Biomechanical methods and error analysis related to chronic musculoskeletal pain

by

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Front cover:

The cover is designed by Print & Media. The coordinate system in the upper left corner illustrates the use of objective methods when examining people’s neck function.

This dissertation is dedicated to my parents, Lars and Elna Öhberg, and to my beloved family Helena, Oscar, Salomé and Carla.

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If I have seen further than others, it is by standing upon the shoulders of giants.

Newton, Isaac
Abstract

Background Spinal pain is one of humanity’s most frequent complaints with high costs for the individual and society, and is commonly related to spinal disorders. There are many origins behind these disorders e.g., trauma, disc hernia or of other organic origins. However, for many of the disorders, the origin is not known. Thus, more knowledge is needed about how pain affects the neck and neural function in pain affected regions. The purpose of this dissertation was to improve the medical examination of patients suffering from chronic whiplash-associated disorders or other pain related neck-disorders.

Methods A new assessment tool for objective movement analysis was developed. In addition, basic aspects of proprioceptive information transmission, which can be of relevance for muscular tension and pain, are investigated by studying the coding of populations of different types of sensory afferents by using a new spike sorting method. Both experiments in animal models and humans were studied to accomplish the goals of this dissertation. Four cats where were studied in acute animal experiments. Mixed ensembles of afferents were recorded from L7-S1 dorsal root filaments when mechanical stimulating the innervated muscle. A real-time spike sorting method was developed to sort units in a multi-unit recording. The quantification of population coding was performed using a method based on principal component analysis. In the human studies, 3D neck movement data were collected from 59 subjects with whiplash-associated disorders (WAD) and 56 control subjects. Neck movement patterns were identified by processing movement data into parameters describing the rotation of the head for each subject. Classification of neck movement patterns was performed using a neural
network using processed collected data as input. Finally, the effect of marker position error on the estimated rotation of the head was evaluated by computer simulations.

**Results** Animal experiments showed that mixed ensembles of different types of afferents discriminated better between different muscle stimuli than ensembles of single types of these afferents. All kinds of ensembles showed an increase in discriminative ability with increased ensemble size. It is hypothesized that the main reason for the greater discriminative ability might be the variation in sensitivity tuning among the individual afferents of the mixed ensemble will be larger than that for ensembles of only one type of afferent. In the human studies, the neural networks had a predictivity of 0.89, a sensitivity of 0.90 and a specificity of 0.88 when discriminating between control and WAD subjects. Also, a systematic error along the radial axis of the rigid body added to a single marker had no affect on the estimated rotation of the head.

**Conclusion** The developed spike sorting method, using neural networks, was suitable for sorting a multiunit recording into single units when performing neurophysiological experiments. Also, it was shown that neck movement analysis combined with a neural network could build the basis of a decision support system for classifying suspected WAD or other pain related neck-disorders.

**Keywords:** Cervical spine, Ensemble theory, Error analysis, Helical axis, Kinematics, Movement analysis, Neural coding, Pattern recognition, Spike sorting, Whiplash
Populärvetenskaplig sammanfattning

Syftet med den här avhandlingen är att utveckla en ny objektiv metod som kan användas av sjukvårdspersonal vid bedömningen av graden av funktionsnedsättningen hos patienter med nacksmärta. Det som är unikt med verktyget är den sammanlagda objektiva bedömningen som görs utifrån en mängd rörelseparametrar som beskriver nackens funktionsnedsättning. Vidare har också grundläggande aspekter på proprioceptiv informationsöverföring studerats och som kan vara relevant vid studier av muskulär spänning och smärta.


I avhandlingen är det framför allt patienter med kronisk pisksnärtskada som har undersöks. Avhandlingen visar att personer med denna skada har, i jämförelse med friska försökspersoner, minskat rörelseomfång i nacken, lägre hastighet vid utförandet av rörelser och en större ryckighet i rörelsens utförande som eventuellt kan kopplas till en försämrad motorisk kontroll. Sammanlagt har ca 100 personer deltagit i studien, varav hälften hade en kronisk pisksnärtskada.
Slutsatser från avhandlingen är att den objektiva bedömningen av nackens funktionsnedsättning utgör ett stöd för vårdpersonalen vid bedömning av nackens funktionsnedsättning hos kroniskt pisksnärtskadade. Metoden går också att använda på andra patientgrupper och kan sannolikt även där användas vid utvärderingar av rehabiliteringsinsatser samt efter kirurgiska ingrepp.
Included papers

This dissertation is based on the following papers, which are referred to by their Roman numerals in the text. Papers I - V are reprinted with permission from the publishers.


**Contribution to listed papers**

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a = Main responsibility  
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<td>BP</td>
<td>Back propagation</td>
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<td>BPNN</td>
<td>Back propagation neural network</td>
</tr>
<tr>
<td>CCD</td>
<td>Charge-coupled device</td>
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<td>CNS</td>
<td>Central nervous system</td>
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<tr>
<td>CR</td>
<td>Center of rotation</td>
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<td>DF</td>
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<td>DLT</td>
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<tr>
<td>GS</td>
<td>Gastrocnemius, plantaris &amp; soleus</td>
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<tr>
<td>GTO</td>
<td>Golgi tendon organ</td>
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<tr>
<td>IHA</td>
<td>Instantaneous helical axis</td>
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<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<td>MSA</td>
<td>Muscle spindle afferent</td>
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<td>PCA</td>
<td>Principal component analysis</td>
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<td>Partial least squares regression</td>
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<td>SOM</td>
<td>Self organizing maps</td>
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<td>SVD</td>
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1 Introduction

1.1 Historic background on whiplash associated disorders and neck pain

Spinal pain is a common symptom after different types of neck or back disorders. Even at the time of Hippocrates, spinal injuries such as deformities and fractures were well documented. These findings were found in collected writings from the Greek library at Cos and Cnidus. It was the writings of Galen that were predominant in the area of medicine during that time. Those writings included descriptions of spinal pain as the symptom of many illnesses. There was no description on the cause of pain; the treatment was purely symptomatic [1].

It was not until the beginning of 1930s that the cause of spinal pain was described to have its origin in spinal structures when Mixter and Barr described Disc Hernia [2].

Since the end of the 18th century, different terms (e.g., railway spine or neck sprain) have been proposed to describe the injuries after railway accidents. These injuries caused neck pain and other related symptoms (e.g., headache and stiffness) [3-5].

During World War I, many cases of whiplash were defined as war neurosis or shell shock. This was a description of a physical injury where no signs were present except for the symptoms [6]. Mott thought that the symptoms were caused by a severe psychological trauma [6]. About the same time, reports appeared describing severe injuries to the cervical spine among fighter pilots who has been launched by catapults from ships [7].
Crowe introduced the term whiplash injury at a meeting of the Western Orthopedic Association in San Francisco in 1928 and used it to describe injuries caused by rear-end car accidents [8]. The term whiplash is an attempt to describe the movement of a whip, and the cervical spine is subjected to a similar movement during indirect violence [9]. In addition, the cervical spine is affected by even higher forces and moments because the weight of the head causes greater effects on the structures in the cervical spine [9].

Following the World War II, there was a striking increase in automobile traffic in the Western world and a following increase in the number of whiplash injuries [10].

Gay and Abbott published an article in 1953 about rear-end accidents where they, for the first time, used the term whiplash in the title [10]. Despite efforts (e.g., [11]), the term whiplash has since proven impossible to get rid of. However, it should be emphasized that the term whiplash is limited to the description of the injury mechanism; the term does not imply a specific diagnosis or condition [7].

In 1955, Severy et al. took photographs in order to study the movement of the cervical spine during a low speed rear-end car crash [12]. They found that the movement consists of a stretch followed by a bend in the neck. In addition, they found that the symptoms could come hours after the crash [12].

Injuries related to whiplash were not seen in the world statistics until 1970 [9]. There are some plausible reasons. The amount of traffic increased very rapidly in Sweden, and that caused traffic congestion on many roads inside the larger cities, where most of the accidents occur. In addition, during a long period of
time the cars were constructed such that the metal sheeting and girders yielded when hit by another car [9]. This weak construction prevented the whiplash movement for those who sat in the car. Instead, the drivers were more seriously injured. When the cars became more secure, the number of serious injuries decreased as whiplash injuries increased. The reason behind this was the stiffer construction of the cars [9].

There are many different definitions and classifications of whiplash. The definition by the Quebec task force [11], from 1995, is most commonly used. It defines whiplash as “... an acceleration-deceleration mechanism of energy transfer to the neck. It may result from rear or side impact motor vehicle, but can occur during diving or other mishaps. The impact can result in bony or soft tissue injuries (Whiplash injury) which in turn can lead to a variety of clinical manifestations (Whiplash Associated Disorders, WAD)”.

There is no current consensus among researchers about the injury mechanism behind the symptoms. Several different models for classification of WAD have been used to try to narrow down the symptoms. The Quebec Task Force definition divides WAD into 5 different grades (i.e., grades 0-4) [11]. The symptoms vary from no symptoms (grade 0) up to fractures and dislocations found in grade 4.

The symptoms related to long term WAD of grade 1 and 2 do not differ significantly from other types of chronic neck problems. For medical and insurance reasons it is therefore important with an early diagnosis [9].

According to different studies, the incidence of WAD varies between 0.8-4.2 per thousand inhabitants and per year [9]. A part of the reason for the variation is assumed to be related to the design of the studies [9].
Other feasible explanations could be differences in geography, social structure, insurance system design and type of accident covered in the survey [9].

The cost, related to WAD, for the society has increased by 50% during the 5-year period between 1998 and 2003 according to calculations made by insurance companies in Sweden [9]. Recalculated for the year 2000, there was an annual total cost of 1.8 billion Swedish crowns (i.e., incidence costs) [9].

1.2 Historic background on movement analysis

According to Hay [13], the definition of biomechanics is “the science that examines forces acting upon and within a biological structure and the effects produced by such forces”. For example, the results after such forces could be movements of segments and deformation of the biological structure.

According to Nigg et al., the history of biomechanics can be divided into seven different periods in time [14]. These periods are: Antiquity (650 B.C.-200 A.D.), Middle Ages (200 A.D.-1450 A.D.), Italian Renaissance (1450 A.D.-1600 A.D.), Scientific Revolution (1600 A.D.-1730 A.D.), Enlightenment (1730 A.D.-1800 A.D.), The Gait Century (1800 A.D.-1900 A.D.) and finally the 20th Century (1900 A.D.-).

The Antiquity was influenced by ancient cultures such as the Maya, Egyptians, Mesopotamians and Phoenicians. People during that time tried to understand nature by combining knowledge and myth. The first people who tried to separate knowledge from myth were the ancient Greeks who had relative freedom from political and religious restrictions [14]. In addition, certain wealthy groups of people started to
have some leisure time, which enhanced the opportunity for scientific thinking. The artistic media was influenced by Greek athletes and produced sculptures and paintings of sportsmen in different dynamic postures [14]. During that period mechanical and mathematical paradigms were created by scientists such as Pythagoras, Aristotle and Archimedes. Anatomical and neurophysiological paradigms were also created by scientists such as Hippocrates and Galen. The first book on movement analysis was written by Aristotle, who wrote About the Movements of Animals, which was based on observations [14].

Religious development increased during the Middle Ages at the expense of scientific development [14]. If it had not been for the Arabs, who translated scientific works of the Antiquity from Greek to Arabic, the investigations would have disappeared. Aristotle’s records were translated from Arabic and integrated into Christian beliefs during the 13th century. Universities adopted Aristotle’s philosophy but did not carry out any of their own research [14].

The Italian Renaissance was characterized by freedom of thought as the authority of the Church was questioned [14]. During that period, a foundation for modern anatomy and physiology was created by scientists such as Leonardo da Vinci and Vesalius who based their teaching on observations and dissection of human cadavers. In addition, human movements and factors contributing to human movement were studied [14].

During the Scientific Revolution a Newtonian mechanics were founded, where a complete theory for mechanical analysis was included. In addition, experimentation and theory were used as a complement to scientific investigations. The scope of the
experiments was improved by using new instruments such as telescopes and microscopes [14]. Borelli is often called the father of biomechanics because of his geometrical description of motion. Harvey discovered the circulation of blood and used experimentation to understand the human body and movement. Scientists such as Galileo, Borelli and Harvey created a basis for biomechanics during the 17th century. Newton’s ideas inspired scientists to study movements in a completely new way using Newton’s laws. Newton synthesized Kepler’s law of motion of heavenly bodies, Galileo’s law of falling bodies and Descartes’ law of inertia into his famous four basic laws: (1) The law of inertia, (2) The law of acceleration due to an acting force, (3) The law of action and reaction, and (4) The law of gravity. According to a legend, Descartes’ invented the Cartesian coordinate system while observing a fly. He realized that the movement of the fly could be represented by a Cartesian coordinate system [14].

