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3D morphometric analysis of the human incudomalleal complex using clinical cone-beam CT

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Abstract

Human middle ears show large morphological variations. This could affect our perception of hearing and explain large variation in experimentally obtained transfer functions. Most morphological studies focus on capturing variation by using landmarks on cadaveric temporal bones.

We present statistical shape analysis based on clinical cone beam CT (CBCT) scans of 100 patients. This allowed us to include surface information on the incudomalleal (IM) complex (joint, ligaments and tendon not included) of 123 healthy ears with a scanning resolution of 150 μm and without a priori assumptions. Statistical shape modeling yields an average geometry for the IM complex and the variations present in the population with a high precision.

Mean values, variation and correlations among anatomical features (length of manubrium, combined length of malleus head and neck, lengths of incus long and short process, enclosing angles, ossicular lever ratio, incudomalleal angle, and principal moments of inertia) are reported and compared to results from the literature. Most variation is found in overall size and the angle between incus and malleus. The compact representation provided by statistical shape modeling is demonstrated and its benefits for surface modeling are discussed.

Keywords

Statistical shape modeling; middle ear ossicles; incus; malleus; cone beam CT; morphology

Abbreviations

CT	Computed tomography
CBCT	Cone beam CT
FE	Finite element
IH	incus head
ILP	lenticular process of the incus
ISP	short process of the incus
IM	incudomalleal
IMJip	incudomalleal joint, inferior point.
MAP	anterior process of the malleus
MH	Malleus head (caput malleus)
MLP	Lateral process of the malleus
PC	Principal component
PCA	Principal component analysis
PMI	Principal moment of inertia
SNR	signal to noise ratio
Stdev	standard deviation
SSM	Statistical shape model
uCT	micro CT
Um	Umbo or inferior tip of the malleus

Introduction

Human middle ears show large variations (Kirikae 1960; Ars 1997; Todd and Creighton 2013; Quam et al. 2014). These variations can affect sound transmission, possibly explaining the large variations found in experiments (Rosowski et al. 2007) and affect our individual perception of hearing. Nowadays, middle ear computational (finite element, FE) models (Funnell (1984), Koike et al. (2002), Gan et al. (2002), Steele et al. 2015, Hamanishi et al. 2015, Motallebzadeh et al. 2015) are typically based on tomographic data such as CT, MRI, or histological sections (Decraemer et al. 2003, Lane 2004, 2005) and they are used to predict and understand sound transmission. Some studies investigate the effect of adding more detail on certain middle ear structures. These details can have important effects for middle ear functioning: e.g. the synovial joints (Decraemer et al. 2015, Gerig et al. 2015), the malleus-tympanic membrane connection (de Greef 2015a), and high resolution scans of soft tissue (Sim and Puria 2008, de Greef 2015b). Improving our knowledge of these key structures is important. Nevertheless, it is also important to study the effects of variation and uncertainty to understand normal, pathological, or reconstructed middle ear functioning. For material parameters, this can be done by a sensitivity analysis of the involved parameters (Qi, et al 2006, Hofstetter et al. 2010, Muyshondt et al. 2015, Motallebzadeh et al. 2015). The model geometries of current models, however, are mostly based on data from a single or a few specimens.

Two exceptions to the preceding statement are the study of Lee and co-workers (2006) and the study of Oßmann and co-workers (2015). Each study uses a different approach to incorporate geometric variation, but they did not report on the effect for sound transmission. Lee et al. (2006) showed that it is possible to construct basic ‘patient-specific’ finite element models based on clinical CT scans (slice thickness 0.625 μm) of 31 subjects with normal hearing. Due to the low resolution of their CT scans they lack important details in the model such as tympanic membrane thickness and an incudomalleal (IM) joint. These issues can be overcome by using a parametric hybrid approach. For example the model of Oßmann et al. (2015) is based on μCT images so they can include these important morphological details. Next, their model geometry was made parametric by manually chosen landmarks (distinctive points and dimensions) by a priori assumptions on geometry variation. Finally, the geometric parameters were obtained by fitting this parametric model to clinical cone-beam CT data. Also, some important work has been done by Audette et al. 2008. They report of a method for applying a piecewise affine-initialized thin-plate spline transformation to a high-quality model of the middle and inner ear. Their results indicated that minimally supervised model computation for the guidance of ear surgery is feasible.

We now propose a new technique that uses statistical shape models (SSM) to capture these shape variations. In this way we avoid a priori assumptions about morphology. We will show that the principal components (PC) of the SSM approach will allow us to capture and report the natural anatomical variations in the human population. In this work clinical cone beam CT (CBCT) data has been used to capture the IM complex in 100 patients.

