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New Technologies for On-Demand Hand Rehabilitation in the Living Environment after Neurologic Injury

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New Technologies for On-Demand Hand Rehabilitation in the Living Environment after Neurologic Injury

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Mechanical and Aerospace Engineering

by

Diogo Schwerz de Lucena

Dissertation Committee:
Professor David J. Reinkensmeyer, Chair
Assistant Professor Solmaz S. Kia
Professor J. Michael McCarthy
Professor Zoran Nenadic (COI oversight)

2019

To my fathers, my mothers, and my siblings.

To Mari, amor.

CONTENTS

LIST OF FIGURES

LIST OF TABLES

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CURRICULUM VITAE

Educational Experience

Ph.D. in Mechanical and Aerospace Engineering (2019)
University of California – Irvine (Irvine – USA)
Thesis: Robotic and wearable systems for upper extremity assessment and training in the living environment after neurologic injuries

M. S. in Electrical Engineering (2014)
Universidade Federal do Paraná (Curitiba – Brazil)
Thesis: Comparison of Heuristic Optimization Methods Applied to the Optimization of Multiclass Support Vector Machines in the Identification of Motor Activities

B. S. in Mechatronics (Control and Automation) Engineering (2012)
Pontifícia Universidade Católica do Paraná (Curitiba - Brazil)
Thesis: Multiobjective Differential Evolution applied to Filter Optimization
ProUni Scholarship (sponsored by Federal Government of Brazil).

Exchange Program in Electrical Engineering (2011)
Czech Technical University (Prague – Czech Republic)
Erasmus Mundus Scholarship (sponsored by European Union)

Professional Experience

Journal of NeuroEngineering and Rehabilitation (2015 – current)
Position: **Managing Editor**
Activities: Oversee most aspects of the publication. Triage incoming papers for quality and scope. Support the selection of Associate Editors to handle each publication. Review and support scientific peer-review process.

ARCBYT, INC (2018 – 2019)
Position: **Mechatronic Engineer (consultant)**
Activities: Develop control strategy for a boring robot. Help with vision and planning of future steps towards automation and navigation of the boring process.

University of California, Irvine (Spring, 2018)
Position: **Leader Teacher Assistant in Mechanical Systems Laboratory**
Activities: Lecture classes on microprocessors, steering mechanisms, and robot simulation. Develop robot simulation software. Manage team of 7 teacher assistants and graders. Conduct discussion, laboratory, and quiz sections that supplement lectures. Grade assignments and examinations. Provide input into the development of assignments and exams.

University of California, Irvine (Spring, 2016 – 2017)
Position: **Teacher Assistant in Mechanical Systems Laboratory**
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Volvo Trucks (2012 – 2014)
Position: **Programmer and Leader of Test Automation Team**
Activities: Lead test team automation. Define automation architecture. Develop automation strategies. Design automatic test cases. Develop automated test scripts.

Renault Cars (2012)
Position: **Product Engineering Analyst**
Activities: Design strategies for flex fuel engines in Simulink (Matlab). Generate test cases and reports for module in loop tests. Simulate strategies. Develop and manage code and strategy defects. Design system mock-ups. Support to software validation and integration team.

Renault Cars (2011 – 2012)
Position: **Intern in Calibration/Software development**
Activities: Support calibration and software development for flex engines' control units. Test and evaluate new calibrations in the vehicles. Test calibration equipment.

Awards

ICAMPAM 2017 Travel Grant (2017)
Travel grant to present work on wearable sensors at ICAMPAM 2017 Conference
Science without Borders Scholarship for Ph.D. Students (2013)
Federal Government of Brazil
Full fellowship for 4 years of Ph.D. Program

Academic Honors (2012)
Pontifícia Universidade Católica do Paraná
High academic performance and best student award

Finalist – Go Green in the City, New solutions for energy management (2012)
Schneider Electric's Contest in Paris

Erasmus Mundus Scholarship (2010)
European Union
1 year of studies in Czech Republic

ProUni Scholarship (2007 – 2012)
Federal Government of Brazil

Full fellowship for Bachelor Program

Publications and Presentation

Speaker on Wearables for Hand Rehabilitation After Stroke: Extending Rehabilitation into the Community at **WearRAcon 2019** (Scottsdale, AZ)

Keynote lecture on Robotics for Regenerative Rehabilitation after Neurologic Injury at the **7th Annual International Symposium on Regenerative Rehabilitation** (Seattle, WA) on behalf of Prof. David Reinkensmeyer (available online at https://ar3t.pitt.edu/education/webinars/)

Lucena, D.S., Rowe, J.B., Chan, V., Cramer, S.C., and Reinkensmeyer, D.J. 2018 Using the Manumeter for continuous feedback on hand activity after stroke: preliminary results. **2018 ASNR Annual Meeting**

Da Silva, W. R., Lucena, D.S. Concrete Cracks Detection Based on Deep Learning Image Classification. Proceedings of **ICEM 2018**, 2(8), 489

Lucena, D.S., Stoller, O., Rowe, J.B., Chan, V. and Reinkensmeyer, D.J., 2017. Wearable sensing for rehabilitation after stroke: Bimanual jerk asymmetry encodes unique information about the variability of upper extremity recovery. **IEEE International Conference in Rehabilitation Robotics 2017**, 1603-1608

Jin, B.J., Lucena, D.S., et al., 2017 Combination of Epidural Stimulation, Serotonergic Agonist, and Rehabilitative Training Promotes Forelimb Recovery in Cervical Spinal Cord Injured Rats. **Society for Neuroscience**, Washington DC

Finotto, V.C., Lucena, D.S., da Silva, W.L. and Valášek, M., 2015. Quantum-Inspired Evolutionary Algorithm for Topology Optimization of Modular Cabled-Trusses. **Mechanics of Advanced Materials and Structures**, 22(8), pp.670-680

Lucena, D.S., Sebastiani, M.T. and Coelho, L., 2013. Multiobjective Differential Evolution applied to Filter Optimization. SBAI IX (IX Simpósio Brasileiro de Automação Inteligente).
Sebastiani, M.T., Lucena, D.S. and Coelho, L., 2013. Multiobjective Genetic Algorithm applied to Optimization of Distance and Security in Routes of Transportation. **SBAI IX (IX Simpósio Brasileiro de Automação Inteligente)**

Maidl, G., Lucena, D.S. and dos Santos Coelho, L., 2013. Economic Dispatch Optimization Of Thermal Units Based On A Modified Firefly Algorithm. **COBEM (22nd International Congress of Mechanical Engineering)**

Da Silva, W.R., Lucena, D.S., and Luiz, R., 2011. Surface appearance of precast elements fabricated using self-consolidating concrete. **Concrete International**, 33(10), pp.39-44

Lucena, D.S., Cocco, V. and Coelho, L., 2010. Quantum Evolutionary Algorithm with Multiobjective Approach applied to Optimization of Economic Dispatch in Electric Power Systems. In **XVIII CBA (XVIII Congresso Brasileiro de Automação)**, 1, pp. 1-8

Research Experience

Robotic upper extremity rehabilitation for non-human primates (2014 – current)
Development and exploration of the use of an in-cage upper extremity robotic trainer, called the Bimanual Vending Machine (BVM), for non-human primate models of cervical SCI in a stem-cell therapy treatment

Wearable sensing for hand-use continuous feedback (2015 – current)
Development of the Manumeter, a device that can track and display the number of movements of the wrist and hand using magnetometers in a wristwatch-like unit and a magnetic ring worn on the index finger, as well as arm movements using accelerometry.

