrix \( A \) be a \( k \times k \) square matrix and \( I \) be the \( k \times k \) identity matrix. Then the scalars \( \lambda_1, \lambda_2, \ldots, \lambda_k \) satisfying the polynomial equation \( |A - \lambda I| = 0 \) are called the \textbf{eigenvalues} (characteristic roots, or latent roots) of a matrix \( A \). The equation \( |A - \lambda I| = 0 \) (as a function of \( \lambda \)) is called the characteristic equation. Let \( A \) be a matrix of \( k \times k \) and let \( \lambda \) be an eigenvalue of \( A \). If \( x \) is a nonzero vector such that

\[ Ax = \lambda x \]

then \( x \) is said to be an \textbf{eigenvector} of the matrix \( A \) associated with the eigenvalues \( \lambda \).

Let \( A \) be a \( k \times k \) square symmetric matrix. Then \( A \) has \( k \) pairs of eigenvalues and eigenvectors:

\[ \lambda_1, e_1, \lambda_2, e_2, \ldots, \lambda_k, e_k \]

The eigen vectors can be chosen to be satisfy \( 1 = e_1'e_1 = \ldots = e_k'e_k \) and be mutually perpendicular. The eigenvectors are unique unless two or more eigenvalues are equal.

When a \( k \times k \) symmetric matrix \( A \) is such that

\[ 0 \leq x'Ax \]

for all \( x' = [x_1, x_2, \ldots, x_k] \), \( A \) is said to be non-negative definite. If \( x \) is not a zero vector, then \( x'Ax \) produces only squared terms and it is termed a \textbf{quadratic form}. This definition is important in manipulation of multivariate data for the multivariate analysis dealing with squared distances.
The spectral decomposition of a $k \times k$ symmetric matrix $A$ is such that

$$A = \sum_{i=1}^{k} \lambda_i e_i e_i' + \sum_{i=2}^{k} \lambda_i e_i e_i' + \ldots + \lambda_k e_k e_k'$$

where $\lambda_1, \lambda_2, \ldots, \lambda_k$ are the eigenvalues of $A$ and $e_1, e_2, \ldots, e_k$ are the associated normalized eigenvectors. Hence, $e_i'e_i = 1$, where $i = 1, 2, \ldots, k$ and $e_i'e_j = 0$, $i \neq j$.

4. Singular value decomposition (Strang, 1988)

The singular value decomposition (SVD) is closely related to the eigenvalue-eigenvector factorization of a symmetric matrix $A = U^T D U$. $D$ is a diagonal matrix of the eigenvalues and $U$ is the orthogonal eigenvector matrix: $U^T U = I$. However, if one allows the $U$ on the left and the $V^T$ on the right, then eigen analysis of any two orthogonal matrices becomes possible. Furthermore, the positive entries $\sigma_1, \ldots, \sigma_r$ of the diagonal matrix $\Sigma$ become a singular values of $A$. Hence, SVD is: A $m \times n$ matrix $A$ is decomposed into $A = U \Sigma V^T = (\text{orthogonal})(\text{diagonal})(\text{orthogonal})$. The columns of $U$ ($m \times m$) are eigenvectors of $AA^T$, and the columns of $V$ ($n \times n$) are eigenvectors of $A^T A$. The $r$ singular values on the diagonal of $\Sigma$ ($m \times n$) are the square roots of the nonzero eigenvalues of both $AA^T$ and $A^T A$.

5. Partitioning of matrix (Johnson and Wichern, 1988)

Often, the individual measurements fall into two or more groups in accordance with their characteristics. Subsetting the total collection into several distinct subgroups may occasionally be convenient for appropriate interpretation or calculation. Conversely, sometimes we need to combine two or more separate linear functions to ease calculation.
6. Descriptive statistics (Johnson and Wichern, 1988)

Let \( x_{11}, x_{12}, \ldots, x_{1n} \) be \( n \) measurements on the first variable. The arithmetic average of these measurements, denoted by \( x_1^- \), is given by

\[
x_1^- = \frac{1}{n} \sum_{j=1}^{n} x_{1j}
\]

If the \( n \) measurements represent a subset of the full set of measurements, the \( x_1^- \) is also called the sample mean for the first variable. Thus the sample mean can be denoted as

\[
x_i^- = \frac{1}{n} \sum_{j=1}^{n} x_{ij} \quad i=1,2,\ldots, p
\]

The measurement of data spread, the sample variance, is denoted as:

\[
s_{ii}^2 = \frac{1}{n} \sum_{j=1}^{n} (x_{ij} - x_i^-)^2
\]

The square root of the sample variance, \( s_{ii} \), is known as the sample standard deviation.

Let there be \( n \) pairs of measurements on \( k \) variables. A measure of linear association between the measurements of variables is provided in terms of covariance which is the average product of deviations from their respective means.

\[
s_{ik} = \frac{1}{n} \sum_{j=1}^{n} (x_{ij} - x_i^-)(x_{kj} - x_k^-)
\]

where \( i=1,2,\ldots,p \) and \( k=1,2,\ldots,p \). The sample covariance \( s_{ik} \) measures the association between the \( i \)th and \( k \)th variables. If there is no particular association between the measurements the covariance \( s_{ik} \) will be approximately zero.

The sample correlation coefficient (or Pearson’s product moment correlation coefficient) which is another measure of the linear association not depending on the units of measurements, is defined such that

\[
r_{ik} = \frac{s_{ik}}{s_{ii} s_{kk}} \quad \text{for } i=1,2,\ldots,p \text{ and } k=1,2,\ldots,p.
\]

The sample correlation coefficient is a covariance standardized by the product of the squared root of the sample variances. Therefore, if it is supposed that the original
measurements $x_{ij}$ and $x_{kj}$ are standardized values by their standard deviation, then they will be centered at 0 and expressed in standard deviation units, thus the sample correlation coefficient is nothing but the sample covariance. This concept is important in order to understand the landmark data analysis and PLS. When $n$ measurements on $p$ variables are employed for descriptive statistics calculations, the matrix for $S_n$ and $R$ consists of $p$ rows and $p$ columns.