As compared to non-clinical μCT , the resolution and SNR of CBCT is much lower and CBCT cannot be combined with staining protocols. μCT , on the other hand, can only be used on cadaveric temporal bones (Decraemer et al. 2003, Sim and Puria, 2008, De Greef 2015a). To build a realistic model, this

detailed information obtained from temporal bone studies (histological sectioning, stained μ CT) will be needed. Nevertheless, the use of CBCT allows us to get access to clinical data and much larger inter-human variation in middle ear morphology can be captured. Moreover, this could enable clinical applications in the future. Specifically, the low resolution data coming from the CBCT of an individual can be used to generate the “true” shape of the individual’s ossicles by fitting the low res image to the statistical shape model. In this way, it may become possible to pre-operatively prepare custom made prostheses ossicles, especially now micro-3D printing techniques are coming of age.

The advantages of CBCT over conventional clinical fan beam CT include a lower radiation dose for the patient and a better spatial resolution (in our case 150 μ m). This provides a more reliable morphologic assessment of middle ears (Dahmani-Causse et al. 2011). The disadvantage is the vulnerability to motion artefacts, the longer acquisition time and the lack of Hounsfield units (Casselman et al. 2013).

In this paper, we report the IM complex shape variations obtained *in vivo* by using CBCT scans. Mean values and variations of anatomical features will be compared to the literature and the correlations among these measures will be assessed. Finally, the advantages of using the SSM approach in geometry representation and its implications for future FE implementation will be discussed. In particular, it’s these FE models that in a later stage will allow us to make further conclusions (e.g. about the functional form).

Methods and Materials

2.1 Data acquisition

In this study, clinical cone-beam CT scans of 100 patients were analyzed retrospectively. A NewTom 5G, QR Systems (Italy) with an amorphous silicon flat panel of 20 x 25 cm, a scan field of view of 15 x 8 cm, a voltage of 100 kV resulting in 150 μ m spatial resolution was used. Both temporal bones scanned at the same time for patients with various pathologies. This study was approved by the ethics committee of AZ *Sint-Jan, Bruges, Belgium* (BUN: B049201525222) and all data was anonymized. Diseased ears, e.g. fluid filled, were excluded from this study resulting in a total of 147 healthy middle ears. The average subject age was 51 years with a standard deviation of 17 years (minimum age is 19, maximum is 86). The group included 51 Females and 50 males.

2.2 Individual model generation

First, 3D surface triangulated geometrical models were constructed for the 147 middle ears by specifying the portion (segmentation) of each slice image belonging to IM complex using Amira software (version 5.3). This was done in a semi-automatic way by selecting grayscale values above 500. Where necessary, the ligaments of incus and malleus were removed from the segmentation. Occasionally, parts of stapes head and neck also had higher grayscale values and a manual segmentation was needed. On the other hand, the manubrium and/or distal end of the long process of the incus sometimes had lower grayscale values, in this case these features were added manually. Triangulated surface models were created by using a marching cubes algorithm (surfacegen module). Subsequently, these surface models

were smoothed by shifting vertices to the average position of neighbors (smoothsurface module) and decimated to about 3000 vertices (Fig. 1). All ears are transformed to left ears.

Fig. 1: Geometric model generation (patient #71, right ear). IM joint in (A) transverse plane, (B) coronal plane and (C) sagittal plane, IM complex is labeled in red. (D) Unsmoothed and (E) smoothed 3D geometrical surface model of IM complex after segmentation.

2.3 Statistical shape modeling

Next, a dense correspondence between the CBCT samples was obtained by pair-wise elasticity modulated registration (Danckaers et al. 2014).

The correspondences were obtained in three steps:

- 1) a reference surface was selected and registered to 70 middle ear samples. This reference was a smooth surface with distinct features, which had been uniformly resampled and made watertight,
- 2) a new reference surface with strongly reduced bias was generated by spatially averaging the 70 shapes. The corresponded shapes were aligned by Procrustes analysis. For each surface point of the middle ear, the average point per set of corresponding points was calculated.
- 3) the reference was successfully registered to 123 middle ears. First, an initial global rigid registration is obtained. Then, a global rigid registration and an elasticity modulated registration are iteratively repeated. During the iterations, the stiffness gradually decreases, such that the surface will become more elastic through the iterations.

24 middle ears were excluded, because of the difficulty to find correspondence between rod like protuberances, such as incus long process. This is because the algorithm searches for corresponding

points by casting a normal ray from the template surface to the target surface. If ILP of the template surface is much longer than ILP of the target surface, no correct corresponding points will be found near the end of ILP. This issue will be further explored in future work.

An SSM was built from these corresponding scans by applying principal component analysis (PCA) on the points of the corresponded surfaces, describing the average shape and the main variations of the middle ear within the CBCT population. To build such an SSM, it is important that the surfaces are superimposed by optimally translating and rotating the surfaces. The optimal poses are determined by Procrustes analysis. An SSM can be presented by the following formula: $\mathbf{y} = C(\bar{\mathbf{x}} + \Phi \mathbf{b})$, with $\mathbf{y}$ the matrix that holds the surface points of an instance of the model, $\bar{\mathbf{x}}$ the matrix that holds the surface points of the average surface, C a rigid transformation and $\mathbf{b}$ the vector that holds the shape parameters. Matrix Φ holds the eigenvectors of the shape model. By adapting the shape parameters, the point coordinates will be displaced and a new, realistic surface can be formed (as shown in Fig. 2).

