

Article

Serious Game Platform with Haptic Feedback and EMG Monitoring for Upper Limb Rehabilitation and Smoothness Quantification on Spinal Cord Injury Patients

Álvaro Gutiérrez ^{1,*}, Delia Sepúlveda-Muñoz ¹, Ángel Gil-Agudo ² and Ana de los Reyes Guzmán ²

- ¹ Escuela Técnica Superior de Ingenieros de Telecomunicación, Universidad Politécnica de Madrid, Av. Complutense 30, 28040 Madrid, Spain; delia.sepulvedam@alumnos.upm.es
- ² Biomechanics and Technical Aids Unit, National Hospital for Paraplegics, Finca La Peraleda, 45071 Toledo, Spain; amgila@sescam.jccm.es (Á.G.-A.); adlos@sescam.jccm.es (A.d.I.R.G.)
- * Correspondence: a.gutierrez@upm.es; Tel.: +34-91-06-72452

Received: 4 October 2019; Accepted: 24 January 2020; Published: 2 February 2020



Abstract: Cervical Spinal Cord injury (SCI) is a neurological disease that produces, as a consequence, impairments of the upper limb function. This paper illustrates a virtual reality platform based on three serious games for upper limb rehabilitation with electromyography monitoring, providing force feedback to the patient. In the rehabilitation process proposed, haptic feedback was provided to the patients to strength the arm muscles by means of the Novint Falcon device. This end-effector device was used to manipulate the serious games. During the therapy performance, the system recorded electromyography signals from the patient's arm muscles, which may be used to monitor muscle contraction. The work presented a virtual reality system developed for spinal cord-injured patients. Each virtual reality environment could be modified in strength and duration according to the patients' needs and was implemented for recording quantitative data about the motor performance. The platform was validated as a proof of concept in cervical spinal cord-injured patients. Results showed that this rehabilitation platform could be used for obtaining objective information in relation to motor control characteristics.

Keywords: upper limb rehabilitation; serious games; haptic feedback; electromyography sensors; virtual reality; smoothness

1. Introduction

Spinal Cord Injury (SCI) is one of the most important neurological diseases that produce deficiencies in the field of physical disability [1]. It is often a catastrophic condition requiring chronic care. Despite an enormous amount of research in SCI, the neurological prognosis for a patient with severe SCI remains dismal. Life expectancy after such an injury is markedly reduced due to complications proportional to the severity of injury or remaining neurological functions. Therefore, SCI is associated with a risk of developing secondary conditions that can be debilitating and even life-threatening, such as deep vein thrombosis, urinary tract infections, muscle spasms, osteoporosis, pressure ulcers, chronic pain, and respiratory complications [2]. Acute care, rehabilitation services and ongoing health maintenance are essential for the prevention and management of these conditions [3].

The worldwide incidence of SCI lies between 10 and 83 per million inhabitants per year [4]. In Spain, approximately 1000 new cases of SCI per year occur due to trauma, which is the main cause; half due to traffic accidents, the rest due to falls, blows, sport accidents or other injuries [5].



Most of these people have permanent damages. It is observed that people with SCI have difficulties and limitations in mobility (96.9% of cases), in self-care (81.1% of cases) and in carrying out tasks of domestic life (84.3% of cases) [6]. This situation means that the majority of the population with SCI requires personal and technical support to carry out these activities. The treatment for SCI is often expensive: it can reach up to 55,000 the first 60 days for a patient in acute phase, with an additional 10,000 for the intensive care stay. Hence, the economic and societal impact is enormous, both to the immediate family and the society at large [7]. The inclusion of lower cost technologies is a key aspect for reducing the therapy cost. Therefore, there is a great need for new systems that improve the quality of life for SCI injured patients [8–10].

The impairment of the Upper Limb (UL) is one of the most common sequelae following neurological injuries [11]. The loss of arm and hand function is one of the most devastating consequences in tetraplegia [12]. One important aspect of this lost function is smoothness. Smoothness is a characteristic of a skilled and well-coordinated human movement [13] and it is an independent measure with respect to speed and distance [14]. When moving the hand between pairs of targets, people tend to generate roughly straight hand trajectories with a single-peaked, bell-shaped speed profile [15]. However, in presence of neurological pathologies, the UL movement is characterized by the lack of smoothness [16], the performance of more curved trajectories with directional changes and a higher peaks number in the speed profile. Smoothness has been used as a measure of motor performance in healthy people and neurological pathologies, mainly stroke patients [11,14,17,18], being the neurological injury with the highest incidence and prevalence in the population. This control motor characteristic has been quantified by means of different variables, extracted of the movement analysis as the peaks number in the speed profile, the ratio between the maximal and mean velocity and the jerk metric computed as the time derivative of acceleration [13,19]. As our expertise in this field, after the developmental work of kinematic indices applied to spinal cord injured patients, smoothness metric computed from the peaks number in the speed profile is discriminative between healthy and neurological patients [20,21].

Small progresses in arm and hand function may lead to increase autonomy in activities of daily living [22], improving independence and quality of life. For this reason, rehabilitation for the improvement in UL function after cervical SCI is a top priority in individuals with tetraplegia [23]. In rehabilitation, considerable amounts of practice are required to induce neuroplastic changes and functional recovery of neurological motor deficits [24]. SCI rehabilitation works through mechanisms of experience-dependent plasticity [25]. The process of plasticity consists of changes in the activation pattern, either of structure or function of neural connections. These changes involve the modification of the strength of existing connections or the creation of new neural connections. Although it is likely that some of the reorganization after central nervous system injuries take place in the cortex, plasticity changes may also occur in subcortical structures, such as the spinal cord [26]. Therefore, neuroplasticity is essential in the SCI rehabilitation process.

