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How to Make a Haptic Device Help Touch Virtual Histological Slides

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Contents

Abstract

Virtual reality can be used to simulate features of specific materials in order to provide a sense of direct contact with the simulated object. The present study concentrates on informational aspects related to the transformation of visual into haptic data. The current trial was conducted to compare two studies. Study 1 was carried out to help teach blind and visually impaired people histology while study 2 was initiated to generate the basis for simulated facial cleft surgery. Although both tasks are based on a transferal of histological slides into a polygonal mesh the degree of complexity differed considerably with the respective task. Despite the fact that both studies relied on well-established methods in computer graphics and haptic rendering, study 2 requires a higher degree of computational literacy than does study 1. This led to a hypothesis of why the tranfer of visual to haptic data is not often reported in the biomedical sciences. Future studies need to incorporate touch into virtual environments to enhance realism of virtual medical environments and to make biomedical sciences more accessible to blind and visually impaired individuals.

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1 Introduction

1.1 General

It is generally acknowledged that research is required whenever information has to be converted from one mode into another. A haptic device can convert pictoral data into tactile information. The authors of the present study are therefore evaluating the use of a haptic device in the biomedical sciences. The field of surgery (as in Study 2 see below) may for instance benefit from surgeons trained in simulations (Montgomery et al. 2003, Schendel et al. 2005). It is also possible to use aspects of this approach to teach blind or visually impaired people rather abstract concepts such as microscopic biology (Study 1). The transformation of pictoral information into a tactile representation is the common trunk (Fig. 1). Advanced simulated surgery demands a reduced degree of simplification and steps towards controllable complexity while successful transformation for the blind and visually impaired often requires a considerable reduction in complexity. The present report may give a representation on problems associated with preparations to overcome this dilemma.

1.2 Histology

Histology involves the use of a set of techniques to examine the morphology, composition, and architecture of tissues. The desired tissue is first removed from the organism and then placed in fixative in order to preserve the structure of the tissue. Common fixatives used for light microscopy and histochemistry often include formaldehyde (formalin) as most histological staining methods, but not all, allow its use.

Fixation provides rigidity to the tissue as cross-linking covalent bonds are formed between and within the amine groups of the tissue. The tissue is usually kept in the fixative overnight. Extended fixation times may cause damage to the sample which becomes apparent in artifacts at high levels of magnification. Once cells and tissue have been fixed, they can be kept indefinitely at room temperature as fixation makes it easier to section the sample. After completion of fixation, the macromorphology of the specimens is documented. Large samples are then sectioned for further processing while small samples are directly processed for histochemical staining. In order to do this, tissues are dehydrated by first using graded ethanol solutions, followed by xylene. The graded solutions gradually expose the sample to changes in hydrophobicity, minimizing damage to cells. Usually, tissue samples are then embedded in a material with mechanical properties similar to their mechanical properties which eases subsequent slicing with a microtome. It is common to use paraffin wax for embedment. Once the wax-tissue complex is allowed to solidify it forms a block that can be held in a microtome for plain sectioning.

Samples embedded in paraffin are first mounted in a microtome which holds a sharp blade. It is controlled by a crank that is turned to bring the paraffin block closer to the blade. The microtome can be adjusted for width and angle of cut and so as the crank is operated further, the blade cuts slices of paraffin that contain the tissue. After several slices of the paraffin-embedded tissue have been cut, the slices are gently brushed from the blade and floated atop a water bath to smooth out the sample. The slices are teased apart and floated onto a glass slide. After the slides have dried, they are placed in an oven to “bake” the paraffin. This process is followed by component identification via staining (e.g. histochemistry). Different staining techniques are available to color components of interest referentially. The most commonly applied stain is called Hematoxylin and Eosin (H and E) in which the hematoxylin component makes nuclei appear dark blue while eosin stains the remaining cell components (such as the cytoplasm) reddish (Fig. 2).