Bimanual wearable sensing for rehabilitation after stroke (2017)
Exploration of principal component analysis with bimanual wrist accelerometry collected from stroke survivors during their daily activities to characterize novel kinematic measures of jerk and acceleration asymmetry

Rodent Robot Rehabilitator of the Upper Extremity (2016 – 2017)
Design and development of a robot for the rehabilitation of rodents after neurologic injury

Quantum Evolutionary Algorithm with Multiobjective Approach applied to Optimizing Economic Dispatch in Electric Power Systems (2009 – 2010)
Sponsored by CNPq

Human-Machine Interface for Calculation of Performance Indicators in Industrial Systems (2008 – 2009)
Sponsored by CNPq

Technical Skills

Programming languages: Python; C; C++; Matlab®
ROS (Robotic Operating System)
SolidWorks
Eagle Software – PCB Design

ABSTRACT OF THE DISSERTATION

New Technologies for On-Demand Hand Rehabilitation in the Living Environment after Neurologic Injury

By

Diogo Schwerz de Lucena

Doctor of Philosophy in Mechanical and Aerospace Engineering

University of California, Irvine, 2019

Professor David J. Reinkensmeyer, Chair

High-dosage rehabilitation therapy enhances neuroplasticity and motor recovery after neurologic injuries such as stroke and spinal cord injury. The optimal exercise dosage necessary to promote upper extremity (UE) recovery is unknown. However, occupational and physical therapy sessions are currently orders of magnitude too low to optimally drive recovery. Taking therapy outside of the clinic and into the living environment using sensing and computer technologies is attractive because it could result in a more cost efficient and effective way to extend therapy dosage. This dissertation developed innovative wearable sensing algorithms and a novel robotic system to enhance hand rehabilitation. We used these technologies to provide on-demand exercise in the living environment in ways not previously achieved, as well as to gain new insights into UE use and recovery after neurologic injuries.

Currently, the standard-of-practice for wearable sensing of UE movement after stroke is bimanual wrist accelerometry. While this approach has been validated as a way to monitor amount of UE activity, and has been shown to be correlated with clinical assessments, it is unclear what new information can be obtained with it. We developed two new kinematic metrics of movement quality obtainable from bimanual wrist

accelerometry. Using data from stroke survivors, we applied principal component analysis to show that these metrics encode unique information compared to that typically carried by conventional clinical assessments. We presented these results in a new graphical format that facilitates the identification of limb use asymmetries.

Wrist accelerometry has the limitation that it cannot isolate functional use of the hand. Previously, we had developed a sensing system, the Manumeter, that quantifies finger movement by sensing magnetic field changes induced by movement of a ring worn on the finger, using a magnetometer array worn at the wrist. We developed, optimized, and validated a calibration-free algorithm, the “HAND” algorithm, for real-time counting of isolated, functional hand movements with the Manumeter. Using data from a robotic wrist simulator, unimpaired volunteers and stroke survivors, we showed that HAND counted movements with ~85% accuracy, missing mainly smaller, slower movements. We also showed that HAND counts correlated strongly with clinical assessments of hand function, indicating validity across a range of hand impairment levels.

To date, there have been few attempts to increase hand use and recovery of individuals with a stroke by providing real-time feedback from wearable sensors. We used HAND and the Manumeter to perform a first-of-its-kind randomized controlled trial of the effect of real-time hand movement feedback on hand use and recovery after chronic stroke. We found that real-time feedback on hand movement was ineffective in increasing hand use intensity and improving hand function. We also showed for the first time the non-linear relationship between hand capacity, measured in the laboratory, and actual hand use, measured at-home. Even people with a moderate level of clinical hand function exhibit very low hand use at home.

Finally, the challenge of improving hand function for people with moderate to severe injuries highlights the need for novel approaches to rehabilitation. One emerging technique is regenerative rehabilitation, in which regenerative therapies, such as stem cell engraftment, are coupled with intensive rehabilitation. In collaboration with the Department of Veteran Affairs Gordon Mansfield Spinal Cord Injury Translational Collaborative Consortium, we developed a robot for promoting on-demand, hand rehabilitation in a non-human primate model of hemiparetic spinal cord injury that is being used to synergize hand rehabilitation with novel regenerative therapies. Using an innovative bimanual manipulation paradigm, we show that subjects engaged with the device at a similar rate before and after injury across a range of hand impairment severity. We also demonstrate that we could shape relative use of the arm and increase the number of exercise repetitions per reward by changing parameters of the robot. We then evaluated how the peak grip force that the subjects applied to the robot decreased after SCI, demonstrating that it can serve as a potential marker of recovery.

These developments provide a foundation for future work in technologies for therapeutic movement rehabilitation in the living environment by establishing: 1) new metrics of upper extremity movement quality; 2) a validated algorithm for achieving a “pedometer for the hand” using wearable magnetometry; 3) a negative clinical trial result on the therapeutic effect of real-time hand feedback after stroke, which begs the question of what can be improved in future trials; 4) the nonlinear relationship between hand movement ability and at-home use, supporting the concept of learned non-use; and 5) the first example of robotic regenerative rehabilitation.

CHAPTER 1. INTRODUCTION

1.1. Upper extremity rehabilitation after neurologic injuries

Neurologic injuries are often life-changing events because they typically cause significant sensory motor impairments. Spinal cord injury and stroke are among the most common injuries. There are approximately 300,000 people living with a spinal cord injury (SCI) and approximately 17,000 new cases every year [1]. The statistics for stroke are even more staggering, with an estimate of one new stroke every 40 seconds and more than 7 million survivors currently in the United States alone [2]. Most of the survivors of these injuries will live with impairment of the upper extremity that diminishes quality of life [1], [3]–[6].

After a neurologic injury, spontaneous recovery is expected. The amount of recovery of motor function depends on the location and size of the lesion and the initial residual capacity [7], [8]. Recovery happens with alterations in activation patterns, modulated in response to motor activity, changing the strength of existing (or creating new) neural connections [9] – this process is called neuroplasticity. Neuroplasticity is amplified shortly after injury (days, weeks, or months); however, the ability to reorganize neural circuits is also retained in the chronic phase after a neurologic injury [10].

High-dosage exercise therapy has been proven beneficial to enhance neuroplasticity and drive recovery [11], [12]. The specific exercise dosage necessary for motor recovery is unknown, but from animal models it has been estimated that improvement in motor capacity happens with hundreds to thousands of repetitions every day[13]. However, studies that observed hundreds of occupational and physical therapy sessions for stroke and SCI rehabilitation counted an average ~40 upper extremity repetitions per session [12], [14], orders of magnitude too low to optimally drive recovery.

Robotic technologies can automate hand training, increasing intensity of practice through repetitive, meaningful tasks. Virtual environments and computer gaming can be coupled with robotics to make the therapy more engaging and stimulating. Moreover, robotic therapy has the potential to alleviate some aspects of the labor-intensive of one-on-one physical therapy. A large number of studies have now investigated the safety and shown the efficacy of robotic therapy [15]. However, robotics technologies are bulky, complex, and expensive and therefore typically only used in flagship rehabilitation facilities, drastically limiting accessibility to these devices, particularly in the chronic phase after a neurologic injury.

Extended time in the clinic is desirable, however, costs are prohibitive and there is a limit on how long and intensive therapy sessions can be. Taking therapy outside of the clinic and into the living environment using sensing and computer technologies is attractive because it could result in a more cost efficient and effective way to extend therapy dosage.

1.2. Rehabilitation in the living environment

In the living environment, rehabilitation of the upper limb after stroke is more difficult than rehabilitation of the lower extremity. One of the main reasons for is the phenomenon called upper extremity, learned non-use [16]. For the lower extremity, walking requires both legs to be involved. But, for upper extremity use, most tasks can be accomplished with one hand. Particularly for those more severely impaired, any use of the impaired hand is highly effortful and frustrating. Due to the unilateral nature of the motor impairment after a stroke, patients progressively favor using their unimpaired limb over the impaired. Even though this compensatory behavior helps stroke survivors to be more independent and perform activities of daily living, the lack of exploration and use of the impaired limb further reduces the capacity of the limb perpetuating what has been call the “vicious cycle” [17].

Currently, the most-used method of rehabilitation in the living environment is a booklet of exercises, in which a therapist prescribes several exercises using a printed handout. However, patients find such an approach demotivating and there is low compliance [18].

