GENERAL INTRODUCTION
Over the past four years this PhD research has focused on the development, implementation and evaluation of 3D virtual surgical planning workflows and patient-specific instrumentation for spine surgery. The research includes both qualitative and quantitative studies that has been undertaken to develop new knowledge about how spinal procedures can be virtually planned and how to use custom-made instrumentation to translate the plan to the operating theater. More specifically this thesis aimed to develop and validate surgical planning workflows and patient specific instrumentation for spinal screw placement, deformity corrections and other related spinal surgical procedures that can benefit from 3D technology. In addition to the research goals, this thesis should raise awareness about the wide range of opportunities that 3D technology has for meticulous preoperative spine planning. 3D technology has the potential to cause a paradigm shift towards increased preoperative decision making, particularly for the most challenging cases.

This chapter sets the context for the thesis by exploring the motivation for the research, its justification, the central research aim and the research objectives. Following this, the chapter sets out the thesis structure by introducing the remaining chapters through a thesis overview.

**MEDICAL 3D TECHNOLOGY: A BRIEF BACKGROUND**

In the past two decades, medical 3D planning and printing has evolved and diversified from printing simple anatomical models towards printing entire articulating implantable prosthesis. Together with the rapid adoption of 3D technology in healthcare, a new medical professional field was born, responsible for the virtual preparation of surgery; 3D virtual surgical planning (VSP). The ultimate VSP can serve as the virtual preparation in the run up to surgery, or can, as is the main focus of this thesis, be translated to surgery using 3D-printed patient specific instrumentation (PSI).

**Virtual Surgical Planning (VSP)**
The typical VSP workflow starts with the collection of medical imaging data that are in most cases already obtained as part of clinical routines. Within the field there is general consensus that conventional multi-detector fan beam computed tomography (CT) offers the best quality images for bone related VSP.[1] There is a big variety in scan protocols between different CT vendors but the majority consist of separate reconstructions kernels for soft- and boney tissue. Although associated with increased accentuated noise, the higher sharpness enabled by the bone kernel is beneficial for bony structures that require a higher spatial resolution. This particularly applies for the spine and its complex individual substructures; the vertebrae. To separate bone
voxels from surrounding soft tissues in grey scale image data like CT, a wide range of segmentation techniques is available. Yet, the most widely used and generally acknowledged segmentation method for VSP remains global thresholding. [2] In global thresholding a gray scale value cutoff is chosen, such that all pixels within the chosen range are considered as a certain type of tissue, and stored within a binary image mask. [3] The thresholding technique has been implemented into all FDA approved medical certified VSP software. Although these packages work with standardized grayscale thresholds for cortical and trabecular bone, manual fine-tuning by expert input is needed to define the optimal threshold for the individual case. [4] After segmentation, integrated dedicated reconstruction algorithms guarantee an accurate conversion of the segmented image mask into a triangulated 3D surface model, resulting in sub voxel size accuracies of the bone models. [5]

The next stage of VSP involves the virtual planning of the surgical procedure, which consists of screw- or osteotomy plane positioning, the resection of bone or soft tissue, or the reconstruction of bony defects. This part of the VSP procedure allows preoperative evaluation of multiple treatment scenarios in a complete virtual setting. After establishing the final plan, the 3D models can be exported as interactive 3D content to the surgical team to be studied preoperatively, or, shown on screen during surgery for enhanced 3D anatomical perception. Moreover, a VSP might be transferred to the actual surgical procedure by using computer navigation, or, as is the main focus of this thesis, by using 3D-printed PSI, one of the latest tools in the armamentarium of the spine surgeon. (figure 1)

3D-printing and its historical perspective
In the early 1980s, an employer of a furniture coatings company came with the revolutionary idea to use the same UV curable coating material in a layer-by-layer approach to create three-dimensional (3D) objects. [6] Back then he did not know he had just become the father of 3D-printing, an invention that stood at its very early stage with enormous potential. Overtime, the technology emerged from its niche status and has become a viable alternative to conventional manufacturing processes in an increasing number of industries. Due to the fact that to date the technology not only encompasses the manufacturing of products in a prototype stage, the term rapid prototyping has been gradually replaced by additive manufacturing, or as it is more commonly known; 3D printing. According to a recent report, the 3D-printing industry has shown an average annual growth of 27.4% over the last 10 years. [7] Current state-of-the-art printers build the models by a series of cross-sectional layers of either liquid, solid filament or powder. The final shape is created when the layers are joined by applying heat. The key advantage of 3D-printing, as opposed to injection molding and
subtractive manufacturing, is the ability to make highly customized parts with almost infinite dimensional freedom, making the technology particularly useful for custom-made individualized manufacturing in small quantities. It is for these reasons that no industry has embraced 3D-printing more than healthcare, particularly surgery, which is in line with the trend away from the “One-Size-Fits-All Approach” towards a precise and personalized treatment strategy.