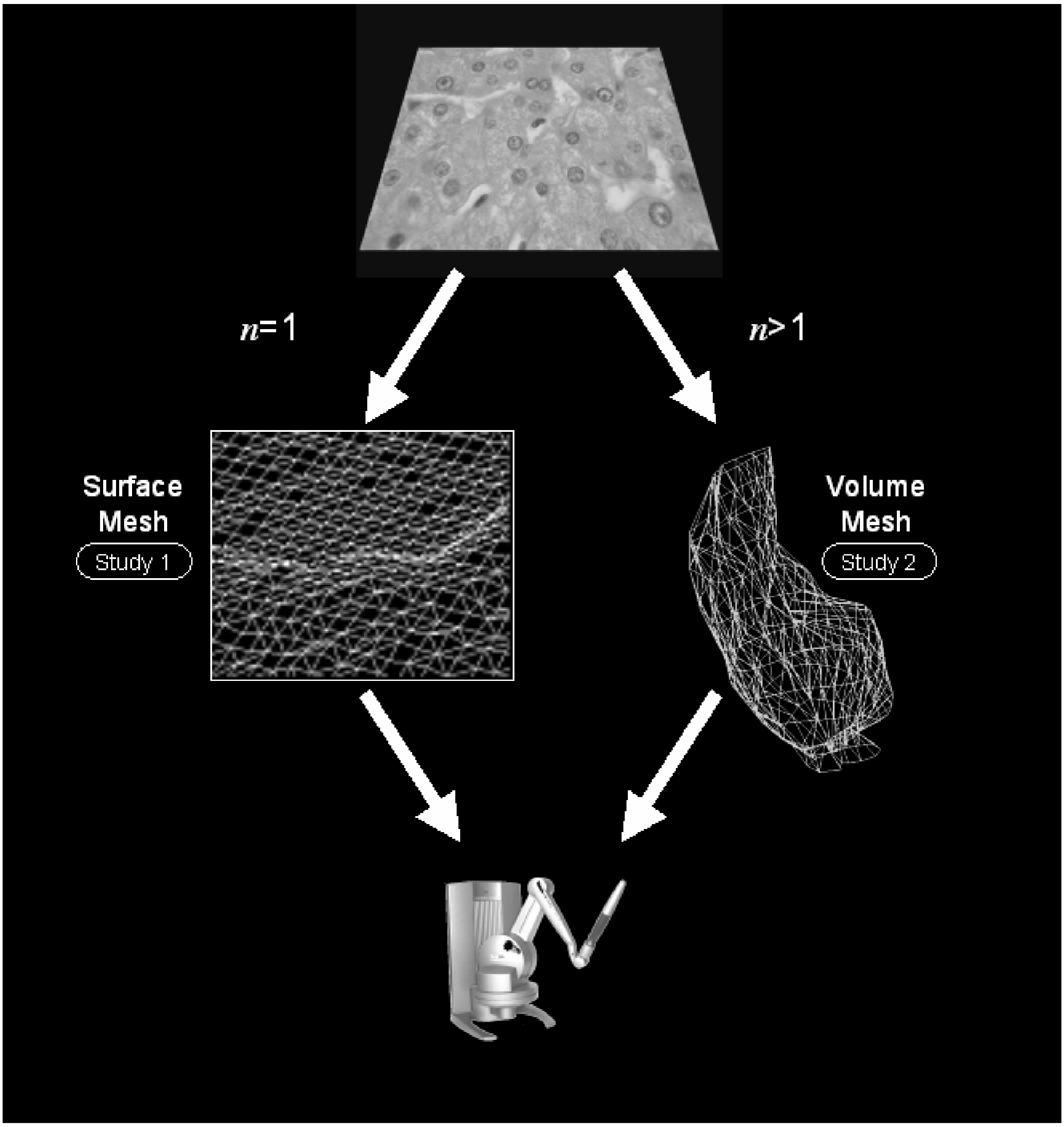

Fig. 1: Information transfer is identical for both studies: for each of the two studies pictoral information is translated into a virtual mesh to be further processed by a haptic device. The term n represents the number of digital images required for translation

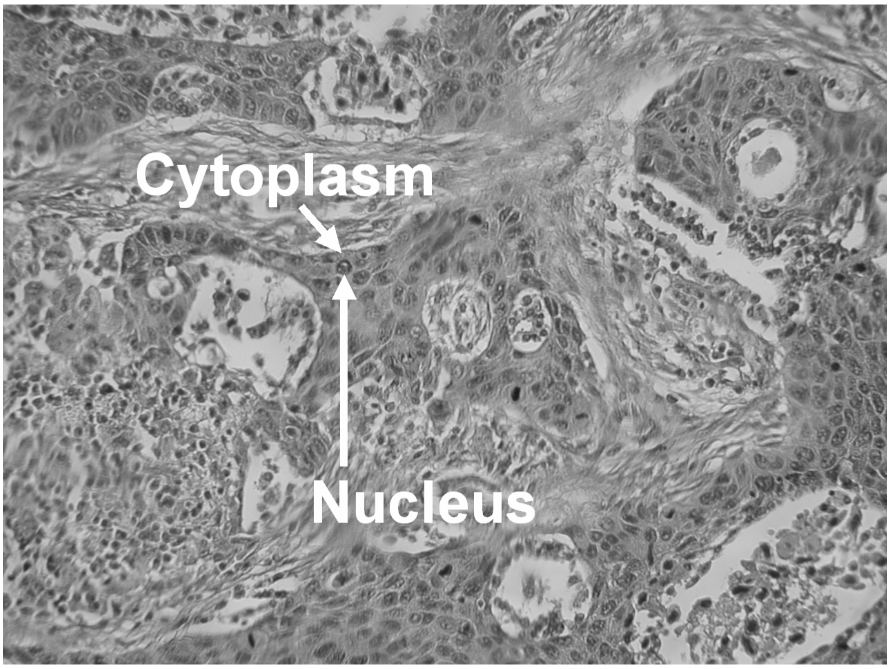

Fig. 2: Real histological slide prior to segmentation. A squamous cell carcinoma with a considerable desmoplastic stroma reaction (H&E staining).

1.3 Segmentation

A variety of digital cameras may be used to obtain photographs that can be further processed by a computer. Digitalization will be followed by segmentation and classification which is performed to break the images into parts, objects or patches with similar properties (Fig. 3).

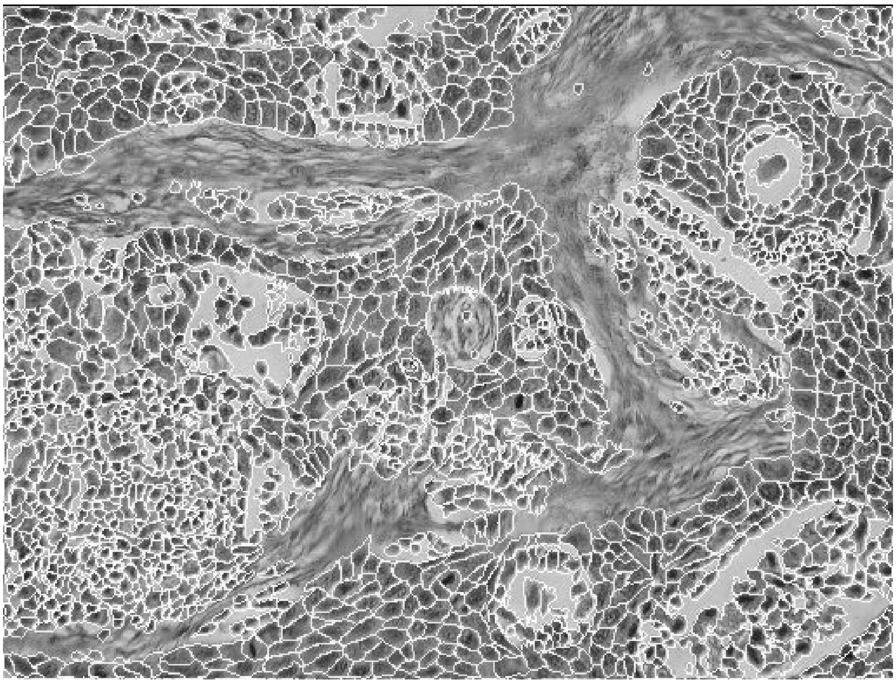

Fig. 3: The real histological slide depicted in Fig. 1, now segmented. The image contains 1,753 classified objects. Most parts of the desmoplastic stroma reaction however are not segmented as they will be modeled mathematically.

1.4 Rendering

The aim of rendering is to generate new synthetic slides adapted from the segmented and classified slides of the previous step.

1.5 Preparation

Information provided by photographs of real histology is too complex for teaching a blind or visually impaired individual histology by the means of a haptic device. This led to the idea to reduce complexity by generating virtual representations of the photographs of real histological slides (Fig. 4).

For simulating microsurgery, a stack of histology pictures has to undergo 3D reconstruction to generate a complex virtual three dimensional object (Fig. 5) that can be manipulated with a haptic device. Virtual surgery benefits from photorealistic visualization and other aspects of increased complexity.