Nowadays, technology is typically involved in rehabilitation. It makes use of high cost devices, such as exoskeletons or robotic devices [27], or low cost devices, such as the Leap Motion, Kinect, or Novint Falcon, among others [28]. In this paper, we make use of the Novint Falcon device, a desktop haptic robot with 3 degrees of freedom (see Section 2). Several studies found in the literature have investigated the use of the Novint Falcon in healthy subjects: Scalona et al. analyzed the motor performance during six reaching movement sessions varying the force levels [29]. The subjects had to reach eight different objectives placed on a circumference (vertical and horizontal line and in each diagonal). Cappa et al. analyzed the response to different force feedback in healthy population with an educational purpose [28]. Palsbo et al. used the Novint Falcon to train fine movements in a group of healthy developing children and noted significant improvements in handwriting performance [30]. However, there is no evidence of research studies with the Novint Falcon in spinal cord injured patients. Nonetheless, some studies have been performed with the Novint Falcon to analyze the UL function in patients who have suffered stroke [31,32]. These studies have been conducted with a rehabilitation purpose. Chortis et al. evaluated the effects of repetitive arm movements with

a group of eight post-stroke subjects by using the commercial virtual games included in Novint Falcon [33]. These games were oriented to reach UL functional tasks, following the rehabilitative principles. The patient performance was compared between pre and post condition by using only clinical tests. Unfortunately, in those studies, smoothness was not analyzed.

Additionally, the use of technology in rehabilitation in combination with virtual reality (VR) environments has increased in the last years [34–37], mainly because the quantity of therapy that patients receive increases. VR has many advantages for intervention, such as enabling the grading of activities, obtaining precise performance measures, providing a safe and ecologically valid environment, and being enjoyable and motivating [24,38]. There is evidence about the acceleration in the rehabilitation process by the combination of these VR treatments with conventional rehabilitation [39]. Moreover, the use of VR environments can increase the intensity of the therapy through the adequate repetitions number [27]. VR reality games increase motivation in patients both in occupational and physical therapy [40]. Therefore, the health care sector is showing steadily increasing interest in serious games [41].

The work presented in this paper is centered in reaching the patient's assessment in an objective way by means of the smoothness movement characteristic. Therefore, the aim of the present paper, an extension of [42], is to develop three serious games based on UL functional tasks, manipulated by the Novint Falcon device, and to collect quantitative data about SCI patients for analyzing movement smoothness. Moreover, this research involves the novelty of applying force feedback to SCI patients while analyzing the movement smoothness. In addition, electromyographic signals are obtained, integrating a Myo Gesture armband into the platform, which could be useful in the future for analyzing impairments in the muscles activation pattern.

The rest of the paper is organized as follows: Section 2 describes the methodology in relation to the integration of a commercial haptic device (Novint Falcon) and a commercial electromyography (EMG) sensor (Myo Gesture armband) into a virtual reality platform; the development of the serious games and the validation proof. Section 3 presents the results of the implemented proof of concept. Section 4 includes the discussion and Section 5 concludes the paper.

2. Materials and Methods

2.1. UL Rehabilitation Platform

The platform was composed of a PC, including the serious games developed in Unity3D, and two hardware devices: Novint Falcon for providing force feedback and manipulating the serious games; and Myo Gesture Arm Band for providing information about muscle contraction (see Figure 1).



Figure 1. Scheduled illustration of the upper limb rehabilitation platform: Myo Gesture armband (left object in image) and Novint Falcon device (right object in image).

2.1.1. Novint Falcon

The Novint Falcon (see Figure 1, right) is a desktop haptic robot device with 3 degrees of freedom (DOF). It provides haptic feedback where the users feel virtual objects as they virtually touch them [43]. The device consists of three motorized arms attached to an interchangeable end-effector providing kinesthetic feedback. It uses a USB 2.0 port, has a capacity of 9 N of force, and provides a $10 \times 10 \times 10 \text{ cm}^3$ working space. The device has a refresh rate up to 1000 times per second [44].

In this paper, the Novint Falcon was selected because of its low cost, at least one order of magnitude, compared to similar devices, such as the Delta.3 [45] or Omega-3 [46], and because it can generate

more force feedback than other low cost haptic devices [28]. It was used as an end-effector robotic device for upper limb rehabilitation. However, the Novint Falcon comes with a standard ball grip which is difficult to use by patients with SCI, as a fine pinch is necessary to perform the grasp [47]. The grip selected for SCI patients was of a cylinder shape for a better hand-grasp. This was a novelty in comparison to previous studies and it was designed and printed on a 3D printer.

In previous studies, tests were performed with an EMG recording system located in the main arm muscles [48]. The tests showed that using the Novint Falcon to give force feedback activates the Anterior Deltoid muscle, which flexes and medially rotates the arm, and the Extensor Carpi Ulnaris muscle, which extends and adducts the hand at the wrist joint. This was demonstrated by applying different degrees of haptic feedback in an exercise where participants would press down on a vibrating cube [48]. Therefore, the tests concluded that, by using the Novint Falcon, the shoulder and the forearm are activated.

2.1.2. Myo Gesture Arm Band

The Myo Gesture armband (see Figure 1, left) is a wearable gesture and motion control device working with EMG sensors to measure electrical pulses in the arm [49]. While muscles expand and contract, the armband sends signals wirelessly to other devices. It uses a Bluetooth 4.0 low energy connection, it has a proprietary muscle activity EMG sensor, a 9-axis inertial measurement unit (IMU), a rechargeable lithium-ion battery with one full day use out of single charge and haptic feedback which provides short, medium or long vibrations.

Deeping into the sensors, the device has 8 EMG sensors and an IMU, containing a three-axis gyroscope, a three-axis accelerometer and a three-axis magnetometer. Thanks to this 9-axis IMU, Myo Gesture armband senses the motion, orientation and rotation of the forearm, used to recognize hand and wrist movements.

In this paper, the device was used for obtaining a correct EMG monitoring during the performance of the rehabilitation games. By using this armband, the muscle contraction and the arm kinematics were stored for a posterior data analysis. Because of the Myo Gesture armband design, the 8 EMG sensors are located equally distributed in the perimeter of the forearm. The EMG data was streamed at 200 Hz by Bluetooth communication to the PC.

Moreover, the rehabilitation platform implemented provided the opportunity to visualize in real time the data obtained from the EMG sensors. This functionality allowed to measure the muscle strength that the patient performs during each game.

2.1.3. Communication Protocol

The communication between the virtual environment and the devices were implemented via sockets. The communication frequency between these devices was very important. Because the user needed to perceive continuity in the images, the frequency of 30 Hz was selected for the graphics. However, for haptic stability without oscillations a sampling rate greater than 500 Hz was mandatory. In this paper, the frequency selected was around 650 Hz.

2.2. Serious Games Development

The first step to create the rehabilitation platform was to implement the virtual end-effector. A software created the socket between the Unity 3D platform and the Novint Falcon device, enabling the bidirectional transmission and reception of information.