To diminish the learned non-use phenomenon, Taub and colleagues proposed constraint-induced movement therapy (CIMT), one of the most successful types of upper extremity therapy after stroke [19]. CIMT and robotic therapy are two rehabilitation techniques with the most evidence to have benefits to patients [7]. In CIMT patients restrain the use of the unimpaired limb (using a mitten) for 90% of their waking hours. Patients are also required to do 6 or more hours a day of massed and intensive movement training with the impaired limb. This increases arm use, promotes neuroplasticity, and helps patients out of the vicious cycle of learn non-use. Several studies have shown the efficacy of CIMT in different phases of stroke recovery [20], including neuroplasticity evidenced by neuroimaging and neurophysiological techniques. CIMT has been successfully extended to be used in the living environment with similar results to those seen in the clinic [21], [22]. However, to my knowledge, there are no commercially available technologies for helping to complete CIMT at home.

Functional electrical stimulation (FES) has also been used out of the clinic. Gabr and colleagues tested the feasibility of FES integrated with electromyography in the home setting and observed increase in active extension of the impaired wrist in 12 stroke survivors [23]. In a similar study, Hara and colleagues used a power-assisted FES system integrated with electromyography signal to induce muscle contraction with twenty stroke survivors that showed significant increases in range of motion and reduction in upper extremity spasticity [24]. A review of FES applied to stroke rehabilitation, at home and in the clinic, concluded that FES can effectively improve arm function in stroke survivors [25] and similar results have been observed for rehabilitation after spinal cord injury [26]. A few devices are commercially available using this technology, e.g. Neuromove NM900, BioMove 3000, and Bioness H200.

Another home rehabilitation method that has had increased attention in the past years is telerehabilitation. Telerehabilitation consists of any rehabilitation service using communication technologies, allowing therapists access to patients from remote areas and easier monitoring people after a neurologic injury. There are a variety of therapeutic techniques that fall under the telerehabilitation class and studies have shown promising results for stroke and spinal cord injury [27], [28]. For example, phone/video conferencing between patients and therapists, in which therapists can guide patients through exercises and reinforce correct behavior [27], [29] and other methods of interacting with virtual reality environments have been used. Recently, a large randomized controlled trial compared the efficacy of home-based telerehabilitation and in-clinic therapy across the United States [30]. One-hundred and twenty-four chronic stroke patients were randomized into the two groups. The telerehabilitation group received a system with a computer and 12 gaming input. For 18 supervised and 18 unsupervised 70-minute therapy sessions, patients exercised, played functional games, and received stroke education. The in-clinic group received matched levels of therapy with a rehabilitation therapist. Both groups had similar level of motor improvements, showing the efficacy of this method.

Robotic-assisted rehabilitation has also been used for telerehabilitation, where low-cost robotic systems coupled to virtual reality environments are used at home while therapists monitor and help progressing patients. For example, the Java Therapy system used a force feedback joystick in which patients interacted with a web-based game and therapists would evaluate progress and prescribe exercises [31]. A more recent study looked at the feasibility of a joystick handle that assist the impaired limb depending on user input [32]. Nineteen stroke survivors that used the device for eight weeks with minimal supervision significantly increased scores in clinical measures. Other studies have shown feasibility and efficacy of robotic rehabilitation in the home setting [33], [34]. However, more studies are still needed to prove their safety and cost-effectiveness in the home setting, and there are few or no commercial robotic therapy devices for home use.

Other home therapy devices that are commercially available have shown positive results. Some of them are the Saebo products (SaeboFlex, SaeboReach, and SaeboStretch) that are functional orthoses for stretching and massed practice of the hand, wrist and elbow [35]. Another promising device is the MusicGlove, an instrumented glove with sensor on the fingertips and on the side of the index finger, which is coupled with a musical computer game similar to GuitarHero in which patients need to perform functional grips to hit the notes scrolling down on the screen [36]. In a randomized controlled trial with the MusicGlove, participants exceeded the target number of recommended completed grips as they engaged with the game over three weeks at home. A significant increase in self-reported amount and quality of use of the impaired hand were reported using this passive device.

Even though these methods of home therapy have shown promise, and in some cases have been shown comparable to in-clinic, one-on-one therapy sessions, they still require patients to stop their daily activities, go to a training station, don devices, and practice for a limited amount of time. People with neurologic injuries engage in many other activities throughout the day, and an intriguing possibility is to use integrated daily activity to increase the use of the upper extremity. Here, we explored wearable sensors that can be worn throughout the day, monitoring quality and quantity of upper extremity and promoting hand use.

1.3. Wearable sensing for monitoring out-of-the-clinic upper extremity use

Advances in miniaturization and processing speed have allowed development of wearable sensing systems for real-world, out-of-the-clinic, monitoring of human activity [37]. There are many commercially available wearable devices for health-related monitoring and feedback, e.g. electrocardiogram, heart rate, body temperature, blood pressure, step counting, and others [38]. To our knowledge, only two devices specifically for providing real-time feedback of upper extremity activity are available in the market, the ARYS by yband therapy AG (different versions are available for clinics and for the end user) and MiGO by Flint Rehab, but neither of them have been tested in clinical trials. In research, several groups are exploring the use of accelerometers placed on the wrist for that end.

For rehabilitation after stroke, the use of wrist-worn accelerometers as a means of quantifying UE use in the community living environment has been increasing [37], [39],

[40]. This approach can quantify people's actual use of their UE as opposed to their capability, which is what is measured by standard clinical assessments, and as opposed to subjectively perceived use of the UE, which is what self-assessment questionnaires measure.

Taub and colleagues [41] were the first to propose the threshold-filtered transformation to measure functional upper extremity out of the lab (even though some other techniques had been previously tested but the results were not satisfactory when compared to electromyography signals [42]). The threshold-filtered algorithm divided the accelerometer data into 2-second bins and classified each bin as active or not active. The number of active bins was the count for that period. This approach had high accuracy and low variability (SD = 3%) for the 5 activities of daily living they tested. However, wearing an accelerometer only on the impaired wrist suffers from overestimation when people are walking and might not be adequate to measure upper extremity use outside of the clinic, when the unimpaired hand is not the dominant hand [43]. Using the ratio of counts of the impaired to unimpaired arm has been reported to be more accurate and better correlate with actual arm use and is mostly used in current studies.

In particular, several studies have used bimanual wrist accelerometry to measure upper extremity in the living environment. Uswatte and colleagues used the ratio between impaired and unimpaired hand to validate the self-report Motor Activity Log [44]. Lang and her group have showed compelling results using accelerometers to quantify bilateral, real-world, upper extremity activity after stroke [45]–[47]. They developed new ways to interpret bimanual accelerometry data and to extract relevant information from it, including showing that bimanual activity asymmetry strongly correlates with clinical assessments. Liao and colleagues showed an increase in bilateral arm use in a randomized controlled trial with robotic therapy, where an increased bilateral arm use was observed for those in the robotic therapy group [48]. Another study determined the usability of bimanual wrist accelerometry pre- and post-CIMT in children with cerebral palsy [49].

Wrist accelerometry for measuring upper extremity activity in stroke survivors has been well-tested in and out of the laboratory. Even though strong correlations with clinical assessments have been observed, those in-lab experiments have shown that accelerometers worn near the hand count acceleration from the whole body as a combination of wrist, arm, trunk, and lower extremity movements rather than isolated hand movement, which is a key indicator of functional upper extremity use [50].

Hand activity can be quantified using instrumented gloves, goniometers, and motion capture systems, but such devices are cumbersome to wear and socially unacceptable, restricting their use to the laboratory. Liu and colleagues have recently proposed the use of a finger accelerometer as a companion to wrist accelerometry and showed correlation to a gold-standard metric of hand use [51]. However, in order to house and power the electronics, the ring is bulky and further studies are needed to prove user acceptability.