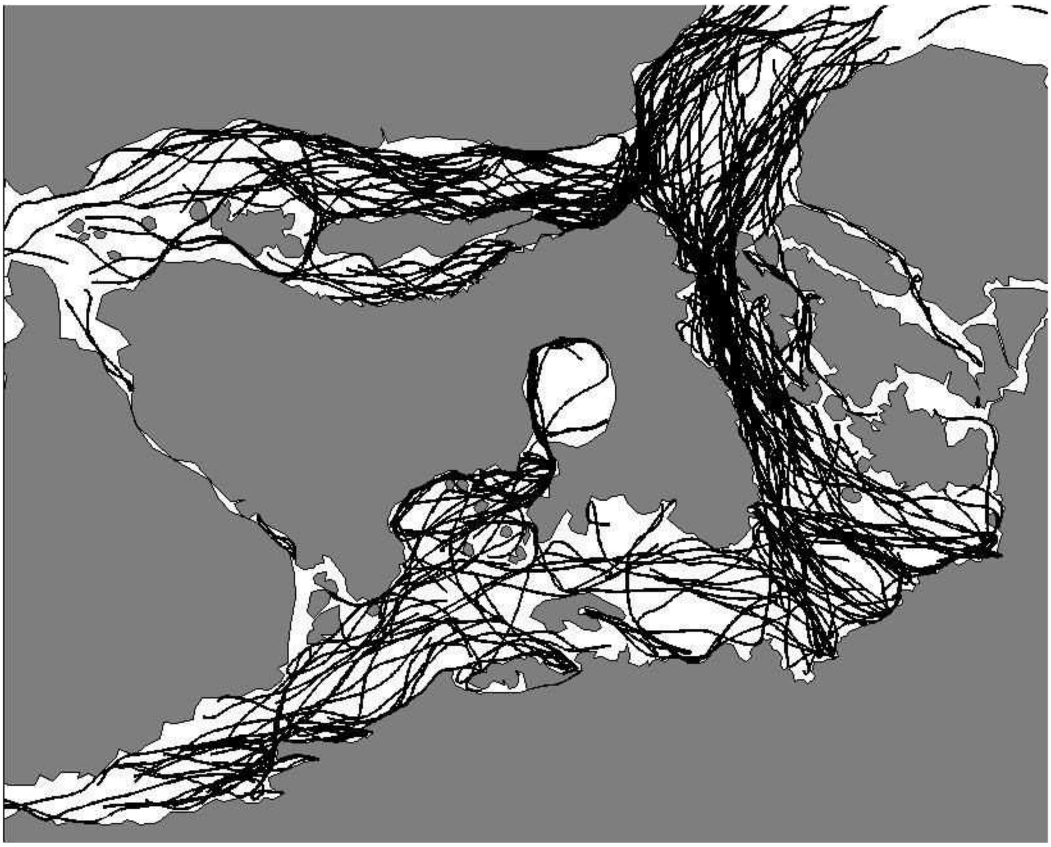

Fig. 4: *Virtual histological slide. Early steps in the mathematical model of the desmoplastic stroma reaction showing trajectories of simulated fibroblasts, smoothed with a Savitzky-Golay filter. In this model, each cell was characterized by its position and velocity both of which are time-dependent. The trajectories are stochastic processes, where for the speed a modified Langevin equation was assumed. Included impulses for the velocity-vector were chemotaxis, contact guidance, friction and random fluctuation. While the cell characteristics were meshfree, this did not hold for the collagen fibres: They were modelled as a vectorfield on regular cartesian grid. So the interactions between the different variables (fibres: discrete, cells: continuum) lead to a hybrid discrete-continuum model. It is clear that because of the enormous complexity of the mathematical model lots of parameters arise. Most of these parameters are unknown at this point of research, so they were estimated by trial-and-error. The stroma was simulated to interact with the virtual representation of the squamous cell carcinoma shown in Fig. 1. The degree of complexity has therefore been reduced which also allows a blind or visually impaired person to "read" the scenario once transformed into haptic signals.*