Fig.2: SSM approach: each target (e.g. $y_n = P100_L$) can be obtained by adding a linear combination of the principal components ($\sum \Phi_n b_n$) to the average model ($\bar{X}$) and applying a similarity transformation (C).

Next, the SSM was used to locate landmarks on the individual ossicle surfaces (Fig. 3). These allow us to present important measures and compare these to values from the literature. Landmark coordinates were acquired by manually annotating the points on the average of the SSM and transforming them to the individual middle-ears using the deformation function for each target. For a subset of landmarks (Um, ILP, MAP, ISP, MLP, and IMJcp), a further local optimization was performed using a geometric construction (based on the mapping of landmarks of the average shape). Three axes were defined by the original transformed landmarks: the ISP-MAP axis, IH-ILP axis, and the MH-Um axis. The Um, ILP, MAP and ISP landmarks were defined on their respective axis by projecting the surface points onto the axis and calculating the farthest surface point on the axis. MLP was defined as the farthest point from the MH-Um axis. IMJcp was defined as the center of gravity of the IMJip-IH-MH triangle. The optimized landmarks were sought within a radius of 0.5mm of the transformed annotated landmarks. The optimization was performed one time.

Landmarks were then used to calculate relevant ossicle features which can be compared to literature:

- The manubrium length (Um-MLP) and neck-head distance (MLP-MH) of the malleus and its enclosing angle (Um-MLP-MH);
- the short (ISP-IH) and long (ILP-IH) process lengths as well as the distance from ISP to ILP and the angle between short and long process of the incus (ILP-IH-ISP); It should be noted that the short

and long process length are here defined as the distance measured till the incus head, and not till the IM joint as in the literature. The reason for this is that the IM joint was not visible in our segmentation.

- other length definitions given by Ars (1977): Um-IMJip, ILP-IMJip, and the enclosing angle (approximately the angle between manubrium and incus long process).
- Important measure is the classic lever arm ratio (hemila et al. 1995). Here defined as the ratio between the perpendicular distance from Um to the anatomical axis (I1,Um-AnAx) and from ILP to the anatomical axis (I2,ILP-AnAx). The anatomical axis is defined by MAP-ISP. This ratio was determined using the same technique as in de Greef et al. (2015b).
- Face breadth is measured on CT scans as the distance between left and right intertragic notch, which is the notch between the tragus and antitragus, situated above the lobule of the auricle. This distance is chosen as a measure of face breadth because it, in contrast to the pinna or lobule, was distinguishable on all the scans (by using CBCT, not the whole cranium is visible).

Fig.3: Landmarks used in this study to compare to literature data (shown on mean of SSM): (Um) umbo or inferior tip of the malleus; (ILP) lenticular process of the incus; (MAP) anterior process of the malleus; (ISP) short process of the incus; (MLP) lateral process of the malleus; (MH) malleus head (caput malleus); (IH) incus head; (IMJip) incudomalleal joint, inferior point.

Correspondence quality was assessed by calculating the inter- and intra-observer error. To this end, landmark points were manually annotated by three observers: all landmarks were identified on the average surface of the SSM and ten instances of the middle ear. For each surface and each landmark, the error was calculated as the distance between the manually annotated points and their mean. The calculations were repeated after locally optimizing the landmark locations.

The full 3D representation of the geometrical model also allows us to calculate the volume and the principal moment of inertia of the incudomalleal complex (PMI). A homogeneous ossicle density (2250 kg/m^3 , Sim et al. 2007, de Greef et al. 2015b) was assumed. Next, the principal moments of inertia (PMI) were calculated. Therefore, all surface models need to be filled with tetrahedral elements (tetgen, Si 2006). Center of mass was chosen as origin. For each tetrahedral element, the inertia matrix $I_{x_i x_j, k} = m_k d_{x_i, k} d_{x_j, k}$ was calculated (with m_k mass of tetrahedral element k and $d_{x_i, k}$ the perpendicular distance from axis x_i (x, y, z) to the center of element k). Next, the overall inertia matrix was calculated by taking the sum of all k elements. Eigenvalues of this matrix were the PMI. A custom-made MATLAB script was used for these calculations. These anatomical features are summarized in Table 2.

A multiple linear regression was performed between the principal component weights and the features of each surface, capturing the relationship between them (Allen et al., 2003). The regression matrix could be used to visualize the influence of a specific feature on the principal component weights, and thus on the 3D shape of the middle ear. The variation of a specific feature was represented by a deformation vector and by scaling this vector (by multiplying it with a factor), the underlying correlation between feature and shape could be visualized (Fig. 7).