The name Enlightenment was coined by mathematicians who were convinced that mathematical analysis was the most important force behind the scientific revolution [14]. The concept of force was understood during that period (1730 A.D.-1800 A.D.). In addition, the establishment of theories regarding conservation of momentum and energy was initiated. A mathematical merging of the different laws of mechanics was carried out by scientists such as Euler, d’Alambert and Lagrange. Finally, muscle contraction was identified as an event affected by mechanical, biochemical and electrical forces (e.g., studies made by Albrecht von Haller, Daniel Bernoulli and Charles Dufay). Leonhard Euler was the most productive scientist of the 18th century (e.g., he expanded Newton’s law to rigid bodies). His famous rotation theorem states: “an arbitrary rotation may be described by only three parameters” (i.e., any rotation may be described
using three angles). In addition, in another famous theorem, he stated that “any displacement of a rigid body such that a point on the rigid body, say O, remains fixed, is equivalent to a rotation about a fixed axis through the point O”.

During the Gait Century (1800 A.D.-1900 A.D.) biomechanics was transformed from a study based on observations into a study based on quantitative measurements and mathematical analyses. Scientists such as Marey, Muybridge, Braun and Fisher made this quantification possible by using photographic techniques. A refined analysis of human and animal movements was therefore made possible. In addition, techniques were developed for observation of the internal electrical currents within muscles during activity, e.g., Electromyography (EMG). Michel Chasles was a mathematician who focused on projective geometry. One of his theorems (important for the theory of screw axis) states: “the most general rigid body displacement can be produced by a translation along a line followed (or preceded) by a rotation about that line”. Because this displacement is reminiscent of the displacement of a screw, it is called a screw displacement. The line or axis is called the screw axis.

During the 20th Century biomechanical research was increasingly used in different medical and industrial applications [14]. Sir Robert Stawell Ball developed the screw theory for application to rigid body mechanics. In the screw theory, velocities and forces are expressed in three-dimensional space, combining both rotational and translational parts. New and more sophisticated methods for kinematical measurements were developed, e.g., analogue film or video cameras together with passive or active markers, electro-goniometric techniques [15, 16] and electromagnetic systems [17]. Algorithms were developed to calculate three-
dimensional coordinates from two-dimensional images taken in stereo (e.g., [18]). Methods for improving the precision and accuracy of movement analysis systems were also developed.
2 Non-specific neck pain

Chronic neck or shoulder pain has become a common problem, associated with high costs for the society and individual suffering [19-21]. According to Binder, two-thirds of a general population has neck pain at some point in their lives. Also, most patients with this type of complaint refer to a non-specific neck pain [22]. The cause of non-specific neck pain is usually multifactorial (e.g., poor posture, anxiety, neck strain, and sporting or occupational activities) [22], but in many cases no specific cause can be identified. The pain after a whiplash injury is sometimes referred to as non-specific neck pain, provided no bony injury or neurological deficit is present [22].

Most movement in the neck is performed around the top three joints. This might suggest that impairments are located in the upper parts of the cervical spine. This is also supported by authors who state that C1/C2 is one of the most frequently injured segments among trauma-related cervical spine injuries [23, 24].

Evidence for changed motor performances (that reflect impaired sensorimotor functions) in patients with chronic neck pain is published during the last decades (e.g., [25]). Objective examination methods for movement and motor control function have been used and show that neck pain is associated with slow movements [26], reduced range of motion [26, 27], poor balance [28], impaired function of deep cervical muscles [29, 30] and poor proprioception [31, 32].
2.1 Work-related factors

There are many factors in a work place that can be risk factors for neck and shoulder pain. It is important to know these factors to take actions that reduce the risk for development of neck pain. The occupational factors that affect neck and shoulder pain can be divided into individual, physical and psychosocial factors [33]. According to a recent survey by the Swedish Work Environment Authority, physical risk factors seems to be more important than psychosocial factors [34].

Examples of individual factors include genus (higher risk for women) and age (lower risk for younger subjects) [33]. Examples of physical stress factors include, e.g., static workload [35], bad working posture [33], hand-arm vibration [36] and prolonged sitting time [33]. Psychosocial factors affecting neck and shoulder pain include, e.g., stress, mental tiredness at the end of the day, and shortage of personnel [33].

The knowledge of the mechanisms behind neck and shoulder pain is relatively limited. Objective and quantitative methods for studying movements can provide a basis for improving this knowledge and for developing efficient rehabilitation related to neck and shoulder pain.
2.2 Sensorimotor mechanisms behind neck pain

To clarify the integrated and complex relation between sensory input (afferent nerve signals) and motor control output, Michaelson defined in his doctoral dissertation the term sensorimotor as “processes and variables that might be a result of both sensory input to the CNS and intrinsic motor control properties” [37].

Pain often has its origin in damaged tissues, where nociceptive nerve fibers lying between the muscle fibers mediate pain to the central nervous system (CNS). These nociceptive nerve fibers have a small diameter and a low conduction velocity. In an afferent nerve bundle, a high proportion of the nerve fibers are terminated in free nerve endings with nociceptive properties. These nociceptive nerve endings are sensitive to the chemical substances released from damaged tissue or excessive tissue deformation [38].

There are also many other structures in the neck that may be damaged after a neck injury and therefore a factor that could cause pain. Examples of traumatized structures include muscles, ligaments, facet joints, intervertebral discs and neural structures. In addition, it is suggested that there is a multifactorial cause behind pain [39].

Clinical findings of pain distinguish between negative symptoms (i.e., reduction of sensory input) and positive symptoms (i.e., excessive spontaneous and stimulus related nerve activity) symptoms. Positive findings constitute a basis for pain-related symptoms. Different animal models have been developed to study various aspects of the clinical findings [40]. When evaluating these animal models it is common to use electrophysiological measurements in acute animal
experiments (e.g., [41]). In many of these cases, it is common to use single unit recordings.

Instead, to get a better conformity of these animal models it is important to base the evaluation on sensory input from populations of afferents. To maximize the number of simultaneously recorded afferents, a part of my dissertation was devoted to spike sorting in multiunit recordings (cf. Aims of the dissertation). Some of these animal models are also the foundation to studies describing the neural mechanisms behind pain (e.g., [42]). Examples on human models describing the pain mechanisms are presented in Table 1.

According to Michaelson, there is an overlap between different types of neck pain, regarding different dysfunctions, which indicates that there are common mechanisms behind movement disturbances in these groups of patients [37]. There are also similar neural activation pattern of the cervical muscles when comparing patients with WAD and insidious neck pain [43, 44]. Examples of sensorimotor mechanisms that affect the musculoskeletal pain are found in Table 1 [40].
<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
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<tr>
<td>Changes in motor unit activation patterns</td>
<td>Muscles generate force either by changing muscle fiber discharge rate or by changing motor unit recruitment. The size principle is used, according to Henneman, when recruiting motor units for a special task [45]. The smallest and weakest muscle fibers are always recruited first and are therefore most prone to damage. This has been described as the Cinderella hypotheses [46].</td>
</tr>
<tr>
<td>Disturbed proprioceptive input</td>
<td>Experiments on animals have shown that reduced proprioceptive accuracy is can occur by disturbed fusimotor control of muscle spindles. Inflammatory or traumatic activation of cervical nociceptors triggers this disturbance [47]. This reduced proprioceptive accuracy may result in impaired motor control that can affect neck pain [40].</td>
</tr>
<tr>
<td>Motor control and pain avoidance strategies/pain adaptation model</td>
<td>The expectation of pain or nociceptive reflexes creates a protective strategy which stiffens the spine. This is achieved by increasing the amount of co-activation. Moseley et al. based this idea on EMG measurements from trunk muscles [48]. This increased level of co-activation of muscles could also cause slow and jerky body movements with lower range of movement[40].</td>
</tr>
<tr>
<td>Delay in neck muscle activity</td>
<td>Automatic feed-forward control strategy of the cervical spine is defective in patients with neck pain. The defect is seen as a delayed cervical muscular onset [29]. The feed-forward activation of neck muscles is a mechanism necessary to achieve stability for the visual and vestibular systems, as well as ensuring stabilization and protection of the cervical spine [30].</td>
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3 Whiplash associated disorders

3.1 Classification by the Quebec task force

According to the Quebec task force WAD can be divided into 5 different grades of injury, see Table 2 [11].

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Grading of WAD related injury</th>
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<tbody>
<tr>
<td><strong>Grade 0</strong></td>
<td>No symptom or physical signs.</td>
</tr>
<tr>
<td><strong>Grade 1</strong></td>
<td>Complaint of neck pain, stiffness or tenderness only. No physical signs.</td>
</tr>
<tr>
<td><strong>Grade 2</strong></td>
<td>Complaint of neck symptoms and musculoskeletal signs (e.g., decreased range of movement and point tenderness).</td>
</tr>
<tr>
<td><strong>Grade 3</strong></td>
<td>Complaint of neck symptoms and neurological signs (e.g., decreased or absent deep tendon reflexes, weakness and sensory deficits).</td>
</tr>
<tr>
<td><strong>Grade 4</strong></td>
<td>Complaint of neck symptoms and fracture or dislocation in the cervical spine.</td>
</tr>
</tbody>
</table>
3.2 Diagnosis and symptoms

Many different clinical symptoms are dominant in acute and chronic WAD. Examples of symptoms are headache, stiffness and pain in the neck, paresthesia (i.e., abnormalities of sensation), weakness in arms, visual disturbances and auditory disturbances [11]. There are two main areas of complaints in clinical practice that are reported by WAD patients. First, the muscle tension and pain in the shoulders and neck is increased during monotonous arm and shoulder movements. Secondly, the pain and stiffness during repetitive neck movements is also increased. By clinical experience it is shown that most of the symptoms emerge within 24 hours after the injury or at most within 72 hours [11]. Most symptoms that emerge, for example headache, visual and auditory disturbance, can be explained as a result of chronic pain [9]. The same kind of symptoms are also prevalent in patients who have other neck problems not related to whiplash injury, which is a complicating factor [9].

Palpation of the muscles for pain and range-of-movement in the neck and shoulder joints are often studied during clinical examinations of patients with WAD. WAD is a syndrome (i.e., includes a group of symptoms) and thus heterogeneous. It is difficult to identify subgroups of WAD in clinical practice, and therefore difficult to establish a more precise diagnosis. In addition, imaging techniques (e.g., X-ray or magnetic resonance imaging (MRI)) seldom show any pathological changes [9]. It is common that the only negative sign, in patients with WAD, is muscle pain in muscles of the neck and shoulders. A part of my dissertation was to form a basis to a clinical support system when studying WAD patients (cf. Aims of the dissertation).
3.3 **Risk factors**

The Whiplash commission indicate a couple of important risk factors for developing long-term chronic problems related to WAD: (1) initial neck and shoulder pain, (2) gender (i.e., increased risk for women), (3) place in the car (i.e., increased risk for the driver), (4) position of the head relative the headrest (i.e., a short distance between the head and headrest lowers the risk), (5) type of car (i.e., decreased risk for people in cars with built in whiplash safety systems), and (6) age of the subject (i.e., increased risk for older people) [9].
4 Treatment and rehabilitation of neck pain

As mentioned above, neck and shoulder pain is associated with high costs for the society and individual suffering. However, there is limited knowledge about the effectiveness of the available treatments [49]. The Cervical Overview Group performed a review on different types of conservative treatment strategies for mechanical neck disorders and estimated the clinical evidence for each type of treatment. They concluded that approaches including stretching/strengthening exercise and mobilization/manipulation of the neck had strongest clinical evidence for treatment effect. This treatment reduced the pain and improved the function of the neck. Examples of other types of treatment strategies include: 1) Exercise (e.g., strengthening and stretching, active range of motion exercises or cervical proprioceptive training), 2) Medicine (e.g., intravenous glucocorticoid for pain reduction or epidural injections of steroid for pain reduction). According to Bjordal, the clinical evidence for epidural steroid injections is limited, since weak evidence for effect is seen [50], 3) Low-level laser therapy is used for pain reduction and functional improvement, and 4) Electrotherapy can be used for palliative treatment [49].