In our laboratory, we demonstrated the viability of a device (the “Manumeter”) to detect finger and wrist movement while looking like jewelry. The user wears a small permanent magnet as a ring, and a sensing/logging wristband detects changes in the magnetic field as the ring moves. Distance travel by the finger was calculated by estimating joint angle using a radial basis function network applied to the magnetic field differential. In a first study, Rowe and colleagues showed that the Manumeter could accurately track wrist flexion and extension, radial and ulnar deviation, and finger flexion and extension on a single subject performing 12 tasks at different intensity levels. When compared to angles obtained with a goniometer device, most of the error stayed within 6.4 degrees for all the angles estimated in the 15-minute in lab testing [39]. The same concept was validated for multiple days and multiple subjects (N=7). Consistent levels of accuracy were seen after a week without recalibration of the device and angle estimation accuracy was above 92% on average for multiple days of testing [52].

Rowe and colleagues also compared wrist accelerometry measurements with the Manumeter’s finger distance travelled to evaluate the relationship between arm and hand use in 12 tasks performed in the lab. Even though arm was a significant predictor of hand use, the relationship of arm and hand was substantially different among tasks. For example, hand to arm use was 12 times larger for some distal specific tasks compared to proximal tasks. Four stroke survivors wore the Manumeter at home, during daily activities and a wide spread, consistent with that seen in the laboratory exercises, was observed in the relationship of arm and hand use [53] as participants performed many tasks throughout the day. These results show the utility of measuring hand activity.

1.4. Using feedback to increase upper extremity use

Wearable technologies have been proven useful for reversing disuse and promoting health and function of people without disabilities. For example, a Journal of the American Medical Association review [54] indicated that pedometer feedback is an effective way to increase walking activity and thereby improving difficult-to-change health outcomes such as body mass index and blood pressure.

There is strong evidence that extrinsic feedback can improve motor learning after stroke [55], [56]. In an international effort, Dobkin and colleagues showed that giving a simple time feedback and positive reinforcement after a daily 10-meter walk resulted in significant faster walking speed compared to the age-matched control group. This increase in speed was enough that participants in the feedback group had the ability to walk at a pace associated with unlimited community mobility [57].

Giving feedback on upper extremity use has the potential to help stroke survivors out of the vicious learned non-use cycle into a virtuous cycle of hand usage and increase in performance. Some studies have proposed methods for this type of feedback. Markopoulos and colleagues, in 2011, tested usability and credibility of a wrist accelerometer device with graphical display for continuous feedback. Nine stroke survivors wore the one device on each wrist (wirelessly connected) and survivors gave positive feedback on usability and credibility [58]. Luster and colleagues, in 2013, evaluated the user tolerance and acceptance of a vibro-tactile cueing device embedded in a fabric wristband. Five stroke survivors wore one band on each hand (wirelessly connected) and wrist accelerometry using the filtered-threshold algorithm [41] was applied to measure upper extremity activity. Participants performed in-lab exercises and reported high level of comfort and usability of the device [59]. To our knowledge, no further tests have been reported on these devices.

More recently, in 2018, Held and colleagues proposed a protocol for a multi-center, randomized controlled trial using bimanual wrist accelerometry. They propose giving feedback through lights on a wrist-worn device (ARYS by yband therapy AG) and on the companion Android App. The feedback is given on the activity is counts, calculated as with a 0.1 g threshold over 1-minute aggregated accelerometer data, which is compared to a pre-defined daily goal (not specified). Daily goals will be updated based off measurements of arm use in the previous week. Vibrotactile feedback would be given when 30-minute sedentary periods are detected. All feedback will be regarding the impaired hand and the purpose of the second device is unclear [60]. No further publications on this trial have been found.

Only three trials have evaluated the effects of feedback on upper extremity activity. In [61], chronic stroke survivors wore accelerometers on both wrists and received feedback in terms of amount of use and disparity of use between arms was given twice a week by a therapist. Although the feedback increased participants perception of paretic UE use, no change on actual use of the arm (as measured using the accelerometers) or in functional outcomes were found. A different approach was taken in [62], where subacute stroke survivors wore an accelerometer on the paretic wrist for three continuous hours a day. Participants were prompted to move their arm every five minutes. Significant increase in some clinical outcomes and a significant difference in amount of arm use between groups was observed, however baseline data for amount of arm use were not collected and there is no evidence that groups were balanced at baseline. The WAVES feasibility study has been the only one to give continuous feedback on amount of UE use after stroke, in which LED feedback and vibrotactile reminders on a wrist worn device were used in a multicenter pilot-controlled trial for acute stroke survivors. Amount of arm use as measured with the wrist-worn accelerometer were not presented and no comparative statistical analysis was performed [63].

The effects of continuous feedback on upper extremity use remain unknown. Moreover, all the aforementioned studies used wrist worn accelerometers to measure activity; however, in-lab experiments have shown that UE activity counts obtained using wrist-accelerometry measure accelerations from the whole body as a combination of wrist, arm, trunk and lower extremity movements rather than isolated, more functional hand movements.

1.5. Regenerative rehabilitation in non-human primates

The discussion so far has centered on technological approaches to increasing rehabilitation therapy dosage, or in other words, increasing active use of and practice with the impaired upper extremity. When neurologic damage is severe, increasing limb activity will likely only have only limited ability to improve limb movement ability. Regenerative rehabilitation is an emerging field that seeks to understand and optimize potential synergies between regenerative therapies (such as stem cell therapy) and rehabilitation [64]–[66]. In the context of paralysis following neurologic injuries such as spinal cord injury (SCI), the premise is that any candidate regenerative treatment should be coupled with intensive rehabilitation because sensory motor activity shapes the structure and connectivity of neurons [67], [68]. Optimal functional outcomes will likely depend on optimal forms of movement practice that drive appropriate connectivity.

Regenerative medicine has struggled to scale treatments from rodents to humans, with several failed clinical trials in the context of stroke and spinal cord injury. Inserting an intermediate step of studying non-human primates is helping to address this problem [69]–[71]. However, a key need is emulating the rehabilitative movement training that individuals with neurologic injury will receive in any clinical trial. Failing to intensively train a patient following a stem cell graft would be unethical because it would potentially reduce the chances of functional benefit from the treatment. Yet there are currently few standardized protocols or technologies for delivering intense rehabilitative movement training in large animal models. Thus, it is currently difficult to replicate the movement-related inputs that are likely to modulate the effectiveness of neuroregenerative treatments.

In the context of hand recovery, previous studies have typically used pellet retrieval tasks (such as the Brinkman or Klüver Board), to quantify and train monkey hand function (reviewed in [72]). This task requires subjects to retrieve pellets from wells of different orientations and depths. While performing this task allows hand dexterity to be quantified, it requires substantial finger dexterity to perform, and a human trainer to replenish the wells. Other studies have used sleeves that cover the hand to encourage use of the hand in hemiparetic models, but beneficial neuroplasticity still depends on active training of the hemiparetic hand [73]. One can emulate rehabilitation therapy using chair-based exercises with a human trainer, but this strategy is labor intensive and difficult to quantify.

For humans, as reviewed above, robotics technologies have been developed to automate hand movement training following neurologic injury [74], [75]. Robotic therapy now refers to a diverse set of technologies and algorithms that can match or improve the clinical benefits achievable with conventional rehabilitation therapies [76]. There is currently a need to "reverse-translate" such robotic therapy device to help solve the problem of emulating rehabilitation therapy in large-animal models in regenerative medicine.

1.6. Outline of the dissertation

Rehabilitation of the upper extremity is paramount to achieve independence and increase quality of life after a neurologic injury. This dissertation focuses on understanding upper extremity use after neurologic injuries and developing tools to help the rehabilitative process in the living environment. In particular, we developed a new algorithm for measuring hand activity in the living environment using magnetometry (CHAPTER 2). We performed a first-of-its-kind randomized controlled trial of the effect of real-time hand movement feedback on hand recovery after chronic stroke (CHAPTER 3). We also used wrist accelerometry to develop new metrics of arm movement quality (CHAPTER 4). Finally, we developed an innovative robot for promoting on-demand hand use by non-human primates receiving regenerative treatments for spinal cord injury (CHAPTER 5).