To study the movement of the virtual object, it was necessary to establish a relationship between the Cartesian coordinates of the end of the haptic device and the coordinates of the virtual object. This module updated every frame in the scene with the position of the end-effector. The axes reference of the Novint Falcon and the games are shown in Figure 2, where the *x* and *y* axes are horizontal and vertical movements on the screen respectively, and the *z* axis comes out of the screen.



Figure 2. (a) Novint Falcon and (b) serious games reference axes.

Then, the serious games have been implemented with a therapeutic sense. To create a complete platform, different menus focused on the patients were developed. The configuration of the games attributes was essential to fit the games according to the needs of each patient in relation to the functional capabilities. Within each serious game proposed, patients had to reach the number of objectives selected by the therapist. To achieve this goal, the time of execution was restricted. If the patient did not achieve the objectives in the available time, the game would finish. To help patients in developing this task, the movement made with the end-effector was visualized in the virtual environment.

A summary of the main characteristics analyzed in each game is shown in Table 1. The behavior and characteristics of each serious game are explained in subsequent sections. These features were measured in terms of movement smoothness. Moreover, each serious game included elements of visual feedback, recommended to boost the rehabilitation. Therefore, each serious game sought to check if it was able to positively modify neural mechanisms and improve motor performance by tuning the control structure of a patient. This effect should be analyzed in a future work, where a clinical validation should be carried on. This effect has been mostly analyzed in stroke patients [50] but these feedback sources can be extended to patients who have suffered other neurological diseases. Nevertheless, more studies focused exclusively on SCI upper limb impairments and their recovery are needed to elucidate if there are any difference in the residual motor control after an SCI compared to post-stroke patients.

Game	Exercise Type	Force Type	Therapeutic Objective
Following the path Picking bananas Collecting stars	Path guidance Resistive Resistive	Hooke's law Viscosity Hooke's law	Accuracy Accuracy, Strength Accuracy, Strength

Table 1. Summary with the main characteristics of each game.

2.2.1. Following the Path

The end-effector in the scene was represented by a pencil which emulates a path drawn by the patient. In this game, there was not a selection of the number of the objectives. The path was the same in all configurations. Users had to travel inside the path without going out of the edges and when they got out of it, an opposed force was exerted. When the user completed a segment, it changed its color to a darker one (see Figure 3a) until the user completed all segments or the time was exhausted.

This game was implemented in 2D (x and y axes) because the depth of the scene could cause trajectory disturbance in patients. The range of motion was of 5 cm in x axis and of 7.5 cm in y axis. The path of the trajectory had a width of 0.5 cm.

Therapeutic Objective

This rehabilitation game was based on a path guidance exercise. The therapeutic objective was to improve the precision and smoothness in the UL movement made by the patient and to recover fine

motor control. This training modality using robot-mediated therapy was a combination of assistive and active exercise. When the patient was moving the end-effector inside the path, the active mode was working and the patient felt no force. However, when the patient went out the path, the assistive modality started to push the patient's hand inside. Therefore, the haptic robot assisted by providing force feedback opposing to the movement of the patient.

In this training, the trajectory performed by the patient acquires relevant importance. For this reason, the trajectory made by the patient was collected, so the movement smoothness could be analyzed. The force feedback (F_V) was implemented by using Hooke's law (see Equation (1)).

 $F_V(kT) = -k_V \Delta X(kT), \tag{1}$

where *T* was the sampling time, kT a specific instant in the discrete domain ($k \in [0,1,2,...]$), $\Delta X(kT)$ the distance to the edge of the path, and k_V the stiffness or elasticity simulated in the edge of the path. The force was implemented in the edges of the path, so patients felt these edges like walls that they should not cross.



Figure 3. (a) Serious game "Following the path"; (b) Serious game "Picking bananas".

2.2.2. Picking Bananas

The end-effector was a basket which must collect different bananas that were located in different trees (see Figure 3b). The patient moved into the environment with the basket and when a banana fell from the tree, he had to get it with the basket before it touched the floor.

The therapist selected the number of bananas in the scene and the time for the duration of the task. Then, the game selected the frequency of falling and it randomized the falls for every session. The game notified the user when one banana was going to fall by changing its color and producing a sound. If the banana fell into the basket, the score increased. If it did not fall into it, it simply disappeared. When all the bananas fell, the game ended and the final result screen was visualized.

The force feedback provided by the haptic device was proportional to the number of bananas inside the basket, as a concept of weight and friction. Depending on the user, a high number of bananas could be tiring. Therefore, users could empty the basket in the left corner of the screen when they passed by.

The trees were disposed in the floor using a distance of 6 cm. With this distribution, users had enough space to move the end-effector in the total range of motion offered by the haptic device.

Therapeutic Objective

The rehabilitation exercise implemented in this serious game was resistive, so the robot opposed to the movement that the patient performed. In this kind of exercises, the number of repetitions should be small to avoid fatigue. A rest between exercises should be sufficient for recovery, and the resistance should be modulated to increase it as the patient ability grows.

The force feedback implemented was a viscosity resistance. This force was proportional to the velocity and opposed to the end-effector movement (see Equation (2)). This force (F_V) should increase according to the number of objectives collected.

$$F_V(kT) = -b_V \dot{X}(kT), \tag{2}$$

where *T* was the sampling time, kT a specific instant in the discrete domain ($k \in [0,1,2,...]$), *X* (kT) the velocity of the end-effector and b_V a constant referred to the viscosity. In this exercise, an isotonic muscle contraction was produced. This muscle contraction implied the shortening and lengthening of muscle fibers. Depending on the amount of force working against an individual's body, one of two kinds of isotonic contractions took place: concentric and eccentric contractions. Concentric contractions occur when muscles shorten while its tension is greater than the force opposing it. On the other hand, eccentric contractions occur when muscles extends in length [51].

2.2.3. Collecting Stars

The virtual visualization of the end-effector was a rocket and the objectives were stars which must be eliminated (see Figure 4). To destroy the stars, the patient moved the rocket to the star position. The game finished when the total number of objectives were achieved or the time was up. The stars had different sizes: the bigger ones were easier to catch than the others.



Figure 4. Collecting stars interface; one star has been collected.

A star was eliminated when the rocket collided with it. Once the collision was done, the star disappeared from the scene, the score was incremented and a sound was produced. After collecting a star, the user had to come back to the center of the screen before performing other destruction. To achieve this behavior, the collision detection module was disabled during this period.