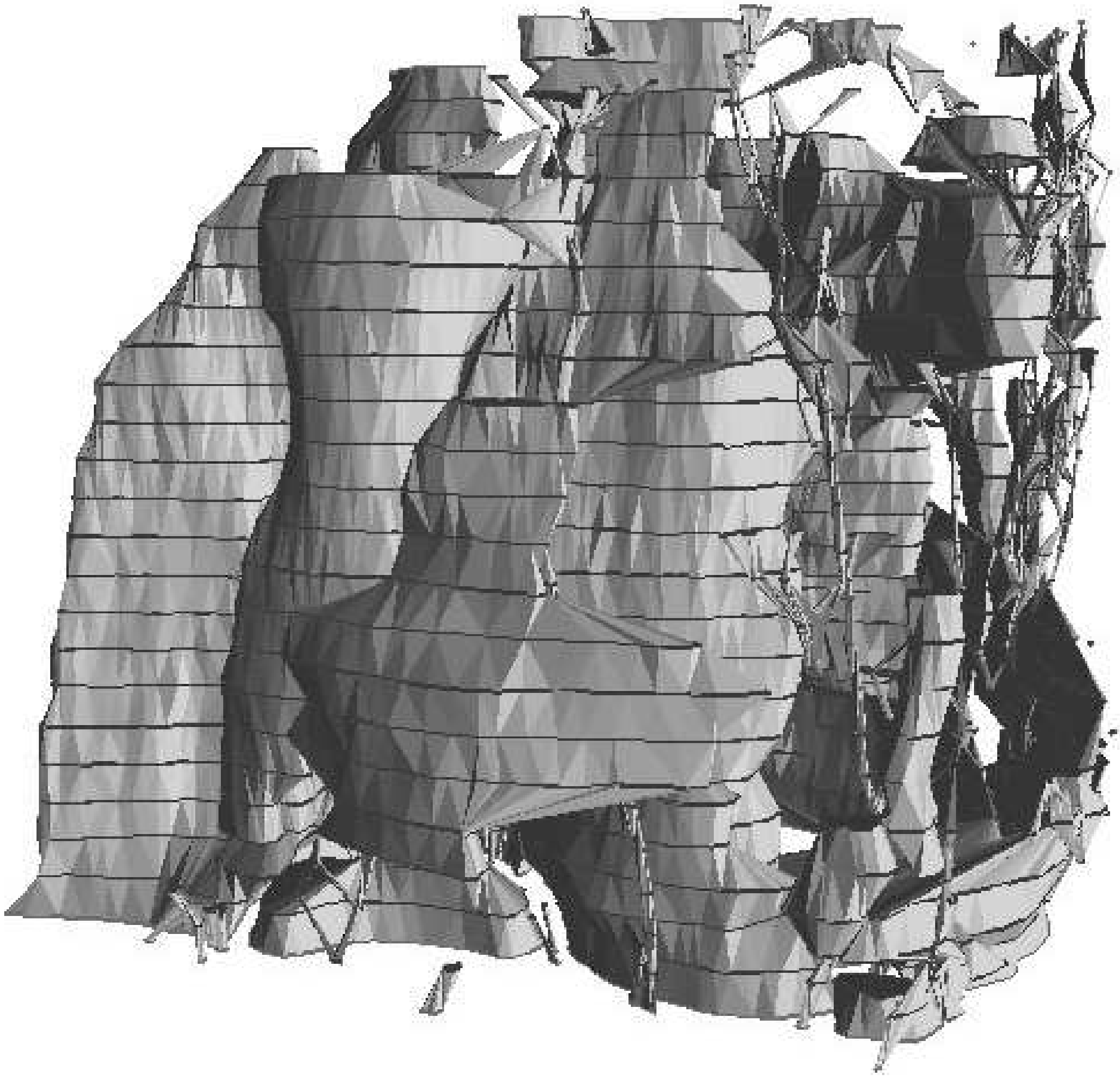

Fig. 5: An early step in a virtual 3D reconstruction based on a stack of histological slides (dark lines) of a fetal cleft palate. Note that the structures are still triangular which represents a reduced degree of realism and thereby complexity. Unlike for study 1, a considerable reduction of controllable complexity appears to not be desirable for study 2. Applicability for surgical training therefore requires an increase in photorealism and other aspects of complexity.

1.6 Haptic Device

A haptic interface can be used to subjoin a sense of touch to interactions in combination with a virtual representation. The forces of interaction between the objects in the virtual scene are calculated and thereafter reflected to the user to give a feeling of real touch (Salisbury et al. 1995, Srinivasan 1995). The object of interest can either be a single virtual histological slide or a stack of histological slides after 3D reconstruction. The procedure of determining the forces of interaction between the different objects in the scene is called haptic rendering (Fig. 6). Haptic rendering methods are based on a geometric surface representation (i.e. polygonal mesh) of the digitalized histological slides. The principle of haptic rendering is that the user interacts with the stylus of the haptic device and the computer registers the new spatial position. The position is then compared with the boundaries of the virtual objects the aim of which is to detect collisions between the virtual hand and the objects. The collision detection feature examines whether two objects overlap and in case they do overlap it quantifies the depth of penetration of the stylus relative to the object boundaries (Basdogan 2001, Cohen et al. 1995, Hubbard 1995), however, if the application detects a collision between the stylus and a boundary of an object the haptic device has to react to this fact. This is done by activating the motors of the device to force the real hand of the user in a diametrical direction. For effective collision detection, the authors of the present study are using binary space partition trees. The basic idea of binary space partition trees is to insert all objects of the virtual scene into the a binary tree and each object partitions the space (Fuchs et al. 1980). For teaching blind or visually impaired individuals histology, the result of collision detection and response is preventing the proxy (i.e., the virtual representation of the stylus of the haptic device) from penetrating the boundary of a virtual object. In case of simulated surgery, however, penetration should be possible as virtual tissues have to be cut.

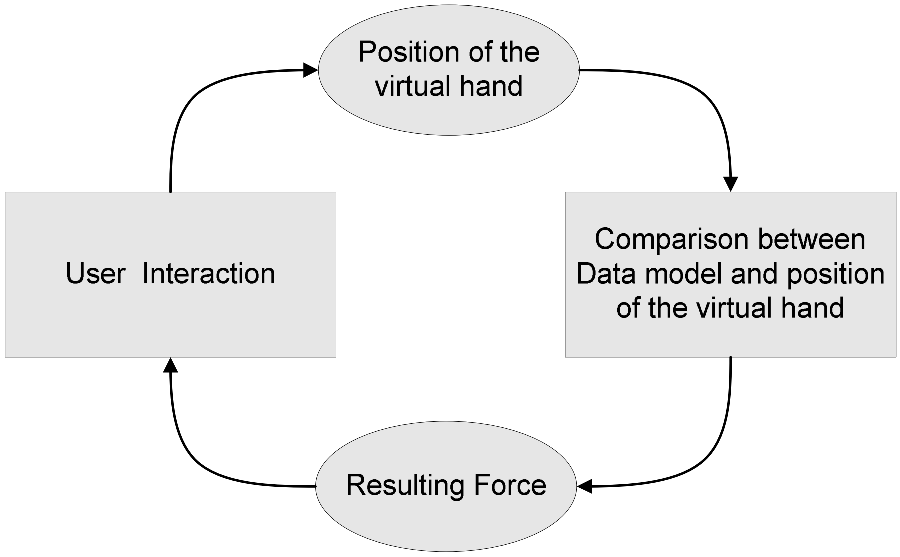

Fig. 6: Principle of the control scheme for haptic rendering (Sjöström 2002, modified).

1.7 Bibliometry

The use of haptic devices in the biomedical sciences can be quantified by conducting a bibliometric survey. Two databases stand out for analysis. PubMed is a biomedical database, developed by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine (NLM), Bethesda, MD, USA, while Inspec is a bibliographic database produced by the Institution of Electrical Engineers (IEE), London, UK, which covers physics, electronics and computing. Analyses of the datasets of references retrieved from the databases give a synoptic overview of how the literature can serve to indicate the status of research activity and therefore give a microcosmic view of the state of research on the topic as it indicates, the currency of the research; the volume of research output in the form of published articles and conference papers; the degree of collaboration among researchers; the preponderance of research output by specific countries; and the predominance of any particular language of the published material.

Medical bibliographic from Pubmed information is available in two databases, Medline, which covers medicine, nursing, dentistry, veterinary medicine, the health care system, and the preclinical sciences in over 4,800 journals published in the United States and 70 other countries. The database contains over 12 million bibliographic citations from 1966 to the present and while coverage is worldwide in scope most records are from English language sources or have English abstracts. So called Old Medline contains approximately 2 million citations to articles from international biomedical journals from 1950 to 1965. PubMed provides users with links to online resources including full-text articles (access being free for some while for others a subscription is required), other databases, and search tools.

Inspec indexes over 4000 journals with journal articles constituting 82% of its bibliographic material; books, dissertations and reports; and conference papers which constitute 21% of its material. This variety in the material covered is a notable difference when compared to Medline which consists entirely of journal articles. The database covers 1969 to the present and to date has over 7.5 million citations.