Specifically, in CHAPTER 2, we describe the development and optimization of a calibration-free, computationally simple algorithm for counting hand movements with a wrist-worn device – the Manumeter. We characterized performance of the “HAND” algorithm in three ways – using a robotic simulator to mimic wrist and finger movement performed with different hand sizes at different speeds and amplitudes; by conducting in-laboratory arm and hand movement experiments with unimpaired and stroke survivors; and lastly with persons with a s stroke wearing the Manumeter for one day at home during their daily activities.

In CHAPTER 3, we report the results of a randomized controlled trial of the “Pedometer for the Fingers” – i.e. the combination of the HAND algorithm with the Manumeter. 20 participants with chronic stroke wore the Manumeter for three weeks. Half of the group did not receive hand movement feedback (the Manumeter display showed the time of day). The other received real-time feedback on amount of hand movement detected with the HAND algorithm, along with a daily goal. We aimed to answer the question of whether real-time feedback on amount of hand use can help people with a chronic stroke increase hand use at home.

In CHAPTER 4, we explore the use of bimanual wrist accelerometry in the living environment with stroke survivors. Most studies using wrist accelerometry found strong correlations between accelerometry metrics and clinical assessments. However, we hypothesized that bimanual wrist accelerometry carries additional information compared to the information that standard clinical assessments typically produce. Using principal component analysis on data from the living environment that we acquired from nine persons with a stroke using bimanual wrist accelerometers, we verified that accelerometry can provide information that is distinct from clinical measurements. In particular, we propose a new measure of the quality of spontaneous UE movement: bimanual jerk asymmetry. We also introduced a new method of data visualization for bimanual wrist accelerometry.

In CHAPTER 5, we present the design of a robot for promoting hand use in a non-human primate model of hemiparetic spinal cord injury. The goal is to synergize hand rehabilitation with novel regenerative therapy. The robot implements a novel bimanual manipulation paradigm that induced use of the impaired limb in the hemiparetic injury model. We show that subjects taught to interact with the robot before injury engaged with the device at a similar rate after injury across a range of hand impairment severity. We show how we could shape relative use of the arm by changing parameters of the robot controller and that we could increase the number of exercise repetitions per reward by lowering reward probabilities or increasing task difficulty. We also evaluate how the peak grip force that the subjects applied to the robot decreased after SCI, demonstrating that it can serve as a potential marker of recovery.

CHAPTER 6 reviews the main contributions of this work and discusses directions for future research.

CHAPTER 2. CALIBRATION-FREE HAND MOVEMENT COUNTING ALGORITHM

2.1. Contributions

Background: Wearable sensors that count steps are useful for monitoring health interventions and increasing walking activity. Currently, however, there are few ways to non-obtrusively count finger and wrist movement, limiting the use of wearable sensing for health applications related to the hand, such as hand rehabilitation after neurologic or orthopedic injury. We previously developed the Manumeter, a wristwatch-like device that uses magnetometers to sense the movement of a magnetic ring worn on a finger. We developed an algorithm for the Manumeter that estimates wrist and finger joint angles during activities of daily living, but the algorithm requires subject-specific calibration and off-line computation. **Methods:** Here, we describe the development and optimization of a calibration-free, computationally-simple algorithm for counting hand movements ("HAND" – Hand Activity estimated by Nonlinear Detection), which uses a thresholding approach based on magnetic field changes. We characterized performance of the HAND algorithm in three ways. First, we used a robotic simulator to mimic wrist and finger movement performed with different hand sizes at different speeds and amplitudes. Second, unimpaired adults (n=8) and persons with hand impairment after a stroke (n=20) performed movement tests in the laboratory, including hand-only and arm-only exercises, upper-extremity clinical assessments, and a walking test. Third, persons with hand impairment after a stroke (n=29) wore the Manumeter for one day at home during their daily activities. **Results:** For the robotic simulator and hand-only movement test, the HAND algorithm counted movements with ~85% accuracy, missing mainly smaller, slower movements. The arm-only exercise caused about 4% crosstalk in HAND counts. HAND counts correlated strongly with the numbers of blocks the persons with a stroke picked up in a minute (i.e. their score on the Box and Blocks Test – BBT, r=0.68), indicating validity across a range of hand impairment levels. Walking caused spurious

HAND counts, but fewer than conventional wrist accelerometry (0.2 counts/step vs 0.95 counts/step). The spontaneous HAND counts that participants achieved at home depended nonlinearly on the BBT score measured in the clinic (r=0.68), consistent with the hypothesis that some people with measurable hand function in lab still rarely use their hand for function at home. **Conclusions:** These results show how the HAND algorithm implements a “pedometer for the hand” for people with varying levels of hand impairment.

2.2. Introduction

Wearable sensing systems are increasingly being used for at-home monitoring of health-related parameters [37]. In the context of movement quantification, there are many systems available for providing feedback about the amount of movement of the lower extremities (i.e. step counters and pedometers [38]), but there are few available for providing feedback about the amount of movement of the upper extremities (UE). For example, to our knowledge, there are only two commercial products that provide real-time feedback about arm movement (ARYS by yband therapy AG and MiGo by FlintRehab). Both devices use wrist accelerometry to quantify arm activity, but neither appears to have been tested in a clinical trial.

Wrist accelerometry has, however, been used in research settings to quantify real-world UE activity, with many studies focusing on adults who have experienced hemiparesis after a stroke [39], [41], [44], [77] [45]–[47]. The most common approach is to count an arm movement every time the wrist acceleration exceeds a threshold, possibly with a weighting factor that scales the count based on the magnitude of the acceleration peak. Studies have shown a strong correlation between the ratio of the activity of the more and less affected limb with clinical UE assessment scores [refs]. Additional information about movement can also be extracted using other kinematic metrics such a jerk asymmetry, and may relate to the quality of movement [78].

Wrist accelerometry has limitations, however. Accelerometers worn on the wrist count acceleration of the whole body, which is a combination of wrist, arm, trunk, and lower extremity movements [50], [79]. This provides a source of noise that is difficult to filter out when attempting to isolate the amount of UE movement. Further, measuring hand activity directly, or combining measures of hand and arm activity, would theoretically allow more accurate feedback about functional use of the UE, since various functional tasks require different combinations of hand and arm movement [80].

Hand activity can be quantified using instrumented gloves, goniometers, and motion capture systems, but such devices are cumbersome to wear and socially unacceptable, restricting their use mainly to the laboratory. Liu and colleagues recently proposed the use of a finger accelerometer as a companion to wrist accelerometry and showed correlation to a gold-standard metric of hand use [51]. However, in order to house and power the electronics, the ring is bulky and further studies are needed to prove user acceptability. In our laboratory, we demonstrated the viability of a device – the Manumeter – to detect finger and wrist movement while looking like jewelry. The user wears a small permanent magnet as a ring, and a sensing/logging wristband uses an array of magnetometers to detect changes in the magnetic field as the ring moves. We developed an algorithm that uses these changes with a neural network to estimate the wrist and finger joint angles. We characterized the accuracy of this algorithm and showed suitability of the Manumeter for at-home use [39], [52], [53]. However, estimating joint angles in this way requires subject-specific calibration and computationally demanding algorithms. In addition, pilot users commented that total angular distance travelled by the joints was not an intuitive measure of their amount of hand use.

To overcome these issues, here we describe the development and testing of a novel algorithm called HAND (Hand Activity estimated by Nonlinear Detection). We had two main goals in developing the HAND algorithm, first the hand counts had to be relatable, similar to steps with a pedometer, where one step is a well-defined, easy-to-understand event, and second the algorithm had to be free of user-specific calibration, yet invariant to hand size. These two characteristics were desirable for creating a practical device capable of giving real-time, quantitative feedback of amount of hand use.