In order to study the effect of the principal components these anatomical features are also shown for the first 6 principal components (Table 1). Finally, a Kolmogorov-Smirnov and Shapiro Wilk test for normality was applied, showing that the data is normally distributed. Such that the Pearson correlation had to be used. This correlation and significance level between the measured values was calculated, corrected with a Bonferroni factor of 136. Data is presented dimensionless because the volume is significantly correlated with most lengths and strongly correlated with PMI. Therefore, lengths are divided by $\text{volume}^{1/3}$ while moments of inertia are divided by total mass and $\text{volume}^{2/3}$ (Table 3).

2.4 Quantitative data of anatomical features

Next, landmarks are used to obtain quantitative data of anatomical features. Therefore Intra- and inter-observer errors are calculated. One observer indicated all landmarks on 5 individual surfaces and did this three times. For each landmark on each surface, the distance between the three trials and the average of their location was calculated and averaged over the five surfaces. The inter observer error thus gives an indication of the error one can expect over multiple selection trials for a single observer.

Next, this error is compared with the variation that can be expected for landmarks obtained via the SSM method described in the previous section. One observer indicated all landmarks on the average and did this three times. These landmarks were then used in the geometric construction of the landmarks for five individual surfaces. Again, for each landmark on each surface, the distance between the three trials and the average of their location was calculated and averaged over the five surfaces.

A similar approach was followed for the evaluation of the inter-observer error (three observers, 10 individual surfaces) and comparison with the variance that can be expected for the landmarks via the SSM method.

Results

3.1 Statistical shape model

The 123 separate surface models acquired from CT data look noisy even after smoothing (e.g. Fig. 1). This is caused by the limited resolution of 150 μm (1/30 of manubrium length) and the poor SNR compared to μCT . Nevertheless, combining data of 123 healthy ears in an average model (Fig. 3) removes this random noise and results in a smooth average model.

The principal components (PC) or eigenshapes added to this average model show the variation present in our dataset and by extension in the human middle ear (Fig 4). An advantage of the decomposition in PCs is that the first PCs explain most variation in data (Fig.5). The principal components are linearly uncorrelated shape variations and do not coincide with single anatomical variations per se. This is shown in Fig. 4 and in Table 1. Some features, such as PMI2,3 are mainly described by a single PC, while other anatomical variations, such as Um-IMJip and ILP-IMJip are described by multiple principle components. Nevertheless, a more qualitative explanation of variations within these eigenshapes (shown in Fig. 4) can be given:

- PC1: 30% of the variation in our population. Mostly scaling of IM complex. Indicated by larger variation (stdev/mean) for lengths, volume and PMI in Table 1 and smaller variations in angles. Also, short process of incus seems to be affected.
- PC2: 18%, mostly the angle between manubrium and long process of incus (around lateral medial axis). Indicated by larger variation of Um-IMJip-ILP in Table 1. Also small effect on lever arm ratio (2% of 1.34 in Table 1), PMI1 and curvature of manubrium (not shown).
- PC3: 7.9%, mostly angle between manubrium and long process of incus (around anterior-posterior axis). Also angle between manubrium and malleus neck.
- PC4: 5.6%, mostly change of manubrium shape. Also thickness of malleus head and incus short process.
- PC5: 4.1%, manubrium shape and incus long process length result in large variation for Um-IMJip-ILP (Table 1).
- PC6: 3.6%, incus short process shape
- PC10: 1.6%, variation tends to be much smaller, incus long process (not shown)
- PC20: 0.64%, small changes in thickness of incus long process and manubrium
- PC22: 0.54%; PC37: 0.20%; PC40: 0.18%, tiny variation, mostly surface perturbations.

PC1-22 capture 90% of the total variation, and PC1-37 95%. The higher PCs (41-122) explain much smaller variation (combined contribution of them is less than 4%) in the population. These variations can for instance be originating from noise. The effect of leaving out higher order PCs is shown in Fig. 6.

Fig. 4: Selected principal components of the middle ear SSM. For each eigenshape $Eig = 1, 2, 3, 4, 5, 6, 20$ and 40 , the average $- 3 \cdot \text{stdev}_i PC_i$ (left) and average $+ 3 \cdot \text{stdev}_i PC_i$ (right) are shown.

Fig.5: Compactness of the model: the amount of eigenshapes / PCs needed to explain the fraction of total variation in the entire middle ear population used in this study. (cum. var. = cumulative variation)

Fig.6: Compactness of the model shown for P14_L: effect of leaving out higher order eigenshapes (10 Eigs: PC1-10, 80% variation all models, 22 Eigs PC1-22 90%, 37 Eigs: PC1-37,95%).