The report from The Swedish Council on Technology Assessment in Health Care (SBU) concluded that multimodal rehabilitation is more effective than separate rehabilitation for treating patients with chronic neck pain. The comparison showed an increased pain relief and a shorter sick leave for subjects exposed to multimodal rehabilitation. The multimodal rehabilitation usually includes a combination of psychological interventions and physical activity, physical exercise or physical therapy. Special
rehabilitation programs are often designed for these patients by a group consisting of different specialist expertise (e.g., doctor, physical therapist and social worker). Note that the group does not only include hospital staff. The report also concluded that cognitive behavioral therapy is important to get a better social and physical function in subjects with chronic pain [51].

In most cases it is important for these patients to start the medical treatment early. Most studies show that people with acute WAD should be active rather than passive in their life [9]. If a patient is passive and tries to get rid of pain and other symptoms by resting, it can be more harmful than helpful. That is because muscles and other tissues that are stimulated (i.e., kept in motion) recover faster [9]. The first impulse for subjects with pain is often to rest and move as little as possible. Thus, it is important for patients to get an early diagnosis and be motivated to start lighter exercises to speed up the recovery process [9, 11].

Still, there are many unanswered questions regarding the treatment of neck pain. The Cervical Overview Group points out that it is particularly important to understand how to combine treatment techniques in an effective way, and which dosages that are optimal, especially when it comes to different types of exercise and manual therapy. Finally, more research is needed to find out if there are prognostic indicators for those who will respond to a certain treatment [49]. Therefore, in this dissertation was an objective multivariate assessment tool developed, which can be used when studying the progress of treatment in WAD patients (cf. Aims of the dissertation).
5 Neural encoding

The perception and control of our body needs a flow of neural input (i.e., afferent nerve signaling) and output (i.e., efferent nerve signaling) to and from the CNS. Action potentials are the main information carrier in this system. One long-lasting challenge has been to understand how the sensory information is encoded when it is transmitted through the afferent nerves to the CNS. As a consequence, it has been an objective for many neurophysiological studies to make simultaneous recordings of as many afferents as possible when stimulating the receptors with different types of stimulus and stimulus intensity (e.g., a mechanical stimulus of a muscle with different amplitudes). This is an objective in many studies when observing the afferent encoding ability (e.g., [41, 42]). A part of this dissertation was devoted to the development of a new method that maximize the number of collected single afferent [52] and to the study of afferent encoding ability (cf. Aims of the dissertation) [53].

Different encoding theories have been developed during the years. Two perspectives have dominated our view on neural input encoding: (1) labeled line theory and (2) population coding theory.

5.1 Labeled line theory

Labeled line theory describes how different types of stimuli are encoded by receptor afferents. This theory tries to explain how we perceive different types of stimuli (e.g., touch, smell, vision, pain) using the assumption that information is transmitted by specific afferents to a dedicated center in the brain that decodes the information.

According to this theory, receptor afferents are active when they signal the presence of a specific stimulus, for
example, a unique taste experience. When these receptor afferents are quiet, it means that this stimulus is missing. Also, each neuronal receptor in the peripheral nervous system is sensitive to a range of stimuli, but this theory assumes that the receptor is tuned to a specific stimulus. This specific stimulus is defined as the receptors’ adequate stimulus. Therefore, if the mediated information is sent by receptors to a dedicated center in the brain, it is implied that there is a single neuronal pathway connecting the receptor and the brain center [54].

5.2 Populaon coding

In population coding the emphasis is put on the collected encoding by many neurons. It is like our democratic society, single neurons give little information while the activity from the population gives a more detailed picture [55]. The accuracy is also improved when using a population of neurons compared to a single neuron [56]. If the accuracy must increase for a single neuron, there are no other alternative except to perform temporal averaging. One difficulty is that when it comes to population coding, the population activation pattern response is never the same for the same stimulus. This can be explained by noise added to each single neuron in the population, and that noise in turn affects the overall activation pattern. The conclusion from this is that population coding is necessarily probabilistic [55] and that the brain cannot know the exact input pattern. Instead, the brain has to estimate the type of stimulus behind the pattern using the population pattern as the only input.
In contrast to the labeled line theory, population encoding predicts that each receptor within the population has different sensitivity range to get a better performance of stimulus encoding. Sensitivity tuning of each receptor is also important and it should be overlapping (i.e., several receptors should have the capacity to respond to the same stimulus) [57].

There are still many interesting questions that are unanswered. For example, how does added noise affect the accuracy of population coding? Also, there are some interesting questions, related to the receptor afferents’ encoding of mechanical stimuli, which have not been answered yet. To shed more light on this encoding, a part of this dissertation was devoted to the encoding of mechanical stimuli by a mixed population of receptor afferents (cf. Aims of the dissertation) [53].
6 Neural spike sorting

As mentioned previously, the aim of many neurophysiological studies are to investigate the encoding ability of populations of receptor afferents when provoked with various stimulus. To be able to collect as many single afferents as possible, various methods are used.

As a first step, extracellular measurements of the afferent activity must be performed (e.g., by using multielectrode arrays [58]). A surgical procedure is often required to dissect the nerve filament to be able to perform the measurements. The purpose of this measurement is often to study the simultaneously transferred information from several neurons located in the same region and how the nervous system responds to different stimuli [59]. The recorded neural signal from a single electrode usually includes action potentials from several neural cells and additive Gaussian white noise. Different approaches for reconstructing neural activity have been published during the past decades as reviewed by Schmidt and Lewicki [60-62]. Most of these methods assume that each neuron generates a distinct and reproducibly shaped waveform [63]. An illustration of an extracellular recording and a following spike sorting feature is shown in Figure 1.

The use of electrodes for multi-unit activity measurements are used more frequently. Efficient algorithms to sort these measurements into single-unit spike trains are needed to make the acquisition easier and to assist the experimenter when doing offline checks of collected data when the number of channels is increasing. The separating algorithm has to produce results of high quality. This requires using the whole waveform as a pattern instead of extracted parameters.
(features describing the waveform) from the waveform. The separating algorithm often tries to find underlying clusters which describe a single-unit spike train [64]. A part of this dissertation was devoted to the development of an efficient algorithm for spike sorting in a multiunit recording (cf. Aims of the dissertation).

There also exist commercial systems for data acquisition (e.g. Experimenter; DataWave Technologies, Longmont, CO, USA or Spike2; CED, Cambridge, England) which include some kind of spike-separating algorithm. Spike2 uses a clustering algorithm, based on waveform templates and principal component analysis, in combination with simple threshold detection for sorting spikes in a multiunit recording. The software Experimenter uses similar algorithms for sorting spikes.
Figure 1. Illustrates an extracellular neural recording containing action potentials from two different neurons. The original waveform is sorted into two waveforms using a separating algorithm. The separating algorithm can be based on features extracted from the original waveform or from the whole raw waveform.
7 Kinematics

7.1 Body position and orientation

In kinematics it is common to describe a rigid body’s attitude in space (i.e., with its position of center of mass in a global coordinate system, $O_G$, and its orientation in space). The orientation can be described by using the matrix method, Euler angles, or the screw/helical angle [65]. The position of the center of mass may also be described relative to another point of reference, e.g., the center of mass of another body segment. The same argument is valid for the description of the orientation (e.g., it might be compared to a reference segment’s orientation). According to Zatsiorsky, kinematics is defined as “a description of motion without regard to the force producing the motion” [65]. In addition, it might be interesting to describe the joint configuration during a certain movement (i.e., relative orientation between adjacent segments).

Cartesian coordinates $(x, y, z)$ are a natural representation of a position in 3D space. There are also many other representations that could be used such as cylindrical notation $(r, \theta, z)$ or spherical notation $(r, \theta, \varphi)$. In clinical applications it is common to choose the Cardan (subgroup of the Euler angles) representation of a segment’s orientation relative to a connected segment (i.e., by a joint). It is also common to choose the Cardan angles such that they can be clinically interpreted. The angles in the knee joint are mostly described by Cardan angles describing the flexion/extension, abduction/adduction and internal/external rotation of the knee. In sports, it might be interesting to describe a diver’s attitude in space during a dive using Cardan angles.
7.2 Euler/Cardan method

As mentioned earlier, Euler’s rotation theorem states that any rotation may be described using three angles. If the rotations are written in terms of rotation matrices, \( A, B, C \) and \( D \), then a general rotation \( A \) can be written as \( A = BCD \). The matrices \( B, C \) and \( D \) are described by three angles called Euler angles. Given two coordinate systems, \( xyz \) and \( XYZ \), with common origin \( (O_C) \), one can specify the orientation of the second in terms of the first using three angles, \( \alpha, \beta, \gamma \), in three equivalent ways, see below. These three angles, \( \alpha, \beta, \gamma \), are called Euler angles, where the ranges of \( \alpha \) and \( \gamma \) are from 0 to 2\( \pi \) radians and the range of \( \beta \) is from 0 to \( \pi \) radians.

(1) Static method

The intersection of the \( xy \) and the \( XY \) coordinate planes is called the line of nodes. \( \alpha \) is the angle between the \( x \)-axis and the line of nodes. \( \beta \) is the angle between the \( z \)-axis and the \( Z \)-axis. \( \gamma \) is the angle between the line of nodes and the \( X \)-axis.

(2) Fixed axes of rotation method

Start with the \( XYZ \) system equaling the \( xyz \) system. Rotate the \( XYZ \)-system about the \( z \)-axis by \( \alpha \); the \( xyz \)-system does not move, now or later. Rotate it again about the \( x \)-axis by \( \beta \). Rotate it a third time about the \( z \)-axis by \( \gamma \).
(3) Moving axes of rotation method

Start with the XYZ system equaling the xyz system. Rotate the XYZ-system about the Z-axis by $\gamma$; the xyz-system does not move, now or later. Rotate it again about the now rotated X-axis by $\beta$. Rotate it a third time about the now doubly rotated Z-axis by $\alpha$.

This means that we can represent an orientation with three numbers. A certain sequence of rotations around orthogonal axes is called an Euler sequence of angles. Assuming we limit ourselves to 3 rotations without successive rotations about the same axis, we could use any of the following 12 sequences: XYZ, XZY, XYX, XZX, YXZ, YZX, YXY, YZY, ZXY, ZYX, ZYZ and ZXZ (shown in Figure 2). Thus, there are 12 redundant ways to store an orientation using Euler angles. The sequences that have different terminal axes of rotations are described as Cardan angles (e.g., XYZ, YZY) [65]. Figure 2 illustrates the ZXZ Euler sequence.

Figure 2. The three groups of arrows illustrates three successive rotations to change the orientation of the reference frame from the xyz system to the x'''y'''z''' system. The intermediate systems are denoted as x'y'z' and x''y''z'', respectively. The Euler angle sequence is ZXZ.
The transformation in Figure 2 is described in the equation below.

\[
\begin{align*}
   [x'] & = R_z(\phi_1) \begin{bmatrix} x \\ y \\ z \end{bmatrix} = \begin{bmatrix} \cos(\phi_1) & -\sin(\phi_1) & 0 \\ \sin(\phi_1) & \cos(\phi_1) & 0 \\ 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} x \\ y \\ z \end{bmatrix} \\
   [y'] & = R_x(\phi) \begin{bmatrix} x' \\ y' \\ z' \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \cos(\phi) & -\sin(\phi) \\ 0 & \sin(\phi) & \cos(\phi) \end{bmatrix} \begin{bmatrix} x' \\ y' \\ z' \end{bmatrix} \\
   [z'] & = R_z(\phi_2) \begin{bmatrix} x'' \\ y'' \\ z'' \end{bmatrix} = \begin{bmatrix} \cos(\phi_2) & -\sin(\phi_2) & 0 \\ \sin(\phi_2) & \cos(\phi_2) & 0 \\ 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} x'' \\ y'' \\ z'' \end{bmatrix} \\
   [y'] & = R_x(\phi) R_y(\phi) R_z(\phi) \begin{bmatrix} x \\ y \\ z \end{bmatrix}
\end{align*}
\]

There are three problems in using Euler angles. (1) The axis of the second rotation, \( \phi \), is the \( x' \)-axis of the intermediate frames, not that of either \( x \) or \( x''' \). This sometimes causes confusion in assigning practical meanings to the Euler angles (i.e., angle \( \phi \) is not relative to the anatomical frame). The anatomical angles are projected angles, not the Euler angles. (2) Euler angles are dependent on the sequence, i.e., different Euler angle sequences give different Euler angles as a result, i.e., the interpretation depends on the chosen sequence. Therefore, it is important to standardize which sequence is used for different clinical applications. (3) Euler angles can suffer from a gimbal lock. That occurs when two axes effectively line up leading to a temporary loss of a degree of freedom (DF).
7.3 Screw (Helical) axis method

The screw axis representation is a description of a rigid body’s orientation in space without referring to an arbitrarily chosen axis of rotation [65]. According to Euler’s theorem, “any motion of a rigid body with one point fixed can be described as a single rotation around an axis through that fixed point” [65]. Also, according to Chasles’ theorem, “any rigid-body can be obtained as the rotation around an axis, known as the screw axis, and a translation parallel to the screw. The rotation and translation may occur in any sequence” [65, 66].