The HAND algorithm achieves the aforementioned goals by thresholding the real-time change in magnetic field – a computationally simple approach. As we show below, by choosing a threshold close to noise level but requiring multiple samples to be above that threshold, the algorithm counts both slow and fast, and small and large, movements (similar to how a pedometer counts different types of steps). We also show that this approach assigns counts in a way that is fairly insensitive to hand size, sensor position on the wrist, and magnet orientation. Thus, it does not require user-specific calibration.

In this paper, we first describe the design of the HAND algorithm and then experiments we ran to optimize its parameters. We then describe a series of experiments with unimpaired adults and persons with hand impairment after a stroke, both in the laboratory setting and at home, to characterize and validate HAND counts.

2.3. Methods

2.3.1. THE MANUMETER

The Manumeter (Figure 1) consists of four magnetometers (LIS3MDL) located at 25 and 42 mm away from each other on the corners of a board enclosed in a rectangular watch-like device (sensing range of ± 4 Gauss with a 16-bit resolution), and a six degrees-of-freedom inertial measurement unit (IMU, LSM6DSL, accelerometer range set to ± 4G and gyroscope range set to ± 500 degrees per second, both with a 16-bit resolution). Time and date are managed by a real time clock (PFC2123).

A system-on-a-chip (NRF52, Nordic Semiconductor) with an ARM Cortex M4 CPU and wireless capabilities is used to collect and store the data from the IMU and magnetometers into an on-board 4GB flash memory (MT29F4G01ADAGDWB-IT:G TR) at 52.6 Hz. The data can later be transferred using the Shockburst Enhanced wireless protocol to a secondary board carrying an SD card. The Manumeter also has an OLED display, status LED, and a push button available, but they were not used for the experiments presented in this paper. The Manumeter is powered with a non-ferromagnetic battery (PGEB-NM651825-PCB) with 250mAH rated capacity that lasts for about 24 hours in continuous use or two weeks in stand-by mode. The companion ring (i.e. the magnetic ring), worn on the index finger, is made of silicone and holds a N52 grade neodymium magnet disk of 12.7 mm in diameter and 3.18 mm of thickness.

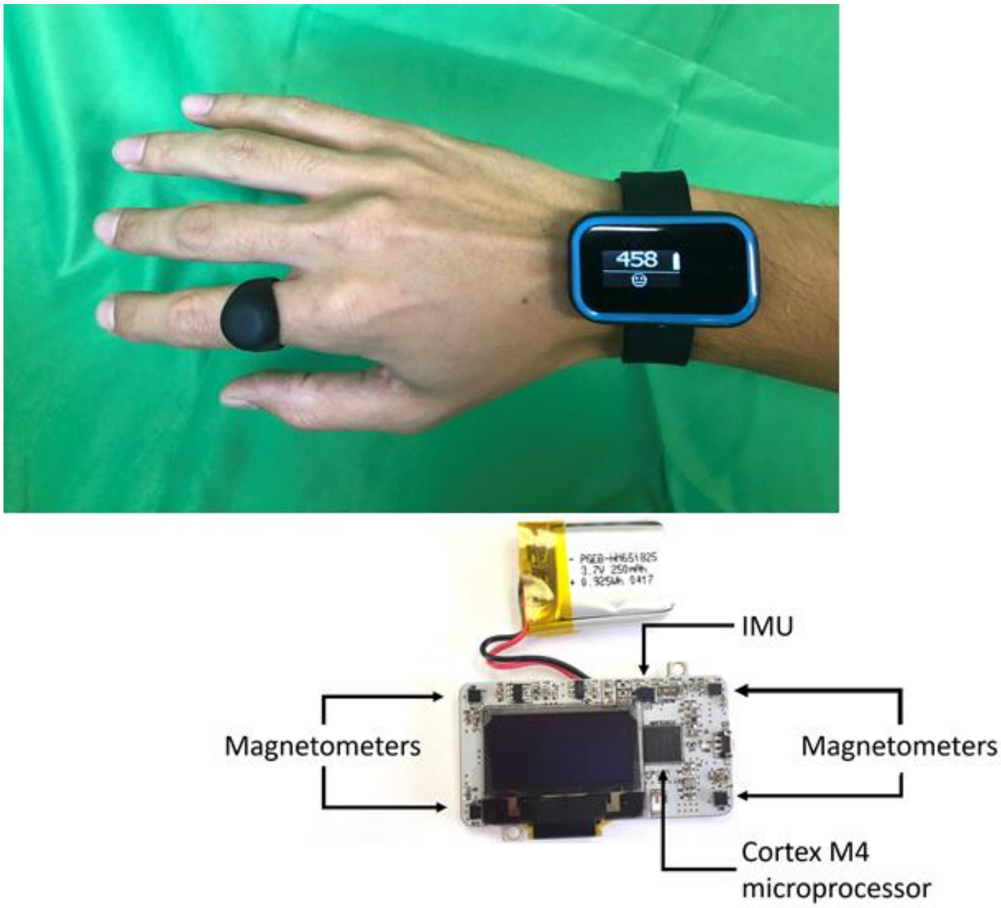


Figure 1. The Manumeter. TOP the Manumeter in the plastic enclosure with the companion magnetic ring. BOTTOM the Manumeter board, with four magnetometers position at the corners of the board, an IMU with 6 degrees of freedom, an OLED display, and the non-ferromagnetic battery. A Cortex M4 microcontroller controls the components.

2.3.1.1. Removing the effects of Earth's magnetic field

As the magnetic field of the Earth is approximately constant over small distances and the strength of the magnetic field of the magnet in the ring drops inversely to the square of the distance, we can remove the effects of the magnetic field of the Earth by taking the differential signal between the magnetometers located closer to the magnetic ring and the ones further away. We used the average of the differential of the two magnetometers on the left side of the housing and the differential of the two magnetometers on the right side of the housing. Because we are taking an average of the two sides, the below algorithm works the same way when the device is placed on either hand. For the remainder of this paper we refer to this average as the “differential reading”. The differential reading ranges in magnitude up to about 0.12 milliGauss, which can be compared to Earth’s magnetic field, which is about 0.5 Gauss in California (and ranges from 0.25 to 0.65 Gauss across the globe).

2.3.2. THE HAND COUNT ALGORITHM

Since we were interested in a threshold-type algorithm, we first analyzed the number of sequential changes of the differential reading in the same direction in each axis; i.e. looking at one axis, how many times in a row did the differential reading increase or how many times in a row did it decrease?. The number of same-direction changes followed a normal distribution with average zero (Figure 3). The HAND algorithm takes advantage of this characteristic applying a semi-heuristic approach. It counts the number of times the differential reading changes in the same direction for two axes with at least a small minimum strength, and considers a hand movement have occurred when this count exceeds a threshold. The algorithm also monitors when one axis changes in the same direction for a (different and larger) minimum number of samples. This method can be interpreted as a peak detection algorithm using a small threshold but takes advantage of the differential reading’s short sampling period, which is approximately an order of magnitude shorter than a typical hand movement (which are 200-700 ms). This allows us to require multiple samples above the threshold before signaling that a movement has occurred.

In total, then, there were four parameters to be selected for the algorithm: 1) *LPcutoff* – which is the low-pass filter cutoff frequency for a 2^{nd}-order Butterworth filter that is applied to the differential readings; 2) the *threshold*, which is the minimum absolute value needed for a differential change in the differential reading (i.e. a “sample”) to be counted as positive or negative for that specific axis (if smaller than the threshold, the sample is ignored); 3) *SDs (2 axes)*, which specifies the minimum sequence length required for samples in the same direction on two axes. This parameter is a scale factor (constrained to be an integer and greater than zero) applied to the standard deviation of the distribution of the same-direction sample sequence length (Figure 2). Note, this distribution (and thus the standard deviation of the distribution) depends on the LPcutoff and threshold parameters, so we calculate the standard deviation after first applying the filter and the threshold to a data set with no hand movement (see arm-exercise below). The scaled standard deviation is rounded to the closest integer and used as the minimum number of same-direction samples required on two axes at the same time to signal that a hand movement has occurred. For example, if the standard deviation of the same-direction sequence length is measured to be 1.5 and we set SDs (2 axes) to 4, at least two axes needed to have 6 or more samples (all positive or all negative) with absolute value greater than the threshold parameter to be counted as a hand movement; 4) *+ SDs (1 axis)* is the number of additional same-direction samples (i.e. over the number indicated by SDs (2 axis)) that we require to occur on a single axis (instead of two axes) to signal that a hand movement has occurred. Expressing it as the number of additional samples makes it explicit that the algorithm applies a more stringent criterion when looking at only a single axis. Figure 3 shows an example of the algorithm applied to wrist extension data.