This game was designed in 2D, because it focused on following a straight trajectory, rejecting the depth of the scene. Therefore, the allowed movements were in the *y* and *x* axes, but not in *z* axis.

The center of the stars was disposed in a circumference with a radius of 4.5 cm, centered in x and y equal to zero. Consequently, the range of motion of the haptic device was fully covered, allowing a range of motion of -5 cm to 5 cm in both axes.

Therapeutic Objective

The exercise implemented in this game was resistive. The robot provided force opposing the movement. Thus, its goal was to obtain the strengthening of the UL muscles. In addition, with this game the linearity of the movement could be checked. Patients with UL lesion usually tried to compensate movements performing curved trajectories when they tried to catch an objective which was in a straight direction.

In this case, there was a zone without force in the middle of the game circle, but when the patient was close to the targets, the force applied increased. The force began to act only in a radius of 2.5 cm from the objective. The force applied followed the Hooke's law (see Equation (1)). Therefore, the force scaled linearly with respect to the distance when the end-effector was entering into the force area.

As in the picking bananas game, the muscle contraction was isotonic, because the force depended on the movement and the position. A shortening and lengthening of the muscle fibers occurred during the game performance.

2.3. Participants

A total of 8 people participated in the study divided into two groups: a group of healthy people (n = 4) and a group of cervical SCI patients (n = 4). All patients fulfilled the following inclusion criteria: age 16 to 65 years, at least 6 months from the injury onset, and cervical injury of the metameric levels between C1 (first cervical vertebra) and C7 (7th cervical vertebra), neurologically classified according to the American Spinal Injury Association (ASIA) scale into grades C or D [52]. Patients who presented any vertebral deformity, joint constraint, surgery on any of the UL, balance disorders, dysmetria due to associated neurologic disorders, visual acuity defects, cognitive deficit, or head injury associated with the SCI were excluded. Background data of patients are provided in Table 2. The healthy subjects were chosen according to reach two groups of similar demographic characteristics (3 males of 19, 21 and 23 years old and a female of 44). The guidelines of the declaration of Helsinki were followed in every case. Informed consent was obtained from all individual participants included in the study, which was approved by the Local Ethics Committee, Toledo, Spain.

 Table 2. Spinal Cord Injury (SCI) patients' characteristics.

Patient	Age	Sex	Injury Level	ASIA
1	19	М	C4	С
2	18	Μ	C4	С
3	45	F	C5	D
4	20	Μ	C6	С

2.4. Experimental Setup

The study was performed during two days, with two sessions per day. Therefore, the study was formed by data obtained from four different sessions. In all sessions, participants performed the test before starting with the serious games. This methodology was used to obtain clear results. In this way, participants had a previous knowledge of the games and the results obtained did not show the variability of the learning process.

The three games were performed in all sessions, always in the same order and with the same characteristics to avoid including variability into the study. First, the "Picking bananas" game was performed for 2 min and 15 objectives were selected. Second, the "Collecting stars" game was performed for a maximum of 2 min and 16 objectives were selected. Finally, the "Following the path" game was also performed for a maximum of 2 min. The maximum force selected in all games was at a value of 4.5 N, half of the maximum available force at the Novint Falcon. This parameter selection was chosen because in all tests participants showed skills to perform the task with this configuration.

All participants were right handed. The end-effector of the Novint Falcon was held with the right hand and the Myo Gesture armband placed in the same arm, specifically in the forearm, with the electrodes located on the flexor and extensor wrist muscles. The tasks were performed in the frontal plane of the patients (see Figure 5).



Figure 5. Example of a healthy trial with the Novint Falcon held on the right hand and the Myo Gesture armband on the right forearm.

2.5. Data Processing

In this study, the UL motor performance of each participant was measured in terms of movement smoothness, computing the peaks number from the velocity profile during the task execution proposed by the serious games.

A processing script was developed by using the software MATLAB (MathWorks[®]). The speed profile was obtained from the position data obtained by the haptic robot. These data were stored into text files during the performance of each serious game. The trajectories were analyzed in 2D.

The statistical non-parametric U Mann-Whitney test was applied to analyze the possible differences between both populations (healthy and patients groups) with a significance level of 5%. The results were expressed as mean and standard deviation for the following variables: mean and peak speed (m/s), number of peaks on the trajectory, and duration of the task.

3. Results

The results in relation to the motor performance in each variable within the serious games are shown in Tables 3 and 4.

Table 3. Results about duration, as well as peak and mean velocity in each serious game for both experimental groups (a, statistical differences p < 0.05).

Following the Path	Healthy Group (n = 4)	SCI Patients (n = 4)
Duration (s)	28.55 (7.91) ^a	49.52 (13.33) ^a
Peak velocity x (m/s)	0.255 (0.121)	0.406 (0.133)
Peak velocity y (m/s)	0.556 (0.203)	0.270 (0.125)
Mean velocity x (m/s)	0.063 (0.008)	0.058 (0.015)
Mean velocity y (m/s)	0.070 (0.018)	0.058 (0.020)
Picking bananas		
Duration (s)	120.00 (0)	120.00 (0)
Peak velocity x (m/s)	1.600 (0.441)	1.752 (0.591)
Peak velocity y (m/s)	0.799 (0.813)	0.818 (0.902)
Mean velocity x (m/s)	0.060 (0.013) ^a	0.141 (0.065) ^a
Mean velocity y (m/s)	0.047 (0.013) ^a	0.091 (0.022) ^a
Collecting stars		
Duration (s)	34.66 (7.91)	41.78 (15.83)
Peak velocity x (m/s)	1.232 (0.223)	0.878 (0.231)
Peak velocity y (m/s)	1.317 (0.387)	0.898 (0.145)
Mean velocity x (m/s)	0.160 (0.082)	0.140 (0.056)
Mean velocity y (m/s)	0.158 (0.054)	0.137 (0.054)

Peaks Number	Healthy Group (n = 4)	SCI Patients (n = 4)
Following the path	51.12 (11.53) ^a	81.32 (22.93) ^a
Picking bananas	154.75 (12.63)	164.72 (17.22)
Collecting stars	54.48 (10.25)	67.42 (24.58)

Table 4. Peaks number in each serious game for both experimental groups (a, statistical differences p < 0.05).