	average all data (N=123)		average model	PC1	PC2	PC3	PC4	PC5	PC6
Um-MLP (mm)	4.53	7%	4.49	4%	0%	1%	2%	0%	0%
MH-MLP (mm)	4.89	5%	4.87	3%	1%	0%	2%	1%	0%
Um-MLP-MH (deg)	118	5%	118	0%	1%	1%	2%	2%	1%
ISP-ILP (mm)	5.68	7%	5.67	4%	2%	1%	0%	1%	1%
IH-ISP (mm)	4.37	8%	4.32	5%	4%	0%	1%	1%	2%
ILP-IH-ISP (deg)	59.5	6%	59.9	0%	1%	1%	0%	2%	2%
Um-IMJip (mm)	4.91	7%	4.88	4%	3%	1%	1%	2%	2%
ILP-IMJip (mm)	3.27	9%	3.21	4%	1%	1%	2%	3%	2%
UM-IMJip-ILP (deg)	37.8	19%	37.0	0%	5%	2%	2%	10%	1%
I1=Um-AnAx (mm)	4.50	6%	4.42	3%	1%	1%	2%	1%	1%
I2=ILP-AnAx (mm)	3.40	9%	3.31	3%	1%	1%	3%	3%	1%
Lever arm ratio	1.33	9%	1.33	0%	2%	0%	0%	4%	1%
Volume (mm ³)	28.8	14%	28.4	12%	3%	2%	3%	1%	2%
PMI1 (mg mm ²)	123	23%	119	22%	8%	3%	4%	4%	0%
PMI2 (mg mm ²)	173	23%	164	22%	1%	0%	0%	1%	1%
PMI3 (mg mm ²)	256	22%	245	22%	4%	2%	2%	1%	0%

Table 1: Measures for important IM features as indicated in Fig 3. 'average all data' is the average of 123 Patients and the relative stdev. Average model is created by SSM. PC1-6 is (average model + 3 stdev_i - (average model - 3stdev_i))/6/average model.

3.2 Anatomical features

The Intra- and inter-observer errors were calculated as described in section 2.4. The maximum intra-observer error (mean $\pm$ stdev) was found for MH (0.12 $\pm$ 0.04 mm) and IH (0.14 $\pm$ 0.05 mm), with an average of 0.08 $\pm$ 0.03 mm. Next, this error is compared with the variation that can be expected for landmarks obtained via the SSM method described in Section 2.3. As such a lower error was obtained for all points (average of 0.06 $\pm$ 0.02 mm) except for MH 0.17 $\pm$ 0.04 and IH 0.20 $\pm$ 0.02 mm). A similar

approach was followed for the evaluation of the inter-observer error and comparison with the variance that can be expected for the landmarks via the SSM method. The maximum inter-observer errors were also for MH and IH (0.25 ± 0.07 mm and 0.24 ± 0.06 mm), with an average of 0.11 ± 0.05 mm (mean $\pm$ stdev between). The SSM landmark method improved the average error for all landmarks (average = 0.07 ± 0.02 mm, IH = 0.23 ± 0.02 mm and MH = 0.18 ± 0.02 mm).

In Table 2, an overview of measures for important anatomical features is given and compared to values from the literature. Relative standard deviation is about 7% for most lengths (Um-MLP, ISP-ILP, IH-ISP, Um-IMJip, l1) . The variation is larger for the angle between manubrium and long process of incus (19%), for volume 14% and for PMI around 23%. As a comparison, the total variation in face breadth is only 4%. Dimensionless values show smaller variation. For PMI1, PMI2 and PMI3 we found (mean value $\pm$ stdev (stdev/mean)) of 0.201 ± 0.013 (6%), 0.284 ± 0.028 (10%) and 0.42 ± 0.029 (7%). As a total mass we found 64.7 ± 8.9 mg by using uniform density of 2250 kg/m^3 .

3.3 Correlations

Finally, the dimensionless features are used to find correlation in data, by using the Pearson correlation coefficient. In Fig. 7 the correlations of these features are compared to the entire shape. By using the dimensionless data, very high correlation between PMI and volume (90% and up) and significant correlation between lengths of the malleus and PMI and volume (40%-60%) due to scaling correspondence are reduced. Indeed, moments of inertia are related with mass and thus volume and lengths. Results found for the dimensionless data are (Table 3):

- PMI1 is strongly correlated with the length of incus short process.
- PMI2 and 3 are correlated with each other and with manubrium length, malleus neck-head and incus long and short process (for PMI3).
- The angle between manubrium and long process of incus (Um-IMJip-ILP) is correlated with long process (IH-ILP) and its lever arm (ILP- AnAx) but not with the manubrium (Um-MLP, Um-AnAx).
- As a result, the lever arm ratio is negatively correlated with this angle.
- The lever arm ratio is also more strongly correlated with the incus long process (IH-ILP, -0.64) than with the manubrium arm (Um-MLP, 0.20).
- Malleus angle is negatively correlated with the manubrium length.
- In general, no middle ear measures correlate significantly with the face breadth (highest correlation for ILP-IH-ISP, $r=0.2$).
- It is noteworthy that there are not so many strong correlations between anatomical features (e.g. only correlation for incus angle is IM complex opening angle (Um-IMJip-ILP)).