Given its diverseness of potential applications, there has been a growing interest in the utilization of 3D printing in many surgical disciplines, with oral and maxillofacial surgery as early adopter. To date, 3D printed PSI is commonly used in the form of drill guides or cutting guides, for various surgical applications. The use of VSP and subsequent PSI are frequently described to improve the accuracy and predictability of surgery.[8]

Figure 1. Three main pillars of the VSP workflow: segmentation, planning, and design and manufacturing of Patient Specific Instruments (PSI).

**SPINE SURGERY AND VSP**

The human spine is a complex structure that provides flexibility and stability to the human torso and protects the spinal cord, cauda equina, neural structures deriving from the spinal cord, and the vertebral artery. The spine is located between the skull and pelvis, and typically consists of 7 cervical vertebrae, 12 thoracic vertebrae, 5 lumbar vertebrae, the sacrum, and coccyx. Each vertebra contains a vertebral body which is connected to the laminae and spinous process by two pedicles. All vertebrae are mobile and articulate with each other through the intervertebral discs and facet joints. The transverse processes arise between the superior and inferior facets at the junction
of the pedicle and laminae and project laterally in the lumbar region, and laterally and posteriorly in the thoracic region. Below the lumbar vertebrae are the sacrum and coccyx bones, a group of fused vertebrae that connect the spine to the pelvis. The spine is further supported and connected by ligaments, tendons and other soft tissue such like muscles.

During lifetime the spine is exposed to substantial loads which might affect its function and can eventually lead to musculoskeletal and neuromuscular diseases and complications. As a result, the spine has been focus of many clinicians, including the spine surgeon. Spine surgeons are operating in complex anatomy containing dedicate neurovascular tissues and deal with a wide range of pathologies, including deformities, trauma, degeneration and tumors. Surgical intervention in this complex anatomy requires detailed preoperative planning, and VSP techniques offer the ability to improve surgical predictability and patient outcomes. The VSP can be translated to the actual procedure by using 3D-printed anatomical models, PSI in the form of drill guides or cutting guides (focus of this thesis), or custom-made implants.

The work in this thesis is divided into 4 main sections. Part 1 forms the thesis’ sound basis, intending to develop a VSP workflow and PSI for spinal screw insertion and evaluating the accuracy of the new technology. Part 2 and 3 then elaborate on this by introducing VSP to deformity and craniocervical surgery. Part 4 concludes the work by developing and validating a new optimized software pathway in order to optimize the VSP workflow so that in future more patients can benefit from 3D technology.

**Part 1: The development of Spinal Drill Guides**

In spinals fusion surgery two or more vertebrae are being fused using screws and rods aiming to improve stability, eliminate motion, reduce pain indications and induce bone fusion overtime. The placement of spinal screws is a complex procedure for which technical expertise is required in order to achieve adequate fixation and to avoid neurovascular injury. The traditional approach of pedicle screw insertion is the free-hand technique, which relies on the identification of anatomical landmarks and standardized insertion angles for each level. The procedure is known to be technically demanding with a long and steep learning curve.

Over the past decades there has been a movement in favor of spinal screw placement with the aid of imaging, including fluoroscopy guidance and more recently computer navigation, commonly referred to as computer assisted surgery (CAS). Many have reported high accuracies with these techniques and resulting in a reduction of screw malpositioning rates. These techniques however involve prolonged...
surgery duration, radiation exposure to patients and operating staff [15], workflow interruptions, and, high investment cost. In addition, modern CAS systems rely on intraoperative acquired 3D fluoroscopy image data and therefore require the ultimate screw positions to be defined by the surgeon on the spot, lacking the ability to preoperatively plan the most optimal trajectory. For all of these reasons adoption in spinal instrumentation might has been slow [16], and the current disadvantages leave room for the development of novel navigational technologies.

With the advent of VSP and PSI, the optimal trajectory can be defined virtually, in the run up to surgery. VSP not only encompasses the ideal trajectory but also the optimal screw angulation, length, and thickness. The virtual plan can be transferred to the procedure using custom-made PSI. In literature various approaches with different guide design characteristics have been described, and the 3D technology reportedly yields accurate screw insertion.[17] Due to varying radiographic analyses and nonuniform outcome parameters, it is however difficult to compare studies side-by-side to determine which guide design is superior.