3.1. Following the Path

The time spent in the performance of the task was significantly different: healthy people spent on average 28.55 s and SCI patients 49.52 s. This indicates that patients needed to perform the movement slowly for avoiding going out of the edges. During the task execution, a counter quantified the number of times that a participant went out of the path. The analysis shows that healthy subjects went out of the path an average of 2.75 times and SCI patients 13.75 times. This fact increases the corrections number of the hand due to the force feedback applied. So, the number of peaks in the speed profile is statistically different between both groups.

3.2. Picking Bananas

In this serious game, all the participants spent 2 min. The average of the speed profile is slightly higher in SCI patients than in healthy subjects. This is because SCI patients made quick movements trying to catch the objectives.

The number of peaks obtained in the analysis shows that SCI patients perform more accelerations and decelerations in the speed profile. However, the number of peaks was very high in both groups, not showing statistical differences. Nonetheless, by observing the speed profile we observe that the speed profile of SCI group is more abrupt than the healthy participants. An example of average speed profile on axis x during the execution of the Picking bananas game for one healthy and one SCI participant is shown in Figure 6. This profile shows a maximum speed peak of 1.3 m/s for the healthy participant and 1.9 m/s for the SCI one. Two peaks higher than 0.5 m/s can be observed in the healthy subject, while this number rises up to fourteen for the SCI participant within the same time frame. Similar results are observed in all axes for all games and participants. However, a larger clinical study should be carried on to better analyze those differences and obtain statistical differences.



Figure 6. Example of a Healthy (blue) and SCI (red) participant speed profile of *x* axis measured from the end-effector of Novint Falcon device in the Picking bananas game.

3.3. Collecting Stars

During the execution of this serious game, SCI patients spent more time for reaching the 16 objectives (41.78 s) than healthy subjects (34.66 s). The duration of the exercise could affect the smoothness of the movement. This was because carrying out the task more slowly produced segmentation of the movement and more peaks appeared in the speed profile. In addition, SCI patients performed longer trajectories with a higher number of peaks than the healthy subjects (see Figure 7 for

11 of 17

an example). This longer trajectories were due to the difficulty of accurately reaching the objectives, both the starts and the center position. For the examples shown in Figure 7, it can be observed how the healthy performed more accurately trajectories both on the center and the start positions. It can also be observed that just one approximation, or two at maximum in some points, was performed to reach every star. On the contrary, the SCI participant performed multiple passes through the same point. Some stars, especially shown at the left-bottom part of the image, needed more than five approximations to be reached. Moreover, the lines accumulation on the center of the image is clearly stronger in the SCI patient plot.



Figure 7. Example of a Healthy (blue) and SCI (red) participant range of motion (ROM) measured from the end-effector of Novint Falcon device in the Collecting stars game.

3.4. Electromyography Recording

An example of the activation pattern in flexors and extensors muscles measured from the Myo Gesture armband placed on the forearm of a healthy subject and an SCI patient during the execution of the serious games is shown in Figure 8. These data were analyzed taking into account the potential values obtained from the Myo Gesture armband. The EMG data provided by the Myo Gesture armband was unitless, 8 bit value. Hence, it provided a potential range between 0 and 255. To represent the muscle contraction, the value of the data collected from the sensor placed in the muscles of interest had been calculated. In all trials, SCI patients showed a stronger activation than healthy people. However, for all users, the muscle contraction was low, obtaining an average of 38.13 in "Following the path" game, 39.64 in "Picking bananas" games, and, finally, 53.35 in "Collecting stars".



```
(a)
```



Figure 8. Activation pattern in the flexors and extensors muscles from Novint Falcon device placed on the forearm for the three serious games for (**a**) a healthy subject and (**b**) an SCI patient. The information provided by the Myo Gesture armband is unitless, with a potential value in the range of [0,255]. EMG = electromyography.

4. Discussion

In the present study, all virtual environments developed focus on reaching UL functional tasks. For the performance, they require a combination of analytical movements in each involved joint. The force feedback delivered by means of Novint Falcon provides sensitive information to the patient that modifies the kinematic patterns performed and, as a consequence, the kinematic variables measured.

An important contribution in this research with respect to previous studies is the integration of the Novint Falcon device and the Myo Gesture armband into a unique platform, obtaining EMG signals from flexors and extensors muscles of the wrist joint. The monitoring of EMG signals could be useful in the future for analyzing impairments in the muscles activation pattern during the serious games performance. The EMG values obtained are low, far from the maximum value provided by the Myo Gesture armband. This effect occurs because the load of the therapy proposed is also moderate. Therefore, the muscle activity that patients need to overcome the force feedback is moderate. It can be appreciated that, in the "Collecting star" game, where the force feedback applied is higher, the muscle contraction is also higher. To represent the muscle contraction, the value of the data collected has been calculated. For that reason, it is necessary to validate this EMG signal with those activation patterns measured from a clinical EMG system. In previous studies, differences in EMG patterns between healthy subjects and patients with cervical SCI have been reported to match with the differences in kinematic results [53]. Therefore, the EMG signal is essential for monitoring the muscle contraction during the games performance. In a posterior analysis, these data could be used to check the changes in the patterns of motor activity during the rehabilitation process. The data provided by the EMG could also be useful for controlling the appearance of peripheral fatigue [54]. Moreover, its supervision is important to avoid damaging the patient's muscle with an overload of work.

In relation to the content of the games, the "Collecting stars" game has been developed similar to those proposed by Scalona et al., where they provide 8 objectives to reach with different levels of force feedback [29]. In our proposal, the game involves 16 objectives around the circumference: four in the vertical and horizontal line, and the other 12 in the diagonal lines. The other two serious games were oriented to complete functional tasks, like the commercial games included in Novint Falcon and used by Chortis et al. [33]: one of them, the "Picking bananas" game, to pick up and carry objects; and the other one, the "Following the path" game, to follow a hand trajectory.