Collaboration in research activity and research output by publication is indicated by the level of co-authorship. Lotka's Law of scientific Productivity of Authors (Lotka 1926) for instance states that the number of authors making n contributions to the literature is about $1/n^2$ of those making one contribution.

2 Materials and Methods

2.1 Bibliometry

Relevant references were sought by interrogating the databases PUBMED and INSPEC (as of August 2005). The search was conducted using the search terms 'haptic device', 'tactile device', 'tactile interface', 'phantom haptic interface', and 'phantom tactile interface'. References were considered for relevance by perusal of the abstracts, review articles and references outside the scope of the topic were eliminated, as an example, an article about the application of haptic device for aircraft engine maintainability. Lotka's Law of scientific Productivity of Authors was considered.

2.2 Histology

Preparations for attempts and trials to teach blind and visually impaired individuals histology were termed Study 1 while preparations for the simulation of surgery were defined as Study 2. The samples used for Study 1 were formalin fixed and embedded in paraffin wax and were subjected to a standard protocol for H&E staining and subsequently digitalized using either an AXIOCAMMRC5 digital camera mounted on a AXIOSKOP 2 light microscope (both CARL ZEISS AG, Göttingen, FRG) or an OLYMPUS CAMEDIA C-3030 Zoom that was fixed to a BX41 light microscope (both OLYMPUS OPTICAL CO Europa GmbH, Hamburg, FRG). More complex preparations were needed for Study 2 (Landes et al. in press, Landes et al. 2005).

2.3 Segmentation

Haptic rendering required a clear cut separation ad classification of anatomical structures. Both were therefore performed using the prototypical SEVISE software, implemented by the authors (Dohrmann et al. 2004, Landes et al. in press). All structures of interest were labeled by creating polygonal contours by mouse click. This resulted in an average of more than 1,000 markers per image.

2.4 Rendering

Rendering virtual cells with artificial textures allowed the authors to modify textural complexity as deemed suitable (Fig. 7). Steerable pyramids were used to generate textures with the potential to resemble the original (Portilla & Simoncelli 2000). The textures may be extracted from any source, e.g. from herpesvirus type 6 infection or zygomycosis in humans (Sudhof 2003, Wagner et al. 1997) or from animal experimentation (Turler et al. 2000).

The classified morphological components of the previous segmentation were added to a database that had a significant number of patterns. Based on textual description language a pyramid based texture analysis/synthesis algorithm was applied. The algorithm was adapted from a previously published approach (Heeger & Bergen 1995). In compliance with the information of the textual description an example of the database was taken, the algorithm was applied and the result was a synthetically generated image. The algorithm started with generating an image of uniform random noise, which was adjusted in an iterative progress to

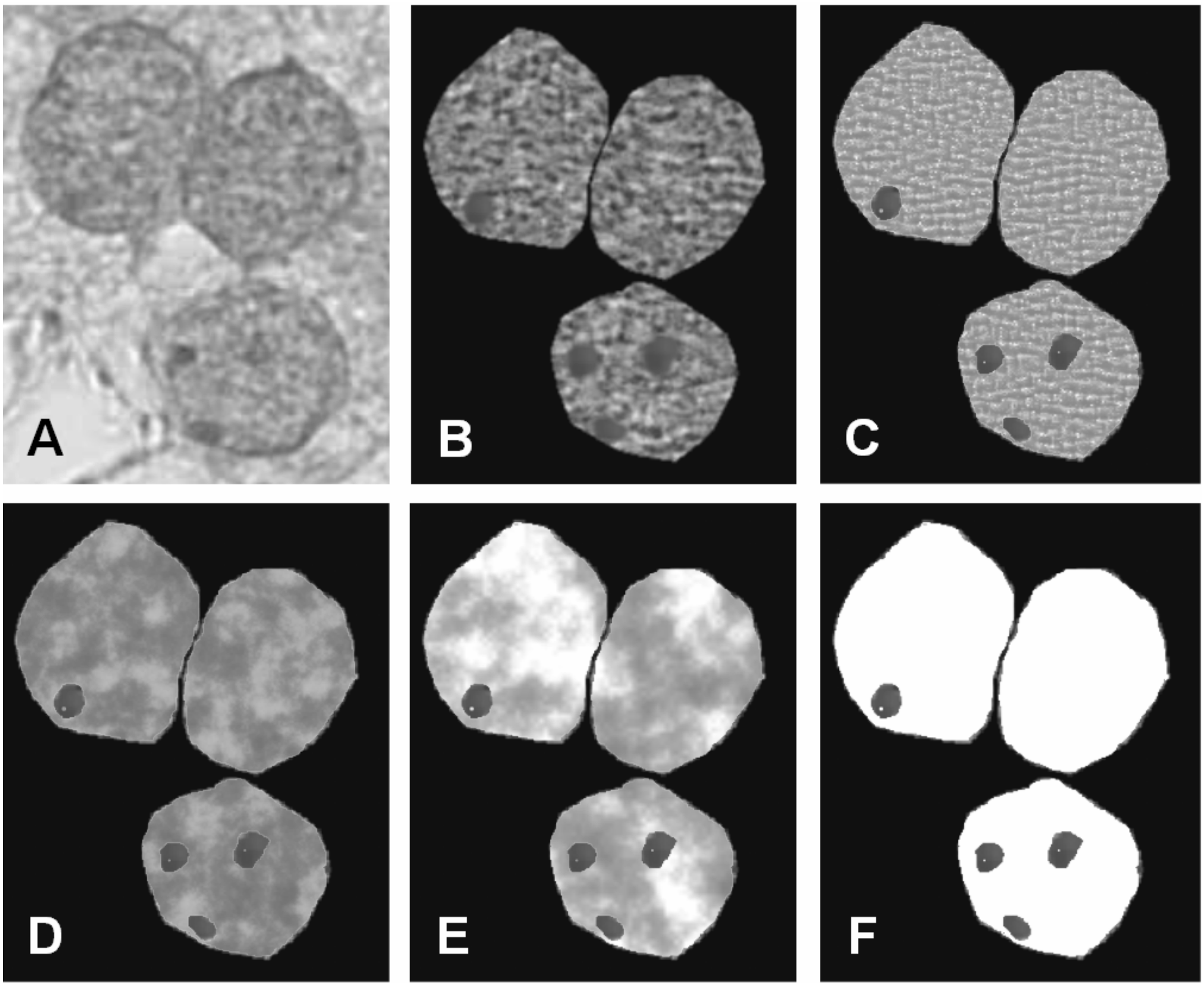

Fig. 7: Real nuclei (A) from a prostate with an adenocarcinoma (H&E) and their virtual representations (B-F). The authors used steerable pyramids to generate textures with different degrees of complexity (density). The mean grey value and the integrated density for instance were 136.1 and 715578 for the real nuclei (A) while the virtual nuclei had a mean grey value and an integrated density of 111.0 and 566569 (B), 144.8 and 699363 (C), 126.7 and 665768 (D), 184.1 and 967631 (E), and 248.7 and 1203507 (F). Such quantification may help specify the best set of textures for each blind or visually impaired person and has to be assessed for each individual separately.

the source. Next, the image was decomposed into an oriented bandpass pyramid. This means it was dissected into a set of subbands by a set of convolution and subsampling operations (De Bonet 1997). The noisy image was subsequently modified by pyramid decomposition and the corresponding subbands of the two pyramids were adjusted by histogram matching. After this, the noise pyramid was collapsed and the example of the database and the new synthetic image were processed in an iterative histogram matching process. The result was a new synthetic image.