![Diagram](image)

**Figure 3.** The diagram illustrates a helical movement of a rigid body. The movement might be described by the translation (t; 1DF) along the screw axis, the point were the screw axis is as closest to the origin (c; 3DF), the rotation around the helical axis (θ; 1DF) and the orientation of the screw axis (n; 3DF). In total, eight parameters described the helical movement. This description is therefore redundant, because the movement only has six degrees of freedom.
If a planar movement of a rigid object is considered (pure translation excluded), there exists a point, called the center of rotation (CR), that does not move during the movement. In three dimensions, the motion of an object from one position to another can be broken down into a rotation about and a translation along the instantaneous axis of rotation. This instantaneous axis of rotation is often called the screw axis, see Figure 3. The screw axis is useful when analyzing the relative motion of a rigid object to another (e.g., joint motions). Joints in the human body have varying degrees of freedom depending on the shapes of the articulated bones (e.g., ball-and-socket (3DF), condyloid (2DF) and hinge (1DF). Degrees of freedom in a joint describe the number orthogonal axes of rotation that are present in the joint. The instantaneous axis of rotation of a joint can be viewed as a screw axis together with a relative translation of the bones along the instantaneous axis of rotation.

One general advantage when using a screw axis representation of a movement, is that a joint may be described even though the actual joint center is moving (e.g., shoulder). This, in turn, gives the possibility to study the actual movement of the center of a joint by deriving the intersection of at least two screw axes.

The drawback is that the orientation and location of the screw axis is badly estimated for small rotations as compared to bigger rotations. In addition, a clinical interpretation of the movement is more difficult to make than when using the Euler representation. A part of this dissertation was dedicated to the development of an objective method, based on screw axis theory, for grading the neck functions in patients with neck pain (cf. Aims of the dissertation).
8 Movement analysis system

8.1 Cameras and markers

A movement analysis system is needed to collect kinematical data during an arbitrary movement. Different kinds of systems exist on the market today, and they are based on ultrasonic digitizers (e.g., [67]), cinephoto-grammetry (e.g., [15]), radiostereometry (e.g., [68]) or electromagnetic systems (e.g., [69]). A cinephotogrammetry method was used for the calculation of screw parameters in Paper III-V of this dissertation (cf. Aims of the dissertation) [26, 70, 71]. Therefore, cinephotogrammetry is described in the following section.

A typical system consists of a group of video cameras (at least two). However, in older systems film cameras were used. The system either consists of active markers and passive cameras or passive markers and active cameras (see Figure 4). In a system with passive markers and active cameras infrared (IR)-light is sent from each camera (in synchrony) with a certain pulse frequency. The light is reflected by markers attached to the segments of interest and captured by the cameras (e.g., using a charge-coupled device (CCD) image sensor). The markers create circular reproductions on the camera’s image sensor. The center of these circular reproductions is then calculated in real-time by using an algorithm, leading to a 2-D representation of the markers.
Figure 4. Illustration of a typical setup for a cinephotogrammetric movement analysis system. The markers on the body are registered by the system and assembled into three-dimensional coordinates for each marker. These coordinates can be used for analysis of the movement.
8.2 Estimation of marker position

The most commonly used method for camera calibration is the direct linear transformation method (DLT) [18]. The DLT method uses a set of control points whose object space/plane coordinates are already known. The control points are normally fixed to a rigid calibration frame. The flexibility of the DLT-based calibration often depends on how easy it is to handle the calibration frame. The main problem of the DLT method is that parameters obtained from the calibration are not mutually independent. This jeopardizes the orthogonality of the rotation matrix. Hatze presented two modified DLT-algorithms (one linear and one non-linear) that improved the accuracy of the DLT algorithm [72].

In Figure 5 there are two reference systems defined: (1) the global system; $O_G$ (i.e., the XYZ-system), and (2) the image plane system; $O_I$ (i.e., the UVW-system). The camera projects a point $P_G(x,y,z)$ in $O_G$ to the point $P_I(u,v,o)$ in $O_I$. The center of the projection is assumed to have the coordinates $(x_0, y_0, z_0)$ in $O_G$ and $(u,v,d)$ in $O_I$. The center of projection, $P_G$ and $P_I$ are thus collinear, and collinearity forms the basis for the DLT algorithm.
Thus, the vector $A$ (drawn from the center of projection to $P_G$) is equal to $(x-x_0, y-y_0, z-z_0)$, which is simply the point $P_G$ in a coordinate system centered in the center of projection and with the same orientation as system $O_G$. The point $P_{I,0}$ is defined as the principal point in the image plane. The line (defined as the principal axis) drawn from the center of the projection to the image plane is parallel to the $W$-axis in $O_I$. The distance $d$ is the distance between points $P_{I,0}$ and the center of projection. Therefore, the vector $B$’s coordinates in a coordinate system centered in the center of projection are simply $(u-u_0, v-v_0, -d)$ with the same orientation as $O_I$. Thus, the expression $A=cB$, where $c$ is a constant, is valid since $A$ and $B$ are collinear. Obviously, $A$ and $B$ are centered in the same point but with different orientations. Thus, it is necessary to describe $A$ and $B$ in a common reference frame. Therefore, to transform vector $A$ into the system $O_I$, see the expression below [15].

Figure 5. This diagram illustrates the projection of a point $(x,y,z)$ in a global system to a point $(u,v,0)$ in the image plane.
\[ \mathbf{B} = c \mathbf{R} \mathbf{A}, \text{ where } \mathbf{R} = \begin{bmatrix} r_{11} & r_{12} & r_{13} \\ r_{21} & r_{22} & r_{23} \\ r_{31} & r_{32} & r_{33} \end{bmatrix} \text{ is a rotation matrix.} \]

By inserting the coordinates for \( \mathbf{A} \) and \( \mathbf{B} \) into the equation above, one gets the following expression.

\[
\begin{bmatrix} u - u_0 \\ v - v_0 \\ -d \end{bmatrix} = c \begin{bmatrix} r_{11}(x - x_0) + r_{12}(y - y_0) + r_{13}(z - z_0) \\ r_{21}(x - x_0) + r_{22}(y - y_0) + r_{23}(z - z_0) \\ r_{31}(x - x_0) + r_{32}(y - y_0) + r_{33}(z - z_0) \end{bmatrix}
\]

Therefore, \( c \) is derived from the following expression.

\[
c = \frac{-d}{r_{31}(x - x_0) + r_{32}(y - y_0) + r_{33}(z - z_0)}
\]

This also leads to an expression for \( u-u_0 \) and \( v-v_0 \).
The equation above must be altered because the coordinates in $O_I$ are described in the real length units (e.g., cm or m) and the digitization camera system use different length units (e.g., pixels). This leads to the following equation, where $\lambda_u$ and $\lambda_v$ are scaling factors from pixels to real length units [15].

$$
\begin{bmatrix}
    u - u_0 \\
    v - v_0
\end{bmatrix} = \frac{-d}{r_{31}(x-x_0)+r_{32}(y-y_0)+r_{33}(z-z_0)} \left[ \frac{1}{\lambda_u} (r_{11}(x-x_0)+r_{12}(y-y_0)+r_{13}(z-z_0)) \right]
$$

After rearranging this equation, the following expressions are found [15]:

$$
\begin{bmatrix}
    u \\
    v
\end{bmatrix} = \frac{1}{L_{9}x + L_{10}y + L_{11}z + L_{12}} \left[ L_{4}x + L_{2}y + L_{3}z + L_{4} \right]
$$

$$
L_1 = D^{-1}(u_0r_{31} - d_u r_{11}) \quad L_2 = D^{-1}(u_0r_{32} - d_u r_{12}) \quad L_3 = D^{-1}(u_0r_{33} - d_u r_{13}) \\
L_4 = D^{-1}(v_0r_{31} - d_v r_{21}) \quad L_5 = D^{-1}(v_0r_{32} - d_v r_{22}) \quad L_6 = D^{-1}(v_0r_{33} - d_v r_{23}) \\
L_7 = D^{-1}(d_u r_{14} - u_0 r_{34})x_0 + (d_u r_{15} - u_0 r_{35})y_0 + (d_u r_{16} - u_0 r_{36})z_0 \\
L_8 = D^{-1}(d_v r_{24} - v_0 r_{34})x_0 + (d_v r_{25} - v_0 r_{35})y_0 + (d_v r_{26} - v_0 r_{36})z_0 \\
L_9 = D^{-1}r_{31} \quad L_{10} = D^{-1}r_{32} \quad L_{11} = D^{-1}r_{33} \quad L_{12} = 1 \\
D = -(x_0r_{31} + y_0r_{32} + z_0r_{33}) \quad [d_u \quad d_v] = [d/\lambda_u \quad d/\lambda_v]
$$

where $L_1, \ldots, L_{12}$ are the DLT-parameters. If $n$ pairs of coordinates are collected during a calibration, then the following matrices should be constructed.
Then, the following homogenous equation must be solved (e.g., using the least square algorithm), and that requires at least six pairs of coordinates to estimate the DLT-parameters [15]. With fewer than six pairs of coordinates the solution will be undetermined.

\[ \mathbf{A} \mathbf{m} = 0 \]

There are some important things to remember when calibrating the system. First, the calibration points must be spread out throughout the entire interesting volume. If they are not well dispersed there will be an increased risk for performing a bad calibration. Secondly, one should use as many cameras as possible to increase the redundancy for the camera setup. This will increase the accuracy of the measurements.
8.3 Singular value decomposition

Singular value decomposition (SVD) is a general mathematical tool that can be used in a variety of applications in signal processing (e.g., computing the pseudo inverse of a matrix when solving a linear least squares problem) and statistics (e.g., related to principal component analysis). In movement analysis it can be used for calculating the orientation matrix, $M$, which is a part of the description of a rigid body movement, as described below. SVD was used in Paper V of this dissertation when studying systematic errors’ effect on a rigid body’s orientation in space [71].

Suppose $C$ is an $m \times n$ matrix with rank $r$ ($r \leq n$). The non-zero eigenvalues of $C^T C$ (i.e., $\lambda_1 \geq \lambda_2 \geq ... \geq \lambda_r$) is then calculated. Define $\mu_i = \sqrt{\lambda_i}$ ($i=1,...,r$) as the singular values of $C$. Any $m \times n$ matrix, $C$, with rank of $r$, can then be decomposed into $C = U D V^T$. $U$ and $V$ are orthonormal matrices and $D$ is a diagonal matrix, which contains singular values. This representation of a factored decomposed matrix is called SVD.