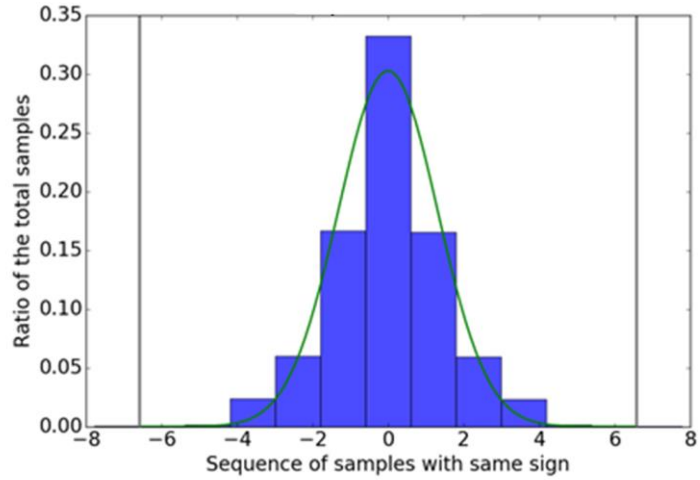


Figure 2. Distribution of the direction of the change in the differential reading for all axes combined.

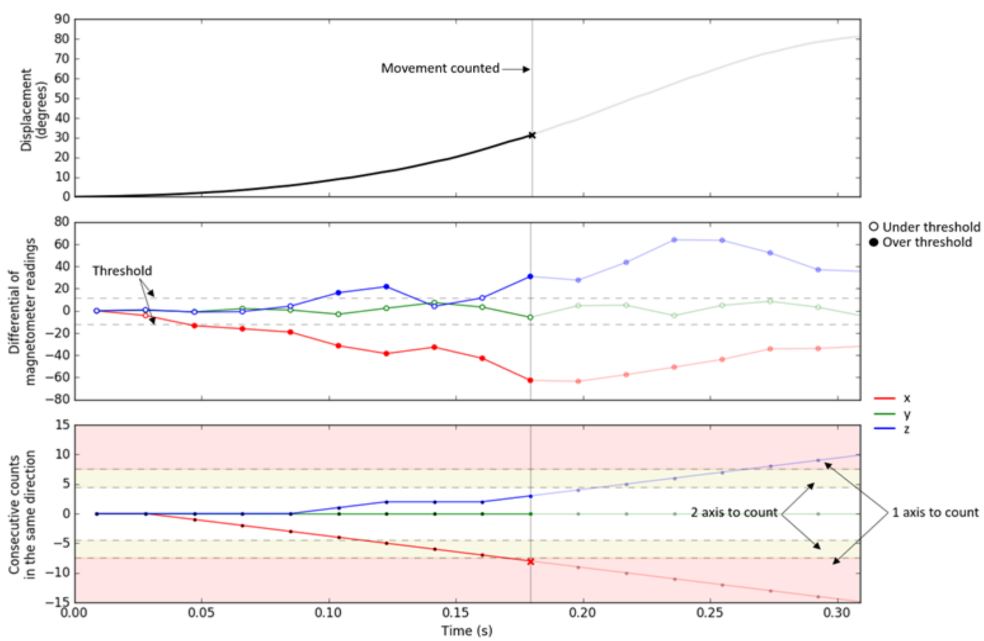


Figure 3. Example of data during a wrist extension with the hand open TOP Displacement in degrees of the wrist during an extension movement; MIDDLE Differential reading for each of the axes (x, y, z); each circle is one data point; dashed lines are the threshold of minimum (positive or negative) change to be counted; empty circles are not counted (within thresholds); filled circles are counted; BOTTOM current count for each of the axes; yellow shaded area is the threshold for two axes together -- when two axes are in the yellow area, it is counted; red shaded area is the threshold for one axis to be counted (in this example, the x axis reached the threshold and the movement was detected). For this figure, LPcutoff = 16 Hz and threshold = 16 differential readings, which results in the standard deviation of 1.2 for the distribution of sample direction count. SDs (2 axes) and + SD (1 axis) were set to 4 and 3, respectively.

2.3.3. UPPER EXTREMITY ACTIVITY COUNTING USING ACCELEROMETRY

To compare the HAND algorithm to another measure of UE activity, we used a variation of the wrist accelerometry algorithm proposed in [41], [79]. Using data acquired from the accelerometers in the Manumeter, we calculated the sum of the absolute change from sample to sample over a running window of 0.25 second (about 13 samples). We applied a peak detection algorithm to the running sum with a threshold of 0.33 g and limited possible detection to a maximum of 4 peaks per second, where each peak was defined as an "activity count". Note that an activity count can be caused by arm movement, but also, by stepping or trunk or hand movement. We selected this variation of an established wrist accelerometry algorithm so that we could compare the output of the HAND algorithm and the activity counts

2.3.4. EXPERIMENTAL PROTOCOL

To evaluate the performance of the HAND algorithm, eight volunteers (six males and two females) with an average age of 26.1 ± 3.0 years performed hand and arm exercises in the laboratory. In addition, two groups of chronic stroke survivors were recruited (see Table 1). All participants provided written consent and the UC Irvine Institutional Review Board approved all experiments.

The first group of participants with a stroke first completed a visit to the laboratory where demographic information was collected. The therapist fitted and donned the Manumeter and the magnetic ring on the affected wrist and index finger of the impaired hand, then performed standard clinical assessments (see below). On leaving the laboratory at the completion of the assessments, participants were instructed to wear the devices throughout the rest of their day, continuing with their normal daily routine until going to take a shower or turning in to sleep, when they were instructed to remove the device. They brought the device back or mailed it back in the next day. We chose to avoid asking the participants to don and doff the device to ensure that they did not swap hands or misplace the device during the data collection. The participants were also asked to log their activities during the day and the time they removed the device, which we used to validate the time stamping of the data.

Table 1. Stroke survivors' demographics for HAND algorithm

	Group 1 (n=9)	**Group 2 (n=20)**
Age	68 ± 9	57 ± 15
Gender (Male [M]/Female [F])	6 M/3 F	16 M/4 F
Time since stroke (monts)	30 ± 23	40 ± 33
Side of hemiparesis (Right [R]/Left [L])	4 R/5 L	12 R/10 L
Type of stroke (Ischemic [I]/Hemorrhagic [H])	6 I/3 H	12 I/10 H
BBT	27 ± 20	21 ± 18
FMUE	43 ± 15	40 ± 13

± standard deviation.

The second group of participants who had experienced a stroke visited the lab two more times (these visits were part of a separate study looking at the effect of real-time hand feedback on motor recovery, the results of which will be presented in the next chapter). The second visit was 4 weeks and the third visit 4 months after the first visit. The clinical assessments were again performed during all visits while wearing the Manumeter. In the last visit, participants performed a 1-minute walk test. Once again, participants were asked to wear the Manumeter at home during their normal daily activities.