2.5 Preparation

Reliable 3D models were generated by taking information from the previous and the following segmentation steps into account.

Especially at the point of mesh generation, the authors had to differentiate between Study 1 and Study 2 as the former requires the transformation of a single virtual slide into a polygonal mesh while for Study 2, a volumetric mesh was needed.

Study 1 made it necessary to expand the 2D-image to the third dimension by generating a mesh for the haptic representation (Fig. 8). The standardized color information was therefore mapped to the third dimension. Afterwards a 3D Delaunay triangulation of the scattered data points was applied which resulted in a 3D mesh (Watson 1981). A subsequent mesh reduction reduced the dataset size, minimized possible artifacts and enhanced the operating speed.

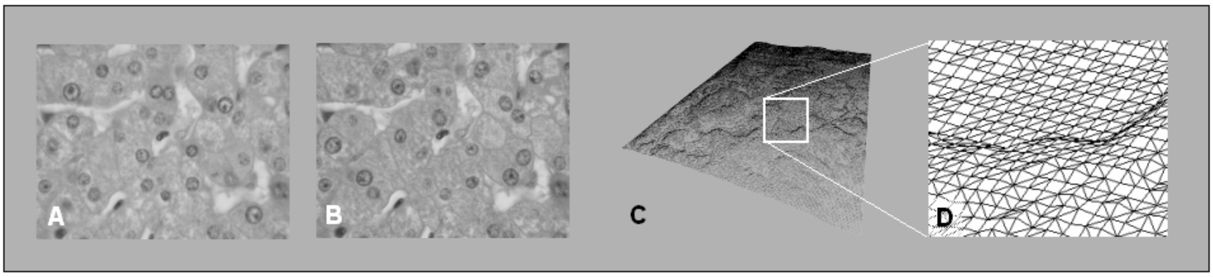

Fig. 8: The mesh generation pipeline from a real histological slide (A) via a virtual histological slide (B) and three dimensionally scattered data points (C) to a 3D Delaunay triangulation (D). Differences in cytoplasmic texture, nuclear sizes and positions help distinguish the real and virtual liver tissue.

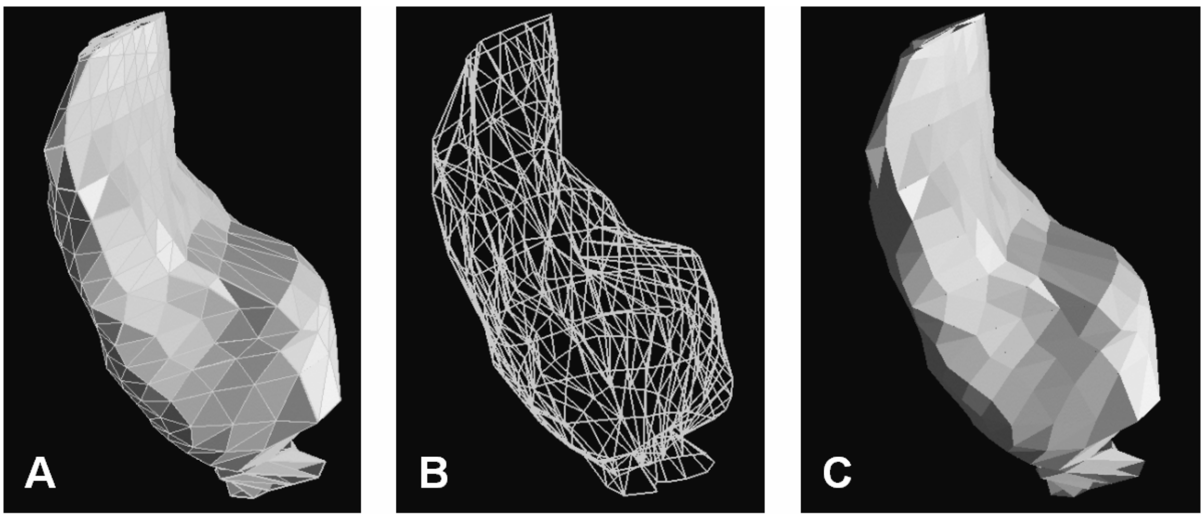

Fig. 9: Meshing a volumetric data set of the lateral pterygoid muscle from a surface mesh (A) to a volume mesh (B) to obtain volume (C).

The volumetric data set associated with Study 2 required a different approach (Fig. 9). The volumetric data set was made up of a sequence of slides having defined metric and relative information on the topology. However, for a correct alignment of the slides as well as the volume it was necessary to apply a registration algorithm. First, a matching algorithm searched the previous layer for polygons that belonged to the identical structure. After matching the image pairs, a reconstruction algorithm arranged the cross sections, copied pixel-by-pixel proportional to their thicknesses into a 3D array, and put them properly in space. This regular 3D model was obtained by resampling the sequence of images in 3D space using local trilinear interpolation.

It was furthermore possible to "smoothen" objects or reduce the surface angularities caused by aberrant vertices, using a modified shortest path algorithm. This resulted in cleaner surface definitions and better rendering by the 3D software. The resulting dataset was visualized by using direct volume rendering techniques at interactive frame-rates. To visualize the segment information of the histological slices in 3D space, the anatomical segments were interpolated and then stored as iso-surfaces. All visualization was performed by combined volume and polygon rendering, offered by the Volume Graphics Library, VGL (VolumeGraphics GmbH: The VolumeGraphics Library, www.volumegraphics.de).