As a next step, assume that the vectors $x_i \in \mathbb{R}^m$ and $y_i \in \mathbb{R}^m$ defines the coordinates of fixed points on a rigid body in space. The expression below are then minimized by estimating the orthogonal matrix $M \in \mathbb{R}^{mxm}$ and the vector $d \in \mathbb{R}^m$.

$$\sum_{i=1}^{n} \left( \| M x_i + d - y_i \|_2 \right)^2$$

The expression below is used for determining the vector $d$ (see [73, 74]).
\[
\bar{y} = \begin{pmatrix} y_1 & y_2 & y_3 \end{pmatrix}^T \quad \text{and} \quad \bar{x} = \begin{pmatrix} x_1 & x_2 & x_3 \end{pmatrix}^T
\]
\[d = \bar{y} - M\bar{x}\]

The orthogonal matrix \(M\) is determined by minimizing the expression below using a substitution of the vector \(d\) from the expression above.

\[
\min \sum_{i=1}^{n} \left( \left\| M(x_i - \bar{x}) - (y_i - \bar{y}) \right\|_2 \right)^2
\]

If two \(m \times n\) matrices are defined as \(A = (x_1 - \bar{x} \cdots x_n - \bar{x})\) and \(B = (y_1 - \bar{y} \cdots y_n - \bar{y})\), then the expression above is minimized if the expression below is maximized (see [74]).

\[
\max \text{Trace}(BA^T M^T)
\]

To solve the problem stated above, SVD of \(BA^T\) is computed, which lead to the expression below,

\[
\text{Trace}(BA^T M^T) = \text{Trace}(U \ast \text{diag}(\sigma_1 \cdots \sigma_m) \ast V^T M^T) = \text{Trace}(\text{diag}(\sigma_1 \cdots \sigma_m) \ast S)
\]
where $\mathbf{B} \mathbf{A}^T \mathbf{M}^T = \mathbf{U}^* \text{diag}(\sigma_1 \cdots \sigma_m)^* \mathbf{V}^T$ and $\mathbf{S} = \mathbf{V}^T \mathbf{M}^T \mathbf{U}$ (see [73]). The expression above is maximized if $\mathbf{S} = \mathbf{I}_m$, giving $\mathbf{M} = \mathbf{U} \mathbf{V}^T$ ($\mathbf{I}_m$ is the identity matrix).

8.4 Errors in landmark coordinates

A movement analysis system always has some internal error tied to its three-dimensional result and may occur for different reasons. According to Nigg, these errors could be divided into four different types [15].

1) Errors due to relative camera placement

Each marker can be visualized as the point where lines connecting a camera and the marker intersect. The error in marker coordinates increases if these lines are close to parallel. The cameras are suggested to be put in a position where adjacent cameras are separated with at least 60 degrees space angle. In addition, increased accuracy is obtained if the cameras are not placed within a plane.

2) Errors due to the number of cameras

In an ideal case, all cameras should “see” every marker present within the measurement volume. Due to practical circumstances this is not the case in a real situation. Markers may be hidden for some of the cameras because they are out of the field of view. The markers may also hide each other (i.e., one marker is placed in front of another marker). This type of error causes a discontinuity in a marker’s trajectory (i.e., as long as it is hidden, a systematic error will be present in its coordinates). This type of error is reduced if the number of cameras is increased.
3) Calibration errors

If the calibration of the system is not performed in an optimal way (e.g., not performed through the whole measurement volume), the accuracy of and precision of the measurement is reduced. In addition, a bad calibration might depend on a lack of correction for lens errors. The accuracy of the measurement varies inside the volume where lens errors are not corrected for (e.g., poorer accuracy far from the cameras’ center of view).

4) Digitization errors

Today’s optical movement analysis systems commonly use video cameras and automatic algorithms for the digitization of the data. The accuracy of these algorithms depends on different factors. The shape and size of the markers affects the accuracy. Relatively large spherical markers give better accuracy. This type of error can be reduced if a proper experimental setup is used.
9 Pattern recognition

The human brain is good at finding similarities in observed data. Similarities can be viewed as putting objects into groups that are similar to each other. This operation of grouping things together is defined as clustering. The clusters may be further subdivided, defined as hierarchical clustering. Clustering is performed because the underlying cluster labels might be meaningful, which could lead to a more efficient description of our data and will help us to choose a better action. Clusters can also aid us when communicating because they allow us to compress data (e.g., describing objects with a few words). Finally, clustering algorithms might serve as models of learning processes in neural systems. The classification methods used in this dissertation are neural networks and partial least squares regression (cf. Aims of the dissertation).

A typical pattern recognition system can be divided into five steps [75], as illustrated in Figure 6. (1) The input is first collected with some kind of sensor (e.g., CCD image sensor). (2) A part of this image is then extracted/segmented (marker coordinates attached to the body of interest). (3) Features are extracted from the collected coordinates (e.g., movement range, segment velocity). (4) The feature is put into a certain category by using a classification algorithm (e.g., using linear discriminant analysis or neural networks). (5) Finally, a post-processing of the classifiers result is performed. This is best viewed as an additional cost that is associated with the result from the classifier (i.e., it applies a cost function to the result which ensures a certain specificity or sensitivity of the system). For example, if the classification system is supposed to classify features from a patient with an expected deadly disease, it is important to have a high specificity of the
result (i.e., you do not want to worry the patient if you are not completely sure of the diagnosis) [75].

![Diagram](image)

**Figure 6.** There are five steps in a pattern recognition system.

### 9.1 Neural networks

Neural networks belong to a group of classifiers that are inspired by biological nervous systems (e.g., the function of the brain). They are composed of simple elements, called neurons, operating in parallel. The function of the network is determined by the connections between the neurons. The neural network is trained to perform a specific task by adjusting the internal values of the connections (i.e., weights) between the neurons. Neural networks have been trained to perform complex functions in various fields such as pattern recognition, identification and classification.

An example of a two-layer backpropagation neural network (BPNN) is illustrated in Figure 7. The network consists of an N-dimensional input layer (with k neurons) connected to a two-dimensional output layer (with 2 neurons). Both layers use a tangent-sigmoid transfer function.
Figure 7. This diagram illustrates a typical, two-layer BPNN with N input (features) and two outputs (specifically trained for a certain category).

A particular input leads to a specific target output when the network is properly trained. Based on a comparison between the output and the target, the network is adjusted until the network output matches the target value. Many pairs of input and output are needed to train the network to get a general behavior for the network.

During batch mode, weights and biases (an extra input presented to the network) are changed when the entire set of input vectors are presented to the network. In incremental training (also called adaptive or on-line training) the weights are changed after each individual input vector has been presented to the neural network. Neural networks can be trained to solve complex problems that otherwise would be difficult to solve for conventional computers or humans.
The training of neural networks can roughly be divided into two classes: (1) In supervised neural networks (the most common method of training) data are given in the form of inputs and targets. The targets are the teacher’s specifications of what the neural network’s response to the input should be. (2) In unsupervised neural networks (see below), data are given in an undivided form, simply as a set of examples. Some learning algorithms are intended for memory applications, where the input data can be recalled in the future. Other algorithms are intended to generalize the network’s behavior for discovering patterns or underlying features in the dataset.

### 9.1.1 Self Organizing Maps algorithm and architecture

Self-Organizing Maps (SOM) can be visualized as neural networks with nodes that become specifically tuned to different input signal patterns in an orderly way. SOM networks use a learning process that is competitive and unsupervised when the input signal patterns are mapped to special output nodes. Only one node at a time is activated for each input pattern [76].

In Paper I, the SOM network analyzes multi-neuronal recordings with superimposed neural spikes [52]. The SOM network divides the neural spikes into different classes depending on their waveform. Neural spike sorting has previously been made with linear methods such as principal component analysis (PCA) [77]. The SOM network uses non-linear mapping instead of linear mapping of clusters. SOM networks can therefore follow non-linearities in a multi-dimensional space. The architecture of the SOM network used in Paper I is illustrated in Figure 8.
Figure 8. Illustration of the SOM network used in Paper I [52]. Twenty samples from a centered neural spike were fed into the input layer. The number of elements in the Kohonen layer was set to the number of different neural spikes to be classified in the recording. Reprinted with permission from Elsevier press. Copyright © 1996 Elsevier.

Centered neural spikes, described as vectors of samples, are fed into the input layer of the SOM network and classified according to similarity. Groups of neural spikes with similar properties are mapped to nodes in the Kohonen layer which are close to each other. The input layer of the SOM network is connected to the Kohonen layer by weight vectors. The weight vectors are allowed to vary during the training period of the SOM network. This is done to get an optimal categorization of the neural spikes. To determine which of these weight vectors that is to be changed during the training cycle, the Euclidean distance $D_i$ between the input vector $X$ (i.e., samples of a neural spike) and each weight vector $W_i$ is calculated ($i=1...N$, where $N$ is the number of nodes in the Kohonen layer), see equation below.

$$D_i = \sqrt{(x_1 - w_{i1})^2 + (x_2 - w_{i2})^2 + \cdots + (x_M - w_{iM})^2}$$
M equals the number of nodes in the input layer, see equation above. The weight vector with the smallest Euclidean distance is adjusted so that the distance to the input vector will be even closer. This adjustment of the weight vectors is decreased (as the number of iterations increases) to get a convergence of the SOM network. The adjustments of the weight vectors are calculated according to the expression below.

\[
W_{ij,\text{new}} = W_{ij,\text{old}} + \alpha (X_j - W_{ij,\text{old}})
\]

In this expression, \(W_{ij,\text{new}}\) is the new weight vector, \(W_{ij,\text{old}}\) is the old weight vector, \(X_j\) is the j:th neural input vector and \(\alpha\) is the momentary learning coefficient.

As a result, the SOM network projected the M dimensions describing a neural spike to one dimension (i.e., class belonging) with topological correct mapping.

### 9.1.2 Backpropagation algorithm and architecture

The Backpropagation algorithm was first created as a generalization of the Widrow-Hoff learning rule to multiple-layer networks [78]. The input vectors are associated with target vectors and are used for training the network. The network is trained until it can estimate a specific output vector (defined by the user) from an input vector. If the architecture of the network includes biases, sigmoid hidden layer and a linear output layer, any function with a finite number of discontinuities can be estimated with the network.
The inputs to each neuron in the network define an N-dimensional space. The neuron draws a hyperplane within that space, and that produces an “on” output at one side of the plane and an “off” output at the other. The hyperplane is fuzzy (i.e., a grey area of intermediate values near the separating plane) if a sigmoid transfer function is used in the neuron. The weights determine where this hyperplane is located in the input space. Without a bias input, this separating plane is constrained to pass through the origin of the hyperspace defined by the inputs. The hyperplane would be more useful if it could be located anywhere within the input space. If many neurons are present in a network layer, they all share the same input space, and without bias they would all be constrained to construct their hyperplanes to pass through the origin.

The transfer functions are needed to introduce nonlinearity into the network. Without nonlinearity, hidden neurons would not make networks more powerful than plain perceptron networks (i.e., a single neuron with an input and output neuron). The most common choice is a sigmoid or a Gaussian transfer function.

The Widrow-Hoff learning rule is the standard backpropagation method, where a gradient descent algorithm is used. The weights in the network are moved along the negative gradient of the performance function. The term backpropagation refers to the computation of the gradient of a neural network. By definition, neural networks are general in their behavior, but if the network is overtrained it loses this property. Regularization and early stopping are two methods designed to improve the network generalization and prevent overtraining (implemented in MATLAB’s neural network toolbox). This behavior is illustrated in Figure 9, where the error in the test set is
increased at the same time as the error for the training set is decreased.

Figure 9. This diagram shows the behavior of an overtrained neural network. For every unit of time (epoch) on the X-axis, the error decreases for the training set, but at a certain stage, the error in the test set increases.

**Regularization**

The performance function on the training set is modified by adding a term that consists of the mean of the sum of the squares of the network weights and biases; this leads to better generalization of the network. This performance function causes the network to have smaller weights and biases. In addition, the network response is forced to be smoother and therefore less likely to overfit.
Early stopping

The available data are divided into three subsets. The first subset is used as a training set (i.e., used for computing the gradient and updating the network’s weights and biases). The second subset is the validation set. The error on the validation set is monitored during training of the network. As long as the validation error decreases the training of the network continues. When the validation error has increased for a specified number of iterations, the training is stopped. The weights and biases of the network at the minimum of the validation error are then returned as a solution. The test set error is not used during the training. Instead, it is used for comparison of different network models. It might be useful to monitor the test set error during the training. A poor division of the data set is indicated if the test set error reaches a minimum at a different iteration number than the validation set error.