Fig.7: Feature plot shows the correlation between a specific feature (± 3 stdev) and the shape. PMI (norm.) is the principal moment of inertia divided by mass and volume^{2/3}.

	Soons et al. (2015) (N=123)	De Greef et al. (2015b) (N=6)	Kirikae (1960) (N=1315)	Ars (1977) (N=200)	Weistenhöfer and Hudde (1999) (N=1)	Unur et al. (2002) (N=20)	Sim et al. (2007) (N=3)	Todd and Creighton (2013) (N=41)	Quam et al. (2014) (N=43)
Um-MLP (mm)	4.53±0.33	4.98±0.39	4.51±0.08			4.70±0.45		4.8±0.4	4.94±0.31
MH-MLP (mm)	4.89±0.23	4.74±0.29	5.0±0.1			4.85±0.29		4.9±0.3	
Um-MLP-MH (deg)	117.5±5.8	-	120.8±3.9					111±14	
ISP-ILP* (mm)	5.68±0.38	5.73±0.16	5.99±0.08			6.12±0.43		5.9±0.4	6.18±0.34
IH-ISP* (mm)	4.37±0.37	5.35±0.21	4.81 ±0.07			4.88±0.47		5.0±0.3	5.07±0.37
ILP-IH-ISP (deg)	59.4±3.5	-	58.7±1.0					73±6	60±4.9
Um-IMJip (mm)	4.91±0.32	4.68±0.34	4.65±0.09	4.5±0.5					
ILP-IMJip (mm)	3.27±0.31	3.19±0.21		3.1±0.5					
UM-IMJip-ILP (deg)	37.8±7.0	35.3±5.4		29±14					
I1=Um-AnAx (mm)	4.50±0.28	4.47±0.30							
I2=ILP-AnAx (mm)	3.40±0.29	3.45±0.15							
Lever arm ratio	1.33±0.12	1.30±0.11							
Volume (mm ³)	28.8±4.0	26.7±2.4					27.6±4.5		
PMI1 (mg mm ²)	123±28	114±10			97.6		133±19		
PMI2 (mg mm ²)	173±39	163±32			165.0		175±21		
PMI3 (mg mm ²)	256±56	237±32			217.4		259±34		
Face breadth (mm)	130.1±5.6								

Table 2: Mean±stdev for important anatomical features, for this study and selected literature (N=number of samples). Note that angle UM-MLP-MH for Kirikae (1960), angle UM-IMJip-ILP for Ars (1977), the angles for Todd and Creighton (2013) and Quam (2014) were not given in original papers and were here calculated by assuming uncorrelated results for propagation of errors. As a result the actual Stdev in their measurements would be lower. * Also note that there is a difference in the definition for these measurements in our case and in literature, as mentioned earlier in 2.3.

	Um-MLP	MH-MLP	Um-MLP-MH	IH-ILP	IH-ISP	ILP-IH-ISP	Um-IMJip	ILP-IMJip	Um-IMJip-ILP	Um-AnAx	ILP-AnAx	ratio	volume	PMI1	PMI2	PMI3	Head diameter
Um-MLP	1.00																
MH-MLP	0.13	1.00															
Um-MLP-MH	-0.37	-0.16	1.00														
IH-ILP	0.17	0.43	-0.08	1.00													
IH-ISP	-0.02	0.18	-0.02	0.33	1.00												
ILP-IH-ISP	-0.14	0.00	0.19	-0.10	0.00	1.00											
Um-IMJip	0.53	0.34	0.36	0.25	-0.01	-0.01	1.00										
ILP-IMJip	0.21	0.34	-0.07	0.88	0.26	-0.19	0.35	1.00									
Um-IMJip-ILP	-0.10	0.04	-0.29	0.55	0.08	-0.37	-0.22	0.71	1.00								
Um-AnAx	0.56	0.42	0.20	0.22	0.10	0.12	0.62	0.19	-0.30	1.00							
ILP-AnAx	0.18	0.28	-0.08	0.82	0.03	-0.02	0.17	0.86	0.72	0.28	1.00						
Lever arm ratio	0.20	0.03	0.22	-0.64	0.05	0.11	0.25	-0.69	-0.88	0.39	-0.77	1.00					
volume	-0.14	-0.51	-0.19	-0.24	0.03	-0.10	-0.41	-0.27	-0.08	-0.33	-0.28	0.01	1.00				
PMI1	0.03	0.30	0.01	0.32	0.75	-0.05	0.07	0.32	0.12	0.19	0.13	0.02	-0.14	1.00			
PMI2	0.59	0.36	-0.02	0.29	-0.03	-0.03	0.69	0.31	-0.05	0.51	0.26	0.09	-0.29	-0.12	1.00		
PMI3	0.51	0.43	0.07	0.40	0.34	-0.06	0.67	0.39	-0.04	0.55	0.25	0.13	-0.32	0.37	0.85	1.00	
Face Breadth	0.03	0.10	-0.06	0.16	0.17	0.20	0.03	0.11	0.05	0.06	0.15	-0.09	0.04	0.03	0.16	0.13	1.00