2.6 Haptic Device

A PHANTOM (Personal Haptic Interface Mechanism) device (Fig. 10) and the GENERAL HAPTICS OPEN SOFTWARE TOOLKIT (both SENSABLE TECHNOLOGIES, INC., Woburn, MA, USA) were chosen to give tactile access to the virtual representation of the tissues. The device follows the principles of an industrial robot with a stylus that has an additional button at the end of an arm. They were needed to bring the end effector in any position and the “hand” of the user in a definite orientation to the object. The orientations of the hand could be rolling, yawing and pitching. By this, it was possible to achieve any position in the virtual environment with the tip of the haptic device arm. The positions were presented in a Cartesian coordinate system. Because the phantom device has a six degree of freedom of movement, the position of the link can be described by six-tuple. To arbitrate a haptic feedback, the phantom device decreed three motors providing controllable forces along three of those freedoms with a maximum obtainable force of about 8.5N by a nominal position resolution of 1,100dpi (0.00023cm). The Software Toolkit is a C++ object-oriented library that assists developers by a hierarchical collection of geometric objects and a spatial control. By using the GHOST SDK, the virtual environment is administered as a haptic scene graph.

2.7 Haptic Rendering

Segmentation classified the histological slices into different structures, corresponding to different textures. Different textures implicated in a haptic context were made to feel different as well. Hence, every object of classification was inserted into a scene graph as a separate node but administrated by the scene graph of the SDK as objects that belong to each other. Objects could be added, deleted and properly arranged in space. Furthermore, the SDK supported the calculation of the resulting force for the motors of the haptic device.

The hardware equipment for the developed prototypical application consisted of a dual processor Pentium 4 (XEON) 3.0 GHz WINDOWS XP personal computer with two gigabytes of RAM and a GEFORCE4 6800 graphics card. The application was multi-threaded, with the haptic rendering computation thread running at a high priority to ensure fast update rates.

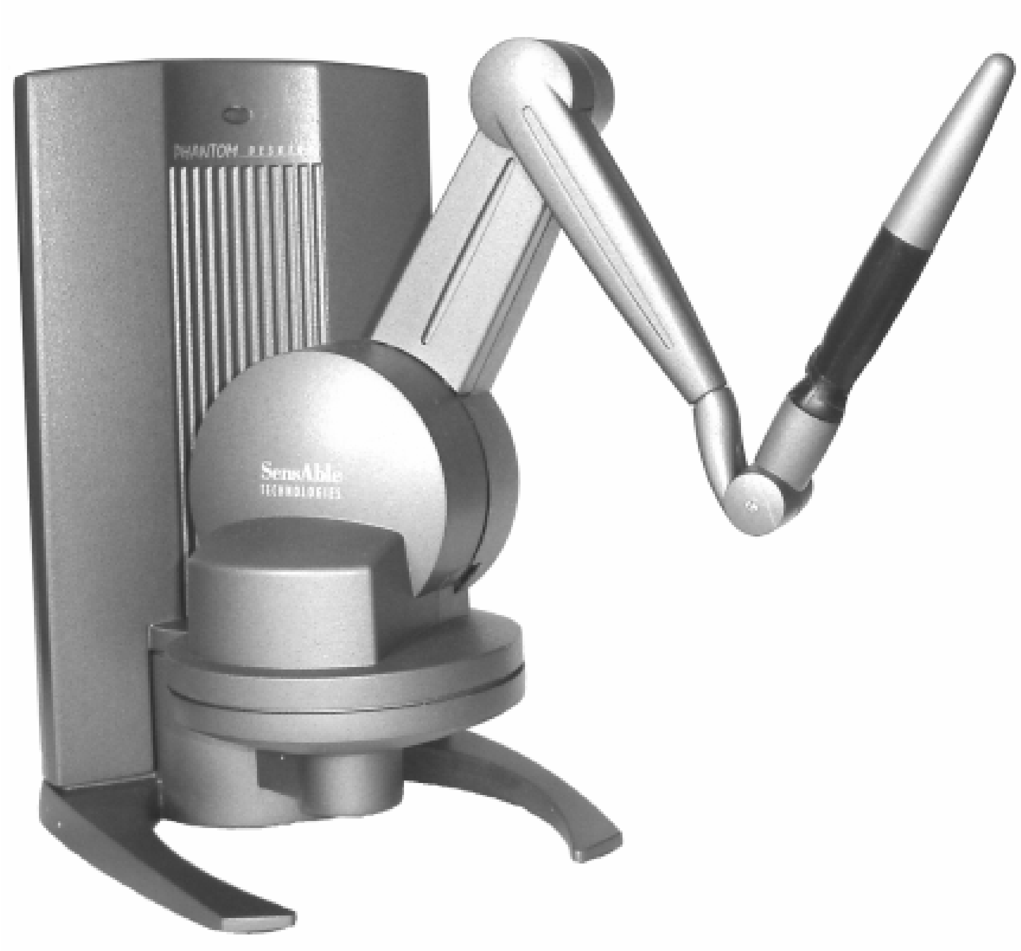

Fig. 10: SensAble Phantom Device – An interface to simulate haptic interaction.

3 Results

The search in PUBMED yielded 121 relevant references. The dataset of references from PubMed shows that the majority of references was published between 2000 and 2005, which can be construed to be indicative of increasing research interest and consequently increasing research output as seen in numbers of publications over time (Fig. 11A). The data also indicate that there was a trend toward collaboration (Fig. 11B).

There are 17 countries which contributed to the research output and this serves as an indicator of the countries currently involved in research activity on this topic (Fig. 11C). Canada, Belgium and Greece contributed 0.8% of the articles each, Norway and Denmark 1.65%, France, Switzerland and Italy 2.47%, South Korea, Australia and Hong Kong 3.3%, Sweden and the Netherlands 4.13%, the United Kingdom 4.95%, Japan 7.43%, Germany 14.04%, and the United States of America contributed 39.66%. For 2.47% of the articles no country was designated.

English remains the predominant language of publication. There were 114 (94.21%) articles in English; 6 (4.9%) in German; and 1 (0.82%) in Japanese.