9.2 Partial least squares regression

Partial least squares regression (PLS) is an extension of the multiple linear regression model, where a linear model describes the linear relationship between a dependent variable/s $Y$, and a set of predictor variables $x_i$.

\[
Y = \begin{bmatrix} b_0 & b_1 & \ldots & b_p \end{bmatrix} \begin{bmatrix} x_1 & \ldots & x_p \end{bmatrix}^T + E = b^* X^T + E
\]

In this equation, $b_0$ is the regression coefficient for the intercept and $b_i$ are the regression coefficients (for variables 1 through $p$) estimated from the data. These coefficients are estimated from the collected data. If the
predictor variables are independent this model might be sufficient to describe the linear relationships between the predictor variables when making predictions for new observations. When there are dependencies between the predictor variables this model is not sufficient. The same deficit is valid if multiple dependent variables $Y$ are required and an inherent dependency exists among the dependent variables. Inherent dependencies within $X$ and $Y$ must be removed before calculating multiple linear regression. The multiple linear regression also performs better if variables with less significance can be removed before estimating the model.

These improvements can be achieved if PLS is used instead of multiple linear regression. In short, the PLS model tries to find a multidimensional direction in $X$-space that explains the maximum multidimensional variance direction in $Y$-space. The dependence within $X$ and $Y$ is removed by pre-processing the data using PCA. PCA is a linear method that reduces the dimensionality of a dataset by transforming the data into a new set of uncorrelated variables (e.g., $(x_1, x_2) \rightarrow (x'_1, x'_2)$). Commonly, the variables in $X$ and $Y$ are centered at their respective means and scaled by dividing by their standard deviations; that gives an equal importance to all variables. PLS performs better if principal components with low variance are removed prior to the multiple regression. A simple example is shown in Figure 10, where $Y \in \mathbb{R}^2$ and $X \in \mathbb{R}^2$. 
Figure 10. These X-Y plots illustrate the relationship between the predictor variable $X \in \mathbb{R}^2$ and the dependent variable $Y \in \mathbb{R}^2$ when using PLS. In this example, the variance is lower in the second compared to the first principal component for $X$ and $Y$ respectively, and is therefore removed.
10 Aims of the dissertation

The general aim of this dissertation was the development and evaluation of new biomedical multivariate classification methods, such as:

...a real-time method for sorting spikes in a multi-unit recording, which can be used in neurophysiological studies. A new reliable sorting method is important since the number of simultaneously recorded afferents must be maximized when studying the encoding ability of a population of afferents. Such research on encoding of sensory information are important for studying e.g., how the quality of proprioceptive information is affected during muscle fatigue and pain.

...an objective method, to be used by health care professionals, for grading the neck functions in patients with neck pain. The grading of neck function is important in the evaluation of patients and to assess the effects of rehabilitation in these patients.
The specific aim of each separate paper in this dissertation was to:

...develop a real-time, multi-channel, spike sorting tool, which can lead to reduced preparation time and maximized number of simultaneously recorded afferents (Paper I) [52].

...to evaluate different theories of the encoding of proprioceptive afferent information by studying how mixed ensembles of mechanoreceptive muscle afferents separate simple mechanical stimuli. The mixed ensemble consisted of a mixture of primary and secondary muscle spindle afferents and Golgi tendon organ afferents. The ability of this mixed ensemble was also compared to ensembles consisting only of primary muscle spindle afferents (Paper II) [53].

...develop an objective multivariate assessment tool that extracts neck motion characteristics during natural neck movements. Special focus was on patients with whiplash associated disorders (Paper III) [26].

...evaluate if a resilient back propagation neural network trained with neck movement variables (collected in Paper III) could form a basis for a clinical support system when studying patients with whiplash associated disorders (Paper IV) [70].

...investigate how a rigid body’s orientation is affected by a systematic error added to a single marker (Paper V) [71], using the collected data from paper III as input.
11 General conclusions

The general conclusions from this dissertation were:

...the developed spike sorting method, using an unsupervised neural network, was suitable for sorting a multiunit recording into single units when performing neurophysiological experiments.

...animal experiments showed that mixed ensembles of different types of afferents discriminated better between different muscle stimuli than ensembles of single types of these afferents. It was hypothesized that the main reason for the greater discriminative ability might be the variation in sensitivity tuning among the individual afferents of the mixed ensemble will be larger than that for ensembles of only one type of afferent.

...the neck movement is well described using a helical angle approach.

...neck movement analysis combined with a neural network could build the basis of a decision support system for classifying suspected WAD or other pain related neck-disorders.

... A systematic error along the radial axis of the rigid body added to a single marker had no affect on the estimated rotation of the head.
12 Review of papers

12.1 Materials and methods

12.1.1 Animals and preparation

In Papers I and II, data were collected in acute experiments on cats anaesthetised with $\alpha$-chloralose (70 mg/kg). Conventional nerve-muscle preparations were made in the lateral gastrocnemius, plantaris and soleus muscle (GS) in the left hind limb. The posterior arch was removed between the L3 and S1 level of the spine (i.e., laminectomy).

The cat was attached to a metal frame and the edges of the skin (i.e., around the exposed spinal cord) were sewn up to form a pool. The pool was filled with warm paraffin oil. A small bundle from the L7 dorsal nerve root was dissected free and cut as rostrally as possible. The nerve root was put on a plate and thin filaments were dissected under a microscope and placed on a multi-channel hook electrode [58].

12.1.2 Human subjects

In Papers III and IV, two different groups of subjects were included. One group consisted of 56 controls, 29 males and 27 females (mean age 37.3 ± SD 10.9 years). The other group consisted of 59 subjects with WAD, 29 males and 30 females (mean age 38.1 ± SD 10.6 years). The control group was mainly recruited through local advertisements. All subjects in the WAD group had received their diagnoses by a physician experienced in managing WAD patients. The diagnosis was made in agreement with the definition by the Quebec Task Force [11]. Chronic symptoms lasting longer than three months and different grades of WAD where seen in all patients with WAD.
Seven subjects were excluded because of unstable or ill positioned reflex markers during measurement or inability to perform movements because of pain. In total, 52 controls and 56 WAD subjects were used for further analysis.

12.1.3 Data collection and sampling of neural spikes

In Papers I and II, the activity of GS muscle receptor afferents was recorded simultaneously. The muscle was mechanically stimulated (stretched) with a puller connected to the distal tendon of the muscle. The stimulus was a sinusoidal stretch at 1 Hz with different amplitudes (amplitude from -15 mm to a plateau at -5 mm; plateau duration 2 s) superimposed on a static ramp-and-hold stretch (amplitudes between -15 mm and -5 mm; time duration 2 s). The maximal physiological length of the muscle was set to zero mm. The stimulus was repeated four to five times with a 30 s pause between each repetition. The muscle was fully relaxed during the pause.

Twitch tests were performed to separate muscle spindle afferents (MSAs) from Golgi tendon organ (GTO) afferents before the data collection started. Twitch tests, which consisted of a maximal muscle contraction, evoked by an electrical stimulation of the peripheral nerve, were performed when the muscle was stretched to 1 mm below maximal physiological length. Afferents responding to increasing- and/or peak muscle force during twitch were classified as GTO afferents [79]. The MSAs were further classified as either primary or secondary afferents based on, e.g., their conduction velocity using a cut off at a conduction velocity of 72 m/s [80].
Nerve filaments with two or more superimposed spike trains were chosen and recorded to test the spike sorting software. The signals containing the spike trains were collected using custom made data acquisition equipment located in a special electromagnetically shielded room. The signals were first amplified using a low noise differential amplifier close to the hook-electrode. In a second stage the signal was amplified again and low-pass filtered at 20 kHz. The signal was then sampled at 40 kHz using a data acquisition card. The amplification was adjusted for each channel to make use of the A/D converter’s maximum dynamic range.

A custom made software on the data acquisition card considered spikes with amplitude over a specified voltage threshold to be a valid spike. These valid spikes were further digitized into 20 sample points.

Self Organizing Map (SOM) – networks, implemented on a PC, were used for training and sorting of detected spikes. A superimposed spike train, collected on a single input channel on the data acquisition card was considered a unit. Detected spikes on each recorded channel were first used during training of an SOM network and later during real-time spike sorting. Finally, each detected and sorted spike was stored on a computer. The data acquisition equipment is illustrated in the Figure 11.
Figure 11. Experimental setup and offline computations made in Papers I and II.
12.1.4 Quantification of neural response

The instantaneous firing rate was determined by computing the inverse of the time interval between two adjacent action potentials for each of the identified MSAs and GTOs. These instantaneous firing rate patterns were organized according to the table in Figure 11. One object in the data matrix included the response pattern of all identified MSAs and GTOs for a single stimulus and repetition. The matrix was then subjected to a PCA. The first three principal components were computed in Paper II to reduce the dimension of the data matrix. A custom made algorithm, see expression below, was used to calculate the neural separation between different stimuli. The mean of each object group, \( \bar{x}_i, i \in (1,2); \) (i.e., mean of all repetitions belonging to a specific stimulus), and the standard deviation; \( \sigma_i, i \in (1,2), \) were calculated for each object group.

\[
Separation_{2,1} = \frac{|\bar{x}_2 - \bar{x}_1|}{1.65 \times (\sigma_2 + \sigma_1)}
\]

This separation measure was computed for every principal component and every pair of object groups. The mean separation for each principal component was then calculated and a total separation measure was computed according to the expression below.

\[
TotalSep = \sqrt{\text{mean}(SepPC1)^2 + \text{mean}(SepPC2)^2 + \text{mean}(SepPC3)^2}
\]
This measure was computed for different types and sizes of afferent populations to analyze the muscle afferent populations’ ability to distinguish between different types of stimuli.

12.1.5 Movement patterns

In Papers III and IV, each subject was instructed to perform simple head movements (i.e., flexion-extension and axial rotation). Prior to this movement and after a short practice, the subjects were told to sit a few seconds in an upright natural position during which a reference position was measured. Each subject had to repeat every head movement in a random order during the measurement. In total, 16 head movements were performed by each subject.

The head movement was initiated immediately after an arrow on a board in front of the test subject was illuminated. The movement should be performed to a comfortable extent and as fast as possible according to the pre-recorded verbal instructions given to each test subject. The instructions were pre-recorded to give all subjects the same instructions.

12.1.6 Data acquisition of movement patterns

A movement analysis system (based on cinephotogrammetry) was used in Papers III and IV for collecting movement patterns. The system contains reflective markers, acquisition software and CCD-cameras emitting and detecting infrared light from the markers. A fixed frame (with three markers) was attached to the subject’s head and an ortho-plastic vest (with three markers) was fixed to the torso. Reflected light from the attached markers was collected by four cameras. Each camera estimated two-dimensional
coordinates of markers seen in the camera’s own field-of-view.

Three-dimensional coordinate data was computed by an acquisition software using the two-dimensional data from each camera as input. The computations were based on the photogrammetric methods of Yuan [81] and Zhang and Faugeras [82]. The same software also tried to interpolate trajectories where markers were temporally lost. Three-dimensional data were finally exported to enable further offline calculations of head rotation variables.

12.1.7 Data analysis and pre-processing

The angular rotation of the head was calculated, using the method by Söderkvist and Wedin [73], in Papers III to V. This method has modified the method described by Spoor and Veldpaus [83] and requires coordinates from at least three markers attached to a single body segment. In addition, the three markers are not allowed to be distributed along a straight line. Otherwise, the location and orientation of the rigid body (defined by the markers) is not completely defined.

The vectors $\mathbf{a}_1, \mathbf{a}_2, \ldots, \mathbf{a}_n$ and $\mathbf{b}_1, \mathbf{b}_2, \ldots, \mathbf{b}_n$ contains the marker positions of a rigid body, attached to a body segment, before and after a movement. It is possible to calculate the orthonormal rotation matrix $\mathbf{R} \in \mathbb{R}^{3 \times 3}$ and the displacement vector $\mathbf{v} \in \mathbb{R}^3$ by solving the expression below.

$$\theta = \sum_{i=1}^{n} | \mathbf{b}_i - \mathbf{R} \mathbf{a}_i - \mathbf{v} |, \quad n = \text{number of markers}$$
The exact marker positions \( (\mathbf{b}_i) \) differ from measured marker positions \( (\mathbf{p}_i) \) and the relative positions within the rigid body may vary slightly during the body movements. Therefore, the problem cannot be solved exactly. The expression may instead be minimized using different methods. In Papers III to V, SVD was used for determining which \( \mathbf{R} \) and \( \mathbf{v} \) that minimized the problem below [73].

\[
\min_{\mathbf{R}, \mathbf{v}} \sum_{i=1}^{n} \left( \| \mathbf{p}_i - \mathbf{R} \mathbf{a}_i - \mathbf{v} \| \right)^2, \ n = \text{number of markers}
\]

By solving this problem twice (i.e., both for the head and torso), it was possible to extract pure head movements from the mixed head and shoulder movement. At each time sample, the rotation of the head \( (\Theta(t)) \) was adjusted for shoulder movements, using the reference shoulder positions \( \mathbf{r}_1 - \mathbf{r}_3 \) measured during the initial reference position. The angle \( \Theta \) was zero at the time when illuminating the arrow in front of the subject.