Table 3: Correlation between dimensionless anatomical features. Highlighted values have a significance smaller than 0.05/136, bold values have a significance of 0.001/136

Discussion

4.1 IM complex measures

A good agreement with literature values (mean, Stdev) was obtained. Malleus neck-head lengths show good agreement with all literature values. The manubrium is up to 9% shorter than in most studies, except for Kirikae (1960) and Unur et al. (2002). Incus distance from long to short process is up to 8% shorter. The Incus short process is up to 18% shorter than literature values. This is due to a difference in definition mentioned earlier in 2.3. We do have a very good agreement with lengths for lever arm ratio (I1 and I2). In general, the relative standard deviation values found in this study are similar to those from the literature (~7% in most cases), except for Kirikae (1960) who reports systematically smaller standard deviations.

The volumes we found are slightly higher than those reported in previous literature. Differentiation between bone and air is clear on CBCT, so these slightly higher values show that the dimensions of the material during segmentation were not underestimated. This consequently suggests that the shorter lengths in this study were not caused by too low grayscale values selected during automatic segmentation. Moreover, Buytaert et al. (2014) showed that the effect of segmentation is small. The variation of volume shows to be around 14%. We also found values for PMI in good agreement with previous data, but because we have a statistically relevant amount, we can also report on more reliable data for statistical variation. This variation shows to be quite large (~23%). A better way to present this data could be a dimensionless representation ($\text{PMI} / \text{density} / \text{volume}^{5/3}$). $\text{Volume}^{5/3}$ may seem artificial. Nevertheless, numerical variation of the power in the previous equation shows lowest variation (stdev/mean) for PMI1 for a power of $1.6 \sim 5/3$.

The correlations of dimensionless measures allow us to focus on the shape. Table 3 shows that PMI1 (dimensionless) is strongly correlated (75%) with incus short process and that PMI2 and 3 are correlated with manubrium length, malleus neck-head and long process. This is in correspondence with the rotation axes reported in literature (Weistenhöfer and Hudde 1999, Sim et al. 2007, De Greef et al. 2015b). PMI1 axis is approximately situated along the inferior-superior direction (more or less Um-MAP). Moment of inertia around this axis greatly depends on the mass and length of the incus short process. PMI2 axis is approximately along the anterior-posterior direction (more or less anatomical axis). An increase of the short process, almost located on this axis, will not affect this moment of inertia ($r = -0.03$). On the other hand, increasing the length of the manubrium and malleus head will have a large effect. PMI3 is approximately along the lateral-medial direction. Effects are similar as for PMI2. The effect of a longer incus process is smaller than malleus due to the smaller mass associated with this feature.

Nevertheless the length of the incus long process will affect lever arm ratio more than length of manubrium or malleus neck. The angle between manubrium and long process of incus has a large variation (19%, Table 1) and is also strongly correlated with long process length and not with manubrium length, and will thus affect the lever arm ratio. One could argue that a large variation in anatomical

feature means that the feature has no large effect on the transfer function. On the other hand, the lever arm ratio is part of the pressure amplification function of the middle ear ossicles (Hemilia et al. 1995). This is something that could be investigated with a finite element model with a parametric geometry based on SSM.

In general, only a few anatomical features show mutual correlation. Moreover, large variations are found in the IM complex (~7% for lengths, up to 19% for IM angle). This means that most anatomical variations are not strictly constrained. This is similar to the conclusion of Todd and Creighton (2013). We also found no significant correspondence between IM complex measures and the face breadth. This is similar to the non-correlation between any ossicle dimension and mastoid size (Todd and Creighton, 2013). Finally, we also found no correlation between age and ossicle dimension for ages between 19 and 86 years.

To conclude this discussion, we explicitly want to point out that the middle ear transfer function is not only influenced by anatomical features and inertia properties, but that the mechanical properties of the ligaments also have a major effect on this transfer function.

4.2 Cone beam CT

Literature data presented by Kirikae (1960), Ars (1977), Unur et al. (2002), Todd and Creighton (2013) and Quam et al (2014) were obtained using optical microscopes. Weistenhöfer and Hudde (1999) improved this technique by acquiring different view angles to obtain 3D information on the ossicles. The introduction of (micro)CT opened the possibility for quantitative 3D imaging. The results of de Greef et al. (2015b) and Sim et al. (2007) are based on full 3D data obtained on cadaveric temporal bones with high resolution μ CT. Although CBCT (150 μ m) has a higher resolution compared to standard clinical CT, its resolution is still inferior to (stained) micro-CT (20 μ m). In the present study, we use available clinical data of a large patient population to calculate average morphology and their variation with a high precision. As such our study is limited to 'macroscopic' (~150 μ m) shape variations. To catch these 'microscopic' variations, we would need a large amount of cadaveric temporal bone scans. This amount would even be larger than in this study to catch these 'microscopic' changes.