2.3.4.1. Upper Extremity Exercises

Unimpaired participants and both groups of individuals with a stroke performed the hand-only and arm-only exercises. For the hand-only exercise, subjects sat on a wooden chair with their arms on the chair's armrest. A tablet was placed at a comfortable distance in front of the subject. The subjects were instructed to mimic the hand postures prompted on the tablet. To perform the change in hand posture, participants were asked to perform one single, smooth movement of the hand. The postures were composed by 5 wrist positions: neutral, flexed, extended, ulnar deviated, and radially deviated, each of them with fingers flexed or extended for a total of 10 hand postures. Each posture was prompted 5 times for 2 seconds for a total of 50 prompts. Figure 4 shows two sample hand postures presented to the participants. The accuracy of the Manumeter was calculated as the percentage difference with respect to the total, actual, number of executed hand postures (i.e. 50).

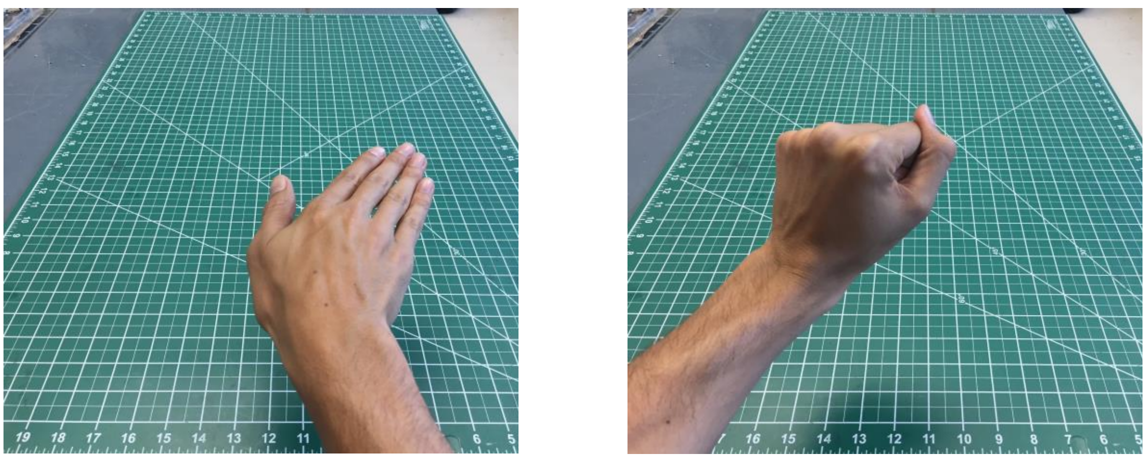


Figure 4. Screenshots of movie that showed desired hand postures to participants during the hand-only exercise.

For the arm-only exercise (AE), subjects donned a splint holding the wrist and the finger in a neutral position and stood. A tablet was again placed at a comfortable distance in front of the subject. Starting with their upper arm next to the body, the elbow flexed at 90 degrees, and the hand in front of the body, participants were asked to perform an arm movement in the direction presented on the screen and come back to the original arm position (two movements per direction). Five directions were used: front, up, right, left, and rotation of the wrist (supination). The directions were presented as text and graphically using arrows. A new direction was prompted every 2 seconds. Each direction was presented 20 times for a total of 200 arm movements (20 x 5 directions x 2 movements/direction). Any hand counts during this exercise were considered false-positives (since the wrist and fingers were held in a splint that prevented their movement), and the “cross-talk” error was calculated as the percentage of the arm movements there were counted as hand movements

2.3.5. CLINICAL EVALUATIONS

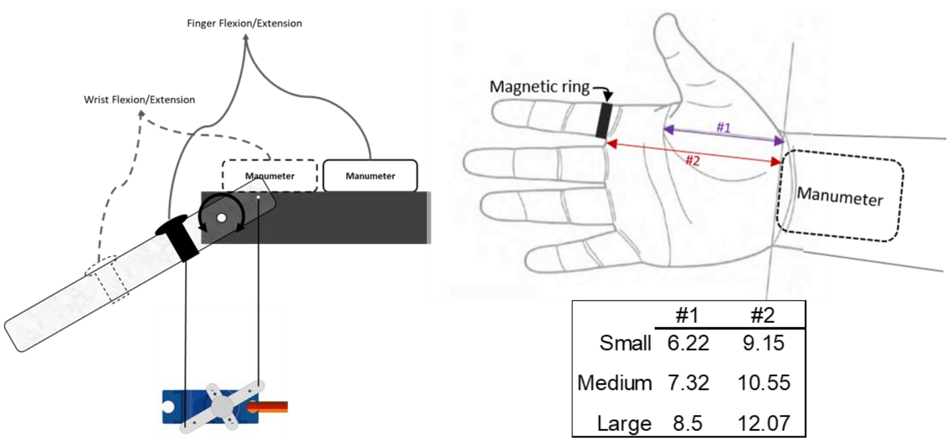
Participants with hand impairment after a stroke were evaluated by an experienced physical therapist on a well-established clinical measure of UE function, the Box and Blocks Test (BBT) [81], and a well-established measure of UE impairment, the Fugl-Meyer Upper-Extremity Subscale (FMUE) [82]. They also walked for one minute while wearing the Manumeter. Participants were instructed to walk at their normal speed in a long hallway while two people counted the number of steps they took. No instructions regarding the Manumeter, hand movements, or finger movements were given during these tests.

2.3.6. ALGORITHM CHARACTERIZATION WITH A ROBOTIC SIMULATOR

To test the HAND algorithm ability to count movements for different hand sizes, movement speeds, and movement amplitudes, we set up a robotic test bed to emulate wrist and finger movements. The test bed had a servo motor connected to an acrylic piece using two strings (Figure 5, left). A magnetic ring was placed on the acrylic piece at different distances depending on the hand size and movement to be emulated. The Manumeter was aligned with the emulated wrist (Figure 5, right).

This setup allowed us to simulate two types of movement: 1) wrist flexion/extension with the metacarpo-phalangeal (MCP) joint extended and 2) finger flexion/extension with the wrist in a neutral position (palm of the hand parallel with the forearm). For wrist flexion/extension, the servo motor emulated the wrist joint and the acrylic piece represented the extended hand and index finger. The distance from the Manumeter to the magnetic ring followed dimension #2 in Figure 5. For the finger flexion/extension, the servo motor emulated the MCP joint of the index finger and the acrylic piece represented the index finger. The distance from the Manumeter to the emulated joint followed the dimension #1 in Figure 5 and the distance from the Manumeter to the ring was kept as dimension #2.

We compared the performance of the algorithm for three simulated hand sizes (small, medium, and large) based on [83]. The small hand used the measurements of the 5th percentile of women's hand, the medium used the average between the median hand sizes of men and women, and the large hand used the 95th percentile of the men's measurements as shown in Figure 5. The movements ranged from 5 to 90 degrees in size with 5 degrees increments. The movement velocity followed a bell-shaped profile with absolute peak angular velocities ranging from 20 to 600 degrees/second with increments of approximately 10 degrees/second. In total, 986 movements were performed for each hand size and each movement type. These movements were then categorized as slow (<200 degrees/second), medium (200 to 400 degrees/second), and fast (>400 degrees/second) based on average absolute wrist movement speed presented in [84].



	#1	#2
Small	6.22	9.15
Medium	7.32	10.55
Large	8.5	12.07

Figure 5. Left: Robotic system to emulate hand movements. For wrist flexion and extension, the wrist joint was emulated, and the acrylic piece represented the hand and index finger together. For finger flexion and extension, the MCP joint of the index finger was emulated and the acrylic piece represented the index finger only. Right: Measurements used for defining the emulated hand sizes in centimeters. The Manumeter was aligned with the wrist crease baseline and the magnetic ring was placed touching the interdigital folds of the index and middle finger. Dimension #1 is from the wrist crease baseline to the intersection of the distal transverse palm crease with the ulnar edge of the palm. This is the best approximation to the center of rotation for the MCP joint of the index finger. Dimension #2 goes from wrist crease baseline (which closely aligns with the center of rotation of the wrist) and the interdigital folds of the index and middle finger.

2.4. Results

2.4.1. SELECTING THE HAND ALGORITHM PARAMETERS

A