Head angular velocity was computed by calculating the time derivative of smoothed (using a cubic smoothing spline algorithm) head rotation angle.

For each head movement a number of variables (e.g., neck range, angular velocity, and reaction time) were computed as described in Table 3. The type of head movement (i.e., flexion, extension and axial rotation) was used for classification purpose of the computed variables. Finally, the mean value for each variable was computed.
<table>
<thead>
<tr>
<th>Variable name</th>
<th>Unit</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>[s]</td>
<td>Reaction time was defined as the time interval that started when the subject saw the arrow and ended when the angular velocity was greater than π/60 rad/s (obtained by studying the background noise).</td>
</tr>
<tr>
<td>Θ</td>
<td>[rad]</td>
<td>Range of motion was defined as the maximum angular range.</td>
</tr>
<tr>
<td>V_{mean}</td>
<td>[rad/s]</td>
<td>Mean angular velocity. Defined as maximum range divided by time at maximum range.</td>
</tr>
<tr>
<td>V_{max}</td>
<td>[rad/s]</td>
<td>Maximum angular velocity in the interval [start position, position for maximum range]</td>
</tr>
<tr>
<td>D</td>
<td>[rad]</td>
<td>Displacement from starting-point after performed movement</td>
</tr>
<tr>
<td>S_{Θ,RL}</td>
<td></td>
<td>Symmetry movement range (right-left)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[ \frac{Θ_R}{</td>
</tr>
<tr>
<td>S_{Θ,FE}</td>
<td></td>
<td>Symmetry movement range (flexion-extension)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[ \frac{Θ_F}{</td>
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<tr>
<td>S_{V,RL}</td>
<td></td>
<td>Symmetry angular velocity (right-left)</td>
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<td>S_{V,FE}</td>
<td></td>
<td>Symmetry angular velocity (flexion-extension)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[ \frac{V_F}{</td>
</tr>
</tbody>
</table>
A vector which included 20 mean values, from the computed variables, described each subject in the control and WAD groups. All these vectors resulted in a data matrix, which was scaled and normalized to zero mean and unit standard deviation. PCA was then used for data reduction. Principal components contributing to less than one percent of the total variance were considered as noise and were eliminated. The remaining principal components were used as input to a BPNN as seen in Figure 12.

![Figure 12. Schematic illustration of the BPNN that were used in Paper IV [70]. Reprinted with permission from IEEE press. Copyright © 2003 IEEE.](image)

During training of the BPNN, a resilient back propagation (BP) algorithm was used, since it is a fast algorithm and appropriate when using sigmoid transfer functions [84]. To generalize the BPNN behavior and prevent overtraining, an early stopping algorithm was used [85]. The dataset was divided into a training set, validation set and test set. The test set included one
subject which was used as input to the BPNN after finishing the training. This was performed to test the prognostic capacity of the BPNN. The leave-one-out method was used to test the overall BPNN behavior (i.e., the test subject was circulated through the whole data set) [86]. The leave-one-out method is a special form of cross-validation. Training and validation sets were constructed from the remaining 107 vectors.

12.1.8 Performance of the chosen BPNN

The performance was measured by following the definitions by Hudson and Cohen [87]. In the equations below, C stands for control, WAD for patient, subscript corr for correct prediction and subscript tot is the total number of subjects in the group.

\[
\text{Predictivity} = \frac{C_{\text{corr}} + WAD_{\text{corr}}}{C_{\text{tot}} + WAD_{\text{tot}}}
\]

\[
\text{Sensitivity} = \frac{WAD_{\text{corr}}}{WAD_{\text{tot}}}
\]

\[
\text{Specificity} = \frac{C_{\text{corr}}}{C_{\text{tot}}}
\]

The general BPNN performance was determined by calculating the specificity, sensitivity and predictivity for 100 different initial conditions of a selected BPNN.
12.1.9 Systematic and random errors

The precision of the motion analysis system was estimated by computing the length of a calibrated wand. The wand had one reflective marker on each side, and the positions of these markers were sampled at 60 Hz during a calibration period of 10 seconds. Similar methods for estimating the precision is described in [88, 89]. The three-dimensional Euclidean distance between the markers defined the length of the wand. The precision was defined as the standard deviation of these Euclidean distances.

The analysis gets more complicated when studying systematic errors added to single markers. The vectors \( \mathbf{x}_i \in \mathbb{R}^m \) and \( \mathbf{y}_i \in \mathbb{R}^m \) (m=3 in a three-dimensional space) define the coordinates of markers attached to a rigid body at different positions and orientation in space. The classical Procrustes problem tries to find a solution that minimizes the expression below, where \( \mathbf{M} \in \mathbb{R}^{mxm} \) is an orthonormal matrix and \( \mathbf{d} \in \mathbb{R}^m \) is a vector (cf. the results in Singular value decomposition).

Therefore, if the systematic error added to a single marker only affects \( \text{diag}(\sigma_1 \cdots \sigma_m) \), then the estimated rotation matrix \( \mathbf{M} \) is unaffected by the systematic error (cf. the results in Singular value decomposition).

Assume that a two-dimensional rigid body is attached to a body segment and is defined by a matrix \( \mathbf{A} \). This rigid body is rotated \( \pi/2 \) rad by applying a rotation matrix \( \mathbf{M} \), as described in the expressions below.
The rotated rigid body $B$ is then described by the expression below.

\[
\begin{bmatrix}
1 & -1 & 0 & 0 \\
0 & 0 & 1 & -1
\end{bmatrix}
\]

Assume that the first column (i.e., marker 1) is displaced along the radial vector and that $B$ is centered in its new center of mass. The displacement is performed by multiplying the first column in $A$ by $k \geq 0$. This gives the expressions below.

\[
\begin{bmatrix}
k & -1 & 0 & 0 \\
0 & 0 & 1 & -1
\end{bmatrix}
\]

\[
\begin{bmatrix}
(3k+1)/4 & (-3-k)/4 & (1-k)/4 & (1-k)/4 \\
0 & 0 & 1 & -1
\end{bmatrix}
\]
The SVD of $\mathbf{BA}^T$ (see expression below) is computed to see the displacement’s effect on the estimated rotation matrix $\mathbf{M}$.

$$\mathbf{C} = \mathbf{BA}^T = \begin{bmatrix} 0 & -k - 1 \\ 2 & 0 \end{bmatrix}$$

In the expressions below are the eigenvalues and eigenvectors of $\mathbf{C}^T\mathbf{C}$ and $\mathbf{C}\mathbf{C}^T$ derived. The result shows that the error only affects the eigenvalues and leaves the eigenvectors unaffected (i.e., the constant $k$ is only present in the expression describing the eigenvalues).

$$\text{Eigval}(\mathbf{C}^T\mathbf{C}) = \text{Eigval}(\mathbf{C}\mathbf{C}^T) = \begin{bmatrix} 4 \\ k^2 + 2k + 1 \end{bmatrix}$$

$$\text{Eigvect}(\mathbf{C}^T\mathbf{C}) = \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix} \text{ and } \text{Eigvect}(\mathbf{C}\mathbf{C}^T) = \begin{bmatrix} 0 \\ 1 \\ 1 \end{bmatrix}$$
12.2 General results

12.2.1 Papers I and II

A tool for real-time spike sorting was developed and evaluated in Paper I. The tool reduced the preparation time and maximized the number of simultaneously recorded afferents during an experiment. An example of a simultaneous recording from 6 dorsal root filaments with multi afferent activity and the output from the real time spike sorting software is seen in Figure 13. It is worth noting that a simple level discriminator would have failed to sort the different afferents present in the recording shown in the bottom row. On the other hand, if there were significant changes of the signal-to-noise ratio or if the waveform of the action potential changed during a measurement the SOM network had to be updated. Another problem with the SOM classifier was that all detected neural spikes in a single recording are forced to one of the categories determined during the training phase of the classifier. Thus, if new afferents start to fire during a measurement, one or more of the sorted spike trains will be contaminated. Also, if two or more neural spikes are superimposed, then that superimposed spike is forced in to one of the existing categories of spikes. An example of superimposed spikes is indicated with arrows in Figure 13. Errors associated with reasonably low rates of superimposed spikes can however be corrected by manual post processing. The correction was made by looking at the instantaneous firing rate of each unit. The robustness of the SOM classifier was evaluated by testing the error classification rate when adding band limited white noise (with different noise levels) to simulated neural spikes. The results were compared with the results from an ordinary level detector. The results show that the SOM classifier performed better in all test cases.
Figure 13. The left column illustrates the collected original data including six multiunit recordings. The right column illustrates the performance of the real-time spike sorting tool developed in Paper I [52]. Reprinted with permission from Elsevier press. Copyright © 1996 Elsevier.
The ability of ensembles of mixed muscle afferents to separate simple mechanical stimuli was studied in Paper II to investigate the effect of the muscle afferents’ sensitivity tuning on stimuli separation (cf. Quantification of neural response) during simple mechanical stimuli of the muscle. A mixture of primary and secondary MSA and GTO afferents was included in the study. The mixed ensemble of afferents was compared to ensembles that included only primary MSA. The results showed that mixed ensembles of afferents had greater separating ability than populations including only primary MSA at all population sizes. Figure 14 shows an example of the computed average of the stimulus separation for a population of 11 primary MSA (filled columns) and a mixed population of 16 afferents (open columns) recorded in the same preparation. The separation was computed for five different mechanical stimuli (i.e., 1 Hz sinusoidal stretches; peak-to-peak amplitude; 3.0, 3.5, 4.0, 4.5 and 5.0 mm). At the top of each column is the standard deviation indicated. The standard deviation for each population size was calculated by using all possible permutations of afferents drawn from the total population. The results also show that the separating ability increased when the population size was increasing (this is significant for all types of afferent populations). Both these findings lend support to the population coding theory in the case of encoding of mechanical muscle stimuli.
12.2.2 Papers III and IV

An objective multivariate assessment tool was developed that extracted neck motion characteristics during natural neck movements. The developed tool was also suggested to form a basis for a clinical support system.

Examples of signals that were calculated by the assessment tool are shown in Figure 15. In the figure, the helical angle ($A; \Theta(t)$) and the angle velocity ($B; \frac{d\Theta}{dt}$) are plotted for a typical control and WAD subject. The WAD subject had a slower reaction time, a limited range of motion in at least one direction and a slower overall movement.
A vector that contained the mean of the selected movement variables in Table 3 was computed for each subject using $\Theta(t)$ and $d\Theta/dt$. In total, 108 vectors were computed. Principal components that contributed to less than one percent to the total variance of the dataset were considered as noise and were eliminated (cf. Data analysis and pre-processing). This reduced the number of input variables to the BPNN from 20 variables (see Table 3) to 10 principal components. The 10 principal components explained 97% of the total variance in the dataset (the score plot of the first two principal components is shown in Figure 16). The component loading plot showed that the variables describing velocity and range in different directions were inter-correlated and described most of the total variance in the dataset. Several BPNNs with one hidden layer were trained, tested and validated using the pre-processed vectors as input (cf. Data analysis and pre-processing).
Figure 16. Illustrates a score plot of the first two principal components of the matrix containing movement variables [26]. Reprinted with permission from IEEE press. Copyright © 2003 IEEE.

BPNNs with one hidden layer (the number of hidden nodes (H) varied from 2 to 50) were examined to test the overall performance. The errors of the network were large for H=2 and tended to have a minimum for H=5. The errors of the network tended to increase for large BPNNs (H>15) even though early stopping was used. This indicated that H should be between 3 and 7 to give a stable network with low error levels. Therefore, BPNN with H=6 was chosen and further evaluated.

Various initial conditions (i.e., 100) of the chosen BPNN were used to calculate the predictivity, sensitivity and specificity of the network according to the definitions by Hudson and Cohen [87] (cf. Performance of the chosen BPNN). Results show that the predictive ability of the BPNN was approximately 90%, see Figure 17. The small standard deviations (2-3%) also showed that the chosen BPNN was stable (i.e., the network performance was independent of the initial condition).
Figure 17. Illustrates the performance of the chosen BPNN with $H=6$ and 100 different initial conditions. Specificity was $0.88 \pm 0.02$, sensitivity was $0.90 \pm 0.03$ and predictivity was $0.89 \pm 0.02$ [70]. Reprinted with permission from IEEE press. Copyright © 2003 IEEE.