IM joint and stapes were visible on most CBCT scans but correct segmentation would be problematic because subtle variation in grayscale values (~Hounsfield unit) occur and limit the automatic segmentation at places with lower grayscale values. We chose automated segmentation, limited to the IM-complex, because of the large data set (147 ears). The absence of Hounsfield units in CBCT also implies that density and material parameters cannot be coupled to grayscale values.

Another limitation is the visibility of soft tissue. General details on ligaments and joints could be obtained from ex-vivo uCT and histological studies (e.g. Sim and Puria 2008, de Greef 2015a). Details on tympanic membrane shape and thickness could be obtained from other in-vivo measures, such as OCT

(Van der Jeught et al. 2013), Moire profilometry, and real-time microscopic phase-shifting profilometry (Van der Jeught et al. 2015).

4.3 Statistical shape modeling

To generate an SSM, surface models, created by segmentation, are needed. Segmentation can be dependent on the operator's subjective input. The influence of the operator's manual segmentation has been quantified by Buytaert et al. (2014). In their study, the standard deviation between results generated by different operators was always smaller than 1.4%. This variation is smaller than the standard deviation of the features presented here and thus will only have a marginal effect. In addition, we use a more automatic segmentation which probably decreases this subjective error caused by manual intervention even more.

Another source of subjective errors is the selection of the landmarks. In most studies, these landmarks need to be selected on each surface model or digital image (for microscopy studies). Using the SSM approach, the anatomical landmarks only need to be selected on the average model. The sensitivity and correctness of this selection is shown to be small for most points ($<50\text{ }\mu\text{m}$ for inter- and intra-observer errors). For IH and MH the error was higher, around $200\text{ }\mu\text{m}$, which is still comparable to the used resolution and the obtained variability. By using the optimization routine these smaller errors ($50\text{ }\mu\text{m}$ instead of $90\text{ }\mu\text{m}$ for most landmarks) are found. The effect is largest for the inter-observer error. Important to reduce these operator-induced errors are to provide a priori guidelines.

A major advantage of SSM is the reduction in the number of parameters that are needed to describe the shape variation. The reason for this is that higher PCs (>40) represent tiny variations (e.g. the combined contribution of PC 41-122 is less than 4%). In this way most of the variation can be represented with a very limited number of parameters. Small variation however does not imply small influence on mechanical behavior. This would only be the case if the mechanics act as a linear function. In this way a higher PC potentially has a non-negligible effect on the mechanics. It is also possible that multiple PCs have an influence on the same small region, whereby the combined results can be large. One could also do parameter studies of the shape without using SSM (e.g. Oßmann et al., 2015), but the advantage of using SSM, however, is that one does not have to make a priori assumptions on the shape variations. Indeed, the shape variations are captured before placing the landmarks, necessary to obtain classic anatomical information, and in this way by using SSM one could study parameter variation in a more natural way. E.g. the angle between malleus and incus change without other geometry variations: in table 3 we see that this variation is correlated with other changes. Another advantage of point-based SSM is the dense correspondence between different shapes because of the large number of landmarks. In this way the relation between the parameters and the global shape can be visualized. The result of a parameter variation can immediately be seen. This delivers not only more qualitative insight into shape variations (which is harder in the case of a 1D parameter), but also allows us to evaluate (using FE-analysis) the influence of a parameter along a variance that is greater than that observed in the specific samples. A disadvantage is that SSM have difficulties to capture outliers. All shapes of SSM need to have the same topology. This will not completely be true if for instance the manubrium is broken. At least

SSM will be a good framework to detect these outliers so they can be dealt with manually. Another disadvantage is the difficulty to find correspondence between rod like protuberances, such as incus long process. This is because the algorithm searches for corresponding points by casting a normal ray from the template surface to the target surface. If ILP of the template surface is longer than ILP of the target surface, no correct corresponding points will be found near the end of ILP. This problem can result in ILP being mapped to manubrium or ILP with a similar shape as ILP of the template surface. This result in the exclusion of 24 ossicles in our analysis (going from 147 healthy ears to 123 analyzed ears).

In future this approach can be used to study the influence of morphology on transfer function. First, having the ‘average middle ear’ model will enable us to study the ‘average mechanics’, without being limited to data of a single specimen which could be a special case. Next, variation and uncertainty on the geometry can be studied by doing a parametric study including the eigenshapes. For the IM complex, only 6 parameters will be needed to explain 69% of all variation, 10 for 80% of variation, 22 for 90%. In addition, a sensitivity analysis can determine the most important eigenshapes for the functioning of the ear. The eigenshapes could also be used to smooth a low resolution CT scan, as shown in Fig. 6. This will allow patient-specific modeling approach. Another possibility is to change certain features, as shown in Fig.7, to test their influence. Finally, knowing the morphometric data of the healthy ear, may be helpful for the classification of middle ear diseases.

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Data availability

Statistical shape model is available from www.uantwerpen.be/bimef (downloads).

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