Nonetheless, the lack of movement smoothness has already been demonstrated in presence of neurological pathologies [16]. It is measured at the distal segment and shows as a consequence longer hand trajectories with a higher number of directional changes. This characteristic provides objective quantitative information of UL motor function and control. The ideal condition when moving the hand between pairs of targets is to generate roughly straight hand trajectories with a single-peaked, bell-shaped speed profile [15]. This behavior was proved to be independent of the part of the work-space in which the movement was performed. Moreover, the results obtained were strong indicators that movement planning takes place in terms of UL distal segment, by means of hand trajectories rather than joint rotations [55,56]. Nevertheless, smoothness metric has shown to be discriminative between healthy and neurological patients when smoothness is computed from the peaks number in the speed profile [20,21]. Therefore, in this paper, smoothness has been measured by computing the peaks number within the speed profile. Results from the proof of concept show that this behavior was maintained, and a higher peaks number was obtained in SCI patients than in healthy people for the three serious games. However, statistical differences were only obtained in the "Following the path" game.

5. Conclusions

The use of new technologies in the rehabilitation field has increased in the last years. Robot aided and VR rehabilitation provide higher motivational environments to the patient, facilitate the performance of the necessary movement repetitions for inducing the UL motor learning and increase the amount of therapy that patients receive. However, these technologies are expensive, and a need for low-cost devices exists. This work takes advantage of low-cost VR systems and robotic haptic devices to enhance involvement and engagement of patients to provide a congruent multisensory afferent feedback during motor exercises and benefit from the flexibility of virtual scenarios.

The low cost platform developed in the present work enables the UL rehabilitation with haptic feedback and EMG monitoring for SCI patients. First of all, three serious games have been designed

and implemented to compute within them the smoothness movement. The design and implementation of each serious game required the definition of a unique interface and physical models related to haptic feedback. In all of them, the movement smoothness has been reported lower in patients than in healthy people, showing an inverse relation with the peaks number obtained. As a conclusion, the three serious games proposed are suitable for measuring movement smoothness, but the most suitable game for discriminating between healthy and SCI patients is the "Following the path" game. This is because, in this game, the order to reach the different nodes has been imposed, being always the same and allowing an identical comparison between participants. Nonetheless, these assumptions should be confirmed with a large clinical validation.

A proof of concept to check the functionality of the platform with SCI patients was made. Results obtained in terms of movement smoothness show differences in the movement patterns. Some benefits drawn from this research are exposed as follows:

- All the devices of the platform are low-cost and easily adaptable for different people, with a short time spent in preparation for the serious games performance.
- The configuration options used in this research allow to create different virtual scenarios, in order to personalize each patient rehabilitation.
- The final design generates a good haptic response and reliable monitoring of the muscle contractions.

Author Contributions: Conceptualization, Á.G., D.S.-M. and A.d.I.R.G.; methodology, Á.G., D.S.-M., A.d.I.R.G.; software, D.S.-M.; validation, D.S.-M., A.d.I.R.G., and Á.G.-A.; formal analysis, A.d.I.R.G., Á.G.; investigation, D.S.-M., A.d.I.R.G.; resources, Á.G. and Á.G.-A.; data curation, D.S.-M. and A.d.I.R.G.; writing—original draft preparation, Á.G., D.S.-M. and A.d.I.R.G.; writing—review and editing, Á.G., A.d.I.R.G. and Á.G.-A.; visualization, Á.G., A.d.I.R.G.; supervision, Á.G., A.d.I.R.G.; project administration, Á.G.-A. and A.d.I.R.G.; funding acquisition, Á.G. and A.d.I.R.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research has been funded by grant from the Spanish Ministry of Economy and Competitivity and co-funded from FEDER, National Plan for Scientific and Technological Research and Innovation. Project RehabHand (Plataforma de bajo coste para rehabilitación del miembro superior basado en Realidad Virtual, ref. DPI2016-77167-R).

Acknowledgments: This work was supported by the National Hospital for Paraplegics in Toledo (Spain) and the Universidad Politécnica de Madrid (Spain). The authors acknowledge the collaboration of the participants in this study.

Conflicts of Interest: The authors declare no conflict of interest.

References

- Chen, Y.; Tang, Y.; Vogel, L.C.; Devivo, M.J. Causes of spinal cord injury. *Top. Spinal Cord Inj. Rehabil.* 2013, 1, 1–8. [CrossRef]
- 2. World Health Organization. Spinal Cord Injury. Available online: http://www.who.int/news-room/fact-sheets/detail/spinal-cord-injury (accessed on 1 August 2019).
- 3. Humphreys, J.S. Key considerations in delivering appropriate and accessible health care for rural and remote populations: Discussant overview. *Aust. J. Rural Health* **2009**, *17*, 34–38. [CrossRef]
- 4. Wyndaele, M.; Wyndaele, J.J. Incidence, prevalence and epidemiology of spinal cord injury: What learns a worldwide literature survey? *Spinal Cord* **2006**, *44*, 523–529. [CrossRef] [PubMed]
- 5. DeVivo, M.; Biering-Sorensen, F.; Charlifue, S.; Noonan, V.; Post, M.; Stripling, T.; Wing, P. International Spinal Cord Injury Core Data Set. *Spinal Cord* **2006**, *44*, 535–540. [CrossRef] [PubMed]
- 6. Pérez, K.; Novoa, A.M.; Santamariña-Rubio, E.; Narvaez, Y.; Arrufat, V.; Borrell, C.; Cabeza, E.; Cirera, E.; Ferrando, J.; García-Altes, A.; et al. Incidence trends of traumatic spinal cord injury and traumatic brain injury in Spain. *Accid. Anal. Prev.* **2012**, *46*, 37–44. [CrossRef] [PubMed]
- 7. Goel, S.; Modi, H.; Dave, B.; Patel, P. Socio-Economic Impact of Cervical Spinal Cord Injury Operated in Patients with Lower Income Group. *Glob. Spine J.* **2016**, *6*, 264. [CrossRef]
- 8. Kemal, N.; Levent, Y.; Volkan, S.; Abdulkadir, A.; Kadriye, O. Rehabilitation of spinal cord injuries. *World J. Orthop.* **2015**, *6*, 8–16.
- 9. Oldrige, N.B. Outcomes Measurement: Health-Related Quality of Life. Assist. Technol. 1996, 8, 82–93. [CrossRef]