The search using INSPEC yielded 150 references of which 45 (30%) were journal articles all published between 2000 and 2005; and 105 (70%) were conference papers all published between 2000 and 2005. From the dataset of 45 journal articles there were 4 (8.8%) by one author; 6 (13.33%) by two authors' 8 (17.77%) by three authors; 19 (42.22%) by four authors; 4 (8.8%) by five authors; 1 (2.22%) by six authors; 2 (4.44%) by eight authors; and 1 (2.22%)

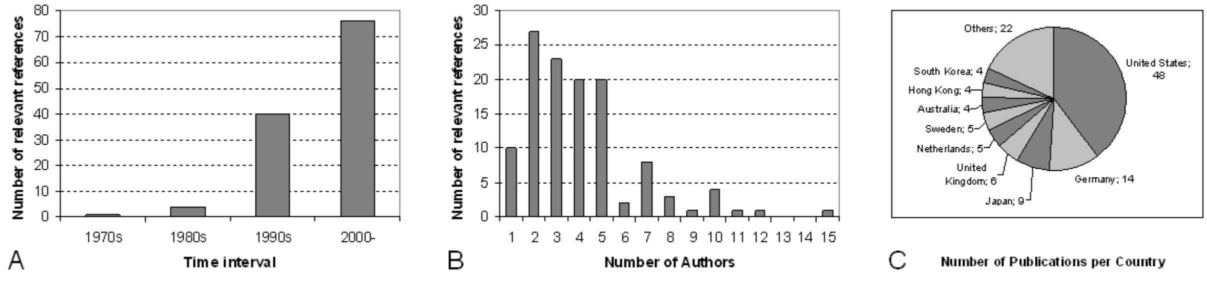

Fig. 11: Results of bibliometry on the use of haptic devices in the biomedical sciences (according to PubMed, August 2005).

by an anonymous source. From the dataset of 105 conference papers, it can be assessed that the trend toward collaboration in research and output is comparable to journal articles. The conference papers indicate that 8 (7.61%) were by one author; 22 (20.95%) were by two authors; 16 (15.23%) were by three authors; 21 (20%) were by four authors; 11 (10.47%) were by five authors; 13 (13.38%) were by six authors; 10 (9.52%) were by seven authors; 2 (1.90%) were by eight authors; and 2 (1.90%) were from anonymous sources.

Spain, Malaysia, Finland, Latvia, Lithuania, Slovenia, the Czech Republic, and Mexico all contributed 1 paper (0.95%) each; the Netherlands, China, Canada, Bulgaria, and Singapore contributed 2 papers (2.85%) each; the United Kingdom and Germany contributed 3 (2.85%) each; Switzerland contributed 4 (3.80%); Italy contributed 6 (5.71%); France contributed 11 (10.47%); South Korea contributed 14 (13.33%); the United States contributed 19 (18.09%)' and Japan contributed 27 (25.7%).

For Study 1, the virtual slide was represented by a dense scattered set of points resulting in a dense mesh the size of which had to be reduced. For blind and visually impaired individuals pronounced data reduction needed to take place. It was therefore necessary to generate a smooth mesh rather than a mesh that offers too many features. This led to compromises on a seemingly authentic haptic feeling. For Study 1, only a surface mesh was needed as only data of single slides had to be transformed. These meshes were relatively easy to generate, had a high operating speed and provided excellent haptic properties.

For simulated surgery (Study 2), however, surface meshes are inadequate as they do not support the penetration of volumes. This approach made it necessary to generate a surface mesh, a volume mesh and finally a volume set to support the virtual cutting of the elaborate three-dimensional models (Dohrmann et al. 2004). It now only depended on virtual properties of the simulated material of the object whether it was more or less easily cut. For example, the virtual scalpel was programmed not to penetrate virtual bone while it should easily cut muscle tissue.

There was no classical data reduction in terms of data compression associated with the transfer of graphic representation to haptic enhanced representation. In fact, the amount of data was reduced although the information content remained constant. This was achieved by increasing the significance of single information units and reducing the entropy of information, respectively.

4 Discussion

The present study shows how much transformation of information may differ with regard to the task. Virtual histological slides may either help generate an output with a reduced or with an augmented data size. The latter is a protracted exercise which may not be in keeping with the "publish or perish" code of practice in the medical sciences. This hypothesis is supported by the results of the bibliometric survey. Its objective was to get a representative perspective of the coverage of the literature on the application of haptic device in biomedical research and practice. There is wide geographic scatter of the contributions of conference papers and in this regard may be considered to indicate wider geographic coverage than journal articles.

The distribution of languages may be attributed to the assertion that it is usually more difficult to get cited when published in non-English journals. The result is that English has become the first language of choice in which to get articles published as researchers will undoubtedly aspire to get their research results accepted for publication and so increase the likelihood of their articles being acknowledged by the academic community and consequently cited in the literature.

Comparing the results for PUBMED and INSPEC suggests that the biomedical sciences may currently provide less applications for haptic devices than other areas.

As described above, calculus for Study 2 was more complex as study 1 required "only" a polygonal mesh while Study 2 was based on a volumetric model. Data reduction was considered helpful with regards to study 1. This was also reflected by the underlying rendering concept which provides virtual cells with textures. First and second order morphometrical statistics can be applied to analyze these structures (Haralick et al. 1973, Julesz 1975). For study 1, rendering results may be systematically reduced in complexity which may be monitored by quantitative texture analysis. Data reduction was therefore possible by either texture modifications (virtual cells) or mesh reduction (3D Delaunay triangulation). It is not known whether preference for any degree of data reduction correlates for instance with low- and high-proficiency blind braille reading (Davidson et al. 1992). Several trials have therefore to be performed to evaluate this methodology.

Study 2 is even farther from being routinely applicable at this point in time. Three-dimensional anatomical reconstruction in virtual environments is expected to permit improved teaching, exploration of the spatial relationships at freely eligible angles, faster acquisition and better long-term maintenance of anatomic knowledge, and the simulation of surgery. The value of such a simulation first depends upon the exactness of the training model. However, earlier attempts e.g. in malformation surgery of cleft-lip and palate have been restricted to mere visual animation (Cutting et al. 2002). Secondly, in-depth education of junior surgeons requires the sensible feedback of tissue resistance under manipulation. Such refined training will prospectively enhance the postoperative results of patient safety as has long been performed in other high hazard activity as for instance aviation. Controllable near real-life complexity is desired for virtual surgery to help the trainee master not only uneventful operations. Photorealistic visualization algorithms are most suitable to optimize such simulation programs (Spicer & Apuzzo 2003) and maybe supported by texture mapping approaches. The application of artificial neural network technology (Linder et al. 2003, Mohamed et al. 2003a, Mohamed et al. 2003b) may help improve the performance of virtual surgery programs even more.

The transformation of visual data to tactile information is expected to become an important input to surgery. Haptic feedback allows the surgeon to perform and compare the feasibility and dynamic results of several operation techniques, e.g., muscle transpositions. Prospective volumetry, mesh and finite-element supported simulation of muscle contraction will help compare force distribution in the normal, pathological and postoperative situation. Application of a haptic device combined with virtual histology will help make individual operation planning possible. The ideal reconstruction technique for a certain patient may then be selected based on data obtained by preoperative simulation.

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