In first section of this thesis we therefore begin with the development of a new method that enables quantitative comparison of accuracy through different VSP and PSI methodologies, called: the 3D deviation analysis. We also aim to develop an optimized 3D workflow and assess and compare the exact drilling accuracy of different PSI design through a cadaveric study (chapter 2). The thesis further elaborates on patient specific instrumentation by analyzing the accuracy with the aid of these in-house developed drill guides, with a specific focus for measuring the ultimate screw position instead of only the drilling hole (chapter 3). Since drill guides only guide the drill and not the subsequent screw insertion, literature advocates to add the use of screw guiding PSI, but the exact effect is never studied. Therefore, in chapter 4, we aim to study the added value of screw guiding instrumentation in addition to drill guides using the same 3D deviation analysis methodology (Chapter 4). Part 1 concludes the section with a systematic comparison between patient specific instrumentation and CAS. (chapter 5)

Part 2: Spinal Deformities
Spinal instrumentation using screws and rods is also required for the correction of deformities due to conditions like scoliosis or kyphosis. Scoliosis is a complex 3D structural deformity affecting between 0.5% and 5.2% of the total population.[18] Scoliosis causes a S- or C-shaped coronal spinal curvature that is traditionally quantified on 2D radiographs using Cobb angle measurements. Surgical correction is typically indicated in case of Cobb angles greater than 45°, aiming for stabilization and correction of the curvature. Kyphosis, as opposed to scoliosis, is a spinal deformity in the sagittal
plane, identified as severe when measuring sagittal Cobb angles above 80° for thoracic region. In case of spinal deformity surgery, screws are first inserted which serves as an anchor for the application of corrective and distractive maneuvers in order to correct the deformity. Surgical planning is made largely by the surgeons’ clinical experience and interpretations of the literature.[19] In addition, the selection of levels that need pedicle screw insertion depends on the surgeon and is not standardized.[20] Therefore neurosurgeons and orthopedic surgeons that handle spinal deformities are highly in demand of more sophisticated methods to preoperative define the best surgical approach. Recently the use of 3D printed anatomical models has been described for enhanced preparation and spatiotemporal perception in the severely deformed spine. [21] These models can be considered as a first step towards more complex VSP, involving the actual virtual preparation of surgery and the fabrication of PSI. Since deformity surgery encompasses the insertion of pedicle screws, and the severely deformed spine impedes easy identification of anatomical landmarks, spine surgeons could benefit from using PSI. The drill guides that will be developed and validated in Part 1 of this thesis might also be applicable for these highly complex deformity cases, but to achieve adequate deformity correction 3-column correction osteotomies (3-CO) can be required for certain severe cases. Given the complexity and extraordinary technical demands these 3-CO procedures are not risk-free.[22] Part 2 of this thesis therefore focuses on the development of VSP pathways for spinal osteotomy planning and associated PSI that includes cutting guides in addition to drill guides (chapter 6). Subsequently, we expand this approach by describing a VSP managed case series with the aim to provide insight on how severe spinal deformity surgery can be virtually prepared using 3D technology. (chapter 7)

**Part 3: Craniocervical junction**

Since the spinal VSP workflow is now constructed and validated, the main objective of the next section will be to explore the possibilities of VSP in other spinal areas, more specifically for the craniocervical junction, involving the cranial occiput (often called C0) and the upper cervical spine. Chapter 8 introduces VSP for Chiari Type 1 malformation surgery, and in chapter 9 we describe the feasibility of VSP for occipital plate positioning and the assistance with pre-contouring of rods.

**Part 4: Workflow Optimization**

Now that the use of 3D technology for all of described applications has been validated, the efficiency of all of current workflow steps should be critically evaluated. Ongoing technological developments have triggered the technical engineers as well as the involved physicians to critically review the current VSP workflow and have a further look to the most time intensive steps. The aim of the research in chapter 9 is to develop and
validate a new algorithm for obtaining individual vertebrae out of 3D surface meshes with the ultimate goal to optimize the VSP workflow and thereby further increase the technology’s cost-effectiveness.

Finally, in chapter 10 a general discussion is presented, in which we summarize the results of this thesis and discuss the future directions that 3D VSP and PSI will take in the upcoming years.
**AIMS OF THE THESIS**

The overall aim of this PhD thesis was to develop, implement and validate 3D virtual surgical planning workflows and patient-specific instrumentation for spine surgery.

**The specific aims were:**

1. Develop a quantitative 3D deviation analysis methodology that enables one-to-one comparisons between different methods and techniques. (Chapter 2)

2. Develop a virtual surgical planning workflow with an optimized drill guide and assess the **drilling accuracy** for pedicle and lateral mass screw trajectories in a cadaveric study. (Chapter 2)

3. Assess the **screw insertion accuracy** of patient specific drill guides in a patient series. (Chapter 3)

4. Exploration of the added value of screw guiding in addition to drill guiding for both intra- and extrapedicular screw trajectories. (chapter 4)

5. Perform a systematic comparison between drill guides and computer assisted surgery, aiming to find radiological non inferiority. (chapter 5)

6. Develop a new method for spinal osteotomy planning and guiding. (chapter 6)

7. Provide an overview of 3D technology managed spinal deformity cases and present the considerations and experience with the assistance of 3D printed guides for screw and osteotomy guiding. (chapter 7)

8. Introduction of 3D technology for applications at the craniocervical junction. (chapter 8 & 9)


10. Introduce a paradigm shift in spine surgery towards increased preoperative decision making using 3D technology. (this thesis)
REFERENCES