- 10. Steel, E.J. Content analysis to locate assistive technology in Queensland's motor injury insurance rehabilitation legislation and guidelines. *Assist. Technol.* **2018**, *13*, 1–5. [CrossRef]
- 11. Murphy, M.A.; Sunnerhagen, K.S.; Johnels, B.; Willen, C. Three-dimensional kinematic motion analysis of a daily activity drinking from a glass: A pilot study. *J. Neuroeng. Rehabil.* **2006**, *3*, 18. [CrossRef]
- 12. Lu, X.; M Zoghi, C.R.; Galea, M.P. Effects of training on upper limb function after cervical spinal cord injury: A systematic review. *Clin. Rehabil.* **2015**, *29*, 3–13. [CrossRef]
- 13. Rohrer, B.; Fasoli, S.; Krebs, H.I.; Hughes, R.; Volpe, B.; Frontera, W.R.; Hogan, N. Movement smoothness changes during stroke recovery. *J. Neurosci.* **2002**, *22*, 8297–8304. [CrossRef]
- Bartolo, M.; De Nunzio, A.M.; Sebastiano, F.; Spicciato, F.; Tortola, P.; Nilsson, J.; Pierelli, F. Arm weight support training improves functional motor outcome and movement smoothness after stroke. *Funct. Neurol.* 2014, 29, 15. [CrossRef]
- 15. Morasso, P. Spatial control of arm movements. Exp. Brain Res. 1981, 42, 223–227. [CrossRef]
- 16. Krebs, H.I.; Aisen, M.L.; Volpe, B.T.; Hogan, N. Quantization of continuous arm movements in humans with brain injury. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 4645–4649. [CrossRef]
- 17. Platz, T.; Denzler, P.; Kaden, B.; Mauritz, K.-H. Motor learning after recovery from hemiparesis. *Neuropsychologia* **1994**, *32*, 1209–1223. [CrossRef]
- Kahn, L.E.; Zygman, M.L.; Rymer, W.Z.; Reinkensmeyer, D.J. Robot-assisted reaching exercise promotes arm movement recovery in chronic hemiparetic stroke: A randomized controlled pilot study. *J. Neuroeng. Rehabil.* 2006, *3*, 12. [CrossRef]
- Casadio, M.; Pressman, A.; Fishbach, A.; Danziger, Z.; Acosta, S.; Chen, D.; Tseng, H.-Y.; Mussa-Ivaldi, F.A. Functional reorganization of upper-body movement after spinal cord injury. *Exp. Brain Res.* 2010, 207, 233–247. [CrossRef]
- De los Reyes-Guzmán, A.; Dimbwadyo-Terrer, I.; Pérez-Nombela, S.; Monasterio-Huelin, F.; Torricelli, D.; Pons, J.L.; Gil-Agudo, A. Novel kinematic indices for quantifying upper limb ability and dexterity after cervical spinal cord injury. *Med. Biol. Eng. Comput.* 2017, 55, 833–844. [CrossRef]
- De los Reyes-Guzman, A.; Dimbwadyo-Terrer, I.; Pérez-Nombela, S.; Monasterio-Huelin, F.; Torricelli, D.; Pons, J.L.; Gil-Agudo, A. Novel kinematic indices for quantifying movement agility and smoothness after cervical Spinal Cord Injury. *NeuroRehabilitation* 2016, *38*, 199–209. [CrossRef]
- 22. Hoffman, H.G.; Patterson, D.R.; Carrougher, G. Use of Virtual Reality for Adjunctive Treatment of Adult Burn Pain During Physical Therapy: A Controlled Study. *Clin. J. Pain* **2000**, *16*, 244–250. [CrossRef] [PubMed]
- 23. Kalsi-Ryan, S.; Curt, A.; Verrier, M.C.; Fehlings, M.G. Development of the Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP): Reviewing measurement specific to the upper limb in tetraplegia. *J. Neurosurg. Spine* **2012**, *17*, 65–76. [CrossRef] [PubMed]
- 24. Lohse, K.R.; Hilderman, C.G.E.; Cheung, K.L.; Tatla, S.; Van Der Loos, H.F.M. Virtual reality therapy for adults poststroke: A systematic review and meta-analysis exploring virtual environments and commercial games in therapy. *PLoS ONE* **2014**, *3*, e93318.
- 25. Ding, Y.; Kastin, A.J.; Pan, W. Neural plasticity after spinal cord injury. *Curr. Pharm. Des.* **2005**, *11*, 41–50. [CrossRef] [PubMed]
- 26. Kaas, J.H. International Encyclopedia of the Social & Behavioral Sciences; Elsevier: Amsterdam, The Netherlands, 2001.
- 27. Yozbatiran, N.; Francisco, G.E. Robot-assisted Therapy for the Upper Limb after Cervical Spinal Cord Injury. *Phys. Med. Rehabil. Clin.* **2019**, *30*, 367–384. [CrossRef]
- Cappa, P.; Clerico, A.; Nov, O.; Porfiri, M. Can Force Feedback and Science Learning Enhance the Effectiveness of Neuro-Rehabilitation? An Experimental Study on Using a Low-Cost 3D Joystick and a Virtual Visit to a Zoo. *PLoS ONE* 2013, *8*, e83945. [CrossRef]
- 29. Scalona, E.; Hayes, D.; del Prete, Z.; Palermo, E.; Rossi, S. Perturbed Point-to-Point Reaching Tasks in a 3D Environment Using a Portable Haptic Device. *Electronics* **2019**, *8*, 32. [CrossRef]
- Palsbo, S.E.; Marr, D.; Streng, T.; Bay, B.K.; Norblad, A.W. Towards a modified consumer haptic device for robotic-assisted fine-motor repetitive motion training. *Disabil. Rehabil. Assist. Technol.* 2011, *6*, 546–551. [CrossRef]
- Andaluz, V.H.; Salazar, P.J.; Silva, S.M.; Escudero, V.M.; Bustamante, D.C. Rehabilitation of upper limb with force feedback. In Proceedings of the 2016 IEEE International Conference on Automatica (ICA-ACCA), Curico, Chile, 19–21 October 2016; pp. 1–6.