12.2.3 Paper V
The effect of adding a systematic error to a single marker on a rigid body’s orientation was performed in this paper. The evaluation was performed as a theoretical derivation of the error’s effect and used computer simulations. The simulations were performed both with and without white noise added to all markers on the rigid body. Results from the computer simulation are seen in Figures 18 and 19.
Estimation of precision

The precision of the measurement system was estimated, during a calibration measurement, by using a fixed-length calibration wand. A standard deviation (i.e., precision of the measurement system) of 0.8 mm was derived. This value was then used as input to the computer simulation when studying the combination of systematic error added to a single marker and superimposed Gaussian white noise.

Simulation of anisotropic systematic error

Computer simulations, showing the estimated helical angle when rotating $\pi/2$ rad are shown in Figure 18 using four (left) and eight (right) markers attached to a rigid body. This rotation was done around a random helical axis. A random linear displacement was also added prior to estimating the helical angle. It is worth noting that different rotations gave similar results. The deviation from the true helical angle was zero when systematic errors were added along the marker’s own radial axis. This is shown in the plots of the upper two rows in Figure 18. The systematic error was never added along the radial axis in plots of the bottom row. As seen in Figure 18, the error also decreased when the number of markers was increased.
Figure 18. Illustration of the deviation from the true simulated rotation (π/2 rad). Left column describes a rigid body defined by four markers and right column describes a rigid body defined by eight markers. No noise was added. The rotation was performed around a random helical axis. A random displacement was also added before calculating the helical angle. Deviations when simulating systematic errors in the plane were defined by: (Upper) \( \Theta = \pi/2 \text{ rad}, \Phi = 0, \ldots, \pi \text{ rad} \) and \( R = 0, \ldots, 0.02 \). (Middle) \( \Phi = 0 \text{ rad}, \Theta = -\pi/2, \ldots, \pi/2 \text{ rad} \) and \( R = 0, \ldots, 0.02 \). (Lower) \( \Phi = \pi/2 \text{ rad}, \Theta = -\pi/2, \ldots, \pi/2 \text{ rad} \) and \( R = 0, \ldots, 0.02 \) \([71]\). Reprinted with permission from Taylor & Francis press. Copyright © 2008 Taylor & Francis.
Simulation of combined errors

The same procedure as in the previous simulation (in which no noise was added) was repeated, but with added Gaussian white noise to all markers attached to the rigid body. Results from simulations with four (left) and eight (right) markers are shown in Figure 19. As before, the deviation from the true helical angle was zero when systematic error was added along the marker’s own radial axis (see plots in the upper two rows). In plots in the bottom row the systematic error was never added along the radial vector. As before, the error also decreased when the number of markers was increased.
Figure 19. Illustrates the deviation from the true simulated rotation ($\pi/2$ rad). Left column describes a rigid body defined by four markers and right column describes a rigid body defined by eight markers. Noise with a standard deviation of 0.001 was added to all markers in the rigid body. The rotation is performed around a random helical axis. A random displacement is also added before calculating the helical angle. Deviations when simulating errors in the plane were defined by: (Upper) $\Theta$=0 rad, $\Phi$=\pi,\ldots,\pi rad and R=0,\ldots,0.02. (Middle) $\Phi$=0 rad, $\Theta$=\pi/2,\ldots, \pi/2 rad and R=0,\ldots,0.02. (Lower) $\Phi$=\pi/2 rad, $\Theta$=\pi/2,\ldots, \pi/2 rad and R=0,\ldots,0.02 [71]. Reprinted with permission from Taylor & Francis press. Copyright © 2008 Taylor & Francis.
12.3 General discussion and conclusions

In Paper I a software-based tool for real-time spike sorting was described. The tool can be used for simultaneous classification of single spikes (i.e., action potentials) in a multi-neuron recording. The SOM network’s benefit is the non-linear unsupervised learning algorithm, since no other guidance except the number of present afferents in the recording is needed. The SOM network itself classified neural spikes according to the number of different MSAs that were present in the recording, without intervention from the user during the learning phase. As a result, the preparation time decreased and the number of simultaneously recorded afferents increased. This is important and of obvious ethical reasons when performing acute animal experiments since the relative time spent on data collection is valuable. When results from a simple level discriminator were compared to results from a SOM classifier (i.e., sorting spikes with different signal-to-noise ratio) it was shown that the performance of the SOM classifier was better (i.e., true classification of spikes). The time spent on manual correction of misclassified spikes reduces if the performance of the classifier is increasing. In contrast, if there were significant changes of the signal-to-noise ratio or if the waveform of the action potential changed during a measurement, the SOM network had to be updated. This did not happen to often during an experiment and therefore had a minor affect. The same effect was seen if new spikes in a single recording started to fire. But since this event happened sporadically it had a minor affect on the experiment. More common was the presence of superimposed neural spikes in a single recording (cf. units indicated with arrows in Figure 13). In this case was the spikes forced into an existing class of spikes. This had some
implications to the experiment since these misclassifications of spikes had to be manually corrected offline by observing the instantaneous firing rate of each unit. If the firing rate was above a certain threshold, one or more spikes were deleted from the recording.

Since Paper I was published, many new methods for sorting spikes in multiunit recordings have been developed. Many of these methods are described in a review in 1998 by Lewicki [60]. Conclusions drawn in this review was that the design of multiple electrodes is important in the future to maximize the number of simultaneously recorded units. Also, sorting algorithms which incorporate both spike shape and spike timing information seems promising in the future. In 2004, Brown et al. stated that multiple electrodes are now a standard tool used in the field of neuroscience, which is in agreement with the prognosis made by Lewicki [90]. Brown et al. also concludes that there is no consensus on which spike sorting method that is best. Recent papers on spike sorting include methods based on wavelet packets [91], Bayesian frameworks [92, 93], Hidden Markov Models [94] or independent component analysis in combination with SOM [64]. Hulata et al. states that the performance of a spike sorting algorithm based on wavelet packets (together with a simple clustering algorithm) is better than an algorithm based on wavelet transform when sorting superimposed spikes (cf. the problem with the SOM classifier) [91]. Also, Herbst et al. solved the problem of superimposed spikes by using Hidden Markov Models [94]. A problem with the SOM classifier was that the number of units present in a recording must be known a priori. The solution to this problem is described in recent papers by e.g., Wood [93]. The drawback of this method was the inability to sort superimposed spikes
and to take the refractory period of the nerve cell into account [93].

At present, many commercial acquisition softwares have included spike sorting features that are based on template matching techniques. These template matching techniques (i.e., clustering) are often multivariate and look at the whole waveform when sorting the spikes (e.g., using independent component analysis ICA or PCA). These feature were not included when Paper I was published.

The method developed in Paper I was also a foundation to the dissertations by Bergenheim [57] and Pedersen [95]. The study by Pedersen [42] has influenced many researcher when studying possible mechanisms behind muscular pain conditions (e.g., [96]).

In Paper II it was shown that the discriminative ability of the mixed ensembles of afferents was greater than ensembles of only primary MSAs. This established an even better argument for the population coding theory than presented in earlier studies on population coding. Most of the knowledge about the responses from MSAs to different mechanical stimuli is based on single sequential or pooled sequential recordings using the assumption of an “ergodic principle” (i.e., all accessible states of an MSA are equally probable over a long period of time). Therefore, studies have suggested that ensemble behavior might be derived from sequential or pooled sequential recordings [97]. Instead, population coding should be studied with simultaneous recordings from populations of MSAs [41, 42, 53]. Also, there is support for the population coding theory in studies where it is demonstrated that ensembles of simultaneously recorded MSAs have a significantly higher degree of discriminative ability than ensembles of sequentially recorded MSAs (e.g., [98]).
Ray and Doetsch described an economy argument suggesting that higher degrees of separation of stimuli express a greater ability to encode various stimuli [99]. This argument was supported by results in Paper II. This argument also gives us a neural safety mechanism when losing a single/few MSAs since there will be a limited loss of neural encoding capacity [99]. The decrease in the standard deviation of the separation of mechanical stimuli with increasing population size (see Figure 14) supported the stability argument stated by Ray and Doetsch [99]. For all types of neural receptors there will be temporal changes to the neural response due to various conditions, e.g., blood circulation, body temperature and chemical environment. For muscle receptors, this is even more evident since fatigue and muscle stiffness influence the receptor response for a certain stimulus [100]. The results implicate that the CNS can “learn” to listen to other neural inputs if a part of the neural population is missing/corrupt due to e.g., peripheral injury of nerves or receptor bearing tissues. This has important implications for rehabilitation of patients with musculoskeletal injuries or disorders.

As there is evidence for changed motor control (i.e., impaired afferent encoding ability) in patients with chronic neck pain (e.g., [25]), it is important to establish new objective examination tools when studying these patients. As a consequence, in Papers III and IV it was demonstrated how an objective movement analysis system may be used for studying disturbed neck movement patterns related to chronic WAD. In Paper IV it was suggested that parameters computed by the system might form the basis for an objective decision-support system when making medical examinations.

Pathological changes in patients with WAD are seldom found with imaging techniques such as X-ray or MRI
Therefore, to describe the pathological changes of patients with WAD, this dissertation was focused on the analysis of simple rapid neck movements. This approach is similar to the physician’s procedure when examining patients with WAD, but gives more detailed information about the mobility of the neck. This method is also objective and may be used during basic examinations and for observing the rehabilitation progress, e.g., during a follow-up examination. The tests did not permanently increase the pain symptoms in the majority of the test subjects. This is crucial if the tool is going to be used in a clinic, e.g., when evaluating different interventions and for ethical reasons.

The IHA method [73] made the comparison easier between test subjects. The positions of the markers were only used for studying the rotation of the head. The exact anatomic position of the markers attached to the body was not that important and could change a little between test subjects as long as the rotation was well described by the markers. It was also easy to subtract movements made by the upper torso from the head movement.

In Paper V of this dissertation, a description was given for a method to study the effect of anisotropic systematic errors added to a single marker on the computed helical angles during known simulated rotations. The noise is often anisotropic due to inadequate camera positioning in an experimental situation. The combined effect of systematic errors and isotropic noise on estimated helical angle was also investigated. The hypothesis was that there exists an intrinsic factor of symmetry within a rigid body (defined by its markers) that affects the computed helical angle. This hypothesis was verified both by mathematical derivations in a simple two-dimensional case and by
simulations in a more general case. Mathematical derivations showed in the simple case that the estimated rotation matrix, \( M \), was not affected by a systematic marker position error along the radial axis. The marker position error only affected the diagonal matrix containing the singular values of \( BA^T \) (as long as \( k \geq 0 \)). Systematic errors along the radial axis only affected the displacement (i.e., \( d \)) of the rigid body instead of \( M \). Simulations verified the mathematical derivations when adding systematic errors in a more general case. Various randomly simulated rotations gave the same general conclusion.

As described in previous studies (cf. [103, 104]), the effect of noise on the estimated helical angle decreased as the number of attached markers to the body increased. The same effect was also seen when systematic errors were added to a single marker. Similar results were also described by Chen et al. who investigated various calibration methods using DLT. They found that the accuracy improved when the number of markers increased [105].

In conclusion, several variables describing the mobility of the neck (i.e., Table 3) showed significant differences between the control and the WAD group. When ranking the variables (using PLS) according to influence on prediction of WAD, it was found that maximum and mean angular velocity were most important (i.e., had highest explained variance). A new decision-support tool for managing WAD and other disorders would improve the medical examination process and rehabilitation process. This tool may also help physicians in their daily work. A basis for a first decision-support tool was presented in Papers III and IV. The tool showed promising results when determining whether a patient with suspected WAD has a neck movement pattern that deviates from that found
in control subjects. Integrating the neck movement pattern into a few describing variables seems to increase the efficiency of the tool. The presented tool still needs to be further enhanced to fit the demands of healthcare. For example, additional data concerning age, proprioception and muscle activity should be added, and the software design could be made more user-friendly. These factors must probably be addressed to develop a tool for clinical use that can discriminate between other groups of patients with neck-related problems.
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