- 32. Yeh, S.C.; Lee, S.H.; Chan, R.C.; Wu, Y.; Zheng, L.R.; Flynn, S. The efficacy of a haptic-enhanced virtual reality system for precision grasp acquisition in stroke rehabilitation. *J. Healthc. Eng.* **2017**, 2017, 9840273. [CrossRef]
- Chortis, A.; Standen, P.J.; Walker, M. Virtual reality system for upper extremity rehabilitation of chronic stroke patients living in the community. In Proceedings of the 7th ICDVRAT with ArtAbilitation, Maia, Portugal, 8–11 September 2008; pp. 221–228.
- 34. Alcover, E.A.; Jaume-i-Capó, A.; Moya-Alcover, B. PROGame: A process framework for serious game development for motor rehabilitation therapy. *PLoS ONE* **2018**, *13*, e0197383.
- 35. Pirovano, M.; Surer, E.; Mainetti, R.; Lanzi, P.L.; Borghese, N.A. Exergaming and rehabilitation: A methodology for the design of effective and safe therapeutic exergames. *Entertain. Comput.* **2016**, *14*, 55–65. [CrossRef]
- 36. Dimbwadyo-Terrer, I.; Trincado-Alonso, F.; los Reyes-Guzmán, A.D.; López-Monteagudo, P.; Polonio-López, B.; Gil-Agudo, A. Activities of daily living assessment in spinal cord injury using the virtual reality system toyra: Functional and kinematic correlations. *Virtual Real.* **2016**, *20*, 17–26. [CrossRef]
- 37. Eckert, M.; Gómez-Martinho, I.; Meneses, J.; Martínez, J.F. New approaches to exciting exergame-experiences for people with motor function impairments. *Sensors* **2017**, *17*, 354. [CrossRef] [PubMed]
- 38. Bart, O.; Agam, T.; Weiss, P.L.; Kizony, R. Using videocapture virtual reality for children with acquired brain injury. *Disabil. Rehabil.* **2011**, *33*, 1579–1586. [CrossRef]
- Dimbwadyo-Terrer, I.; Gil-Agudo, A.; Segura-Fragoso, A.; de los Reyes-Guzman, A.; Trincado-Alonso, F.; Piazza, S.; Polonio-López, B. Effectiveness of the virtual reality system toyra on upper limb function in people with tetraplegia: A pilot randomized clinical trial. *Biomed. Res. Int.* 2016, 2016, 6397828. [CrossRef]
- 40. Omelina, L.; Jansen, B.; Bonnechère, B.; Van Sint Jan, S.; Cornelis, J. Serious games for physical rehabilitation: Designing highly configurable and adaptable games. In Proceedings of the International Conference on Disability, Virtual Reality and Associated Technologies, Laval, France, 10–12 September 2012; The University of Reading: Reading, UK, 2012; pp. 195–202.
- 41. Graafland, M.; Dankbaar, M.; Mert, A.; Lagro, J.; Wit-Zuurendonk, L.D.; Schuit, S.; Schaafstal, A.; Schijven, M. How to systematically assess serious games applied to health care. *JMIR Serious Games* **2014**, *2*, e11. [CrossRef]
- 42. Sepúlveda-Muñoz, D.; de los Reyes Guzmán, A.; Gil-Agudo, A.; Gutiérrez, A. Design and implementation of a Virtual Reality platform for Upper Limb rehabilitation. In Proceedings of the XXXVI Congreso Anual de la Sociedad Española de Ingeniería Biomèdica, Ciudad Real, Spain, 21–23 November 2018; Ediciones Visilab: Ciudad Real, Spain, 2018; pp. 203–206.
- 43. Virtual Reality Society. The Novint Falcon Haptic System—Virtual Reality Society. 2019. Available online: http://www.vrs.org.uk/virtual-reality-gear/haptic/novint-falcon.html (accessed on 1 August 2019).
- 44. Novint Falcon. Wide Variety of Games. 2019. Available online: http://www.robotshop.com/media/files/PDF/ datasheet-nf1-s01.pdf (accessed on 1 August 2019).
- 45. Delta.3. Force Dimension. 2019. Available online: https://www.forcedimension.com/downloads/specs/ specsheet-delta.3.pdf (accessed on 3 December 2019).
- 46. Omega.3. Force Dimension. 2019. Available online: https://www.forcedimension.com/downloads/specs/ specsheet-omega.3.pdf (accessed on 3 December 2019).
- 47. Curtin, M. An Analysis of Tetraplegic Hand Grips. Br. J. Occup. Ther. 1999, 62, 444–450. [CrossRef]
- Nagaraj, S.B.; Constantinescu, D. Effect of Haptic Force Feedback on Upper Limb. In Proceedings of the Second International Conference on Emerging Trends in Engineering & Technology, Nagpur, India, 16–18 December 2009; pp. 55–58.
- 49. ThalmicLabs. Myo Gesture Armband Product Specs—Welcome to Myo Support. 2019. Available online: http://support.getmyo.com/hc/en-us/articles/202648103-Myo-armband-product-specs (accessed on 1 August 2019).
- Urra, O.; Casals, A.; Jané, R. The impact of visual feedback on the motor control of the upper-limb. In Proceedings of the 2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), Milan, Italy, 25–29 August 2015; pp. 3945–3948.
- 51. Muscle Physiology. Muscle Physiology—Types of Contractions. 2006. Available online: http://muscle.ucsd. edu/musintro/contractions.shtml (accessed on 1 August 2019).
- 52. Kirsblum, S.C.; Burns, S.P.; Biering-Sorensen, F.; Donovan, W.; Graves, D.E.; Jha, A. International standards for neurological classification of spinal cord injury (revised 2011). *J. Spinal Cord Med.* **2011**, *34*, 535–546. [CrossRef]

- 53. De los Reyes-Guzmán, A.; López-Dolado, E.; Lozano-Berrio, V.; Pérez-Nombela, S.; Torricelli, D.; Pons, J.L.; Gil-Agudo, A. Upper Limb Electromyographic Analysis Synchronized with Kinematics in Cervical Spinal Cord Injured Patients during the Activity of Daily Living of Drinking. JSM Phys. Med. Rehabil. 2017, 1, 1004.
- 54. Cifrek, M.; Medved, V.; Tonkovic´, S.; Ostojic´, S. Surface EMG based muscle fatigue evaluation in biomechanics. *Clin. Biomech.* **2009**, *24*, 327–340. [CrossRef]
- 55. Flash, T.; Hogan, N. The coordination of arm movements: An experimentally confirmed mathematical model. *J. Neurosci.* **1985**, *5*, 1688–1703. [CrossRef] [PubMed]
- Krebs, H.I.; Ferraro, M.; Buerger, S.P.; Newbery, M.J.; Makiyama, A.; Sandmann, M.; Lynch, D.; Volpe, B.T.; Hogan, N. Rehabilitation robotics: Pilot trial of a spatial extension for MIT-Manus. *J. Neuroeng. Rehabil.* 2004, 1, 5. [CrossRef] [PubMed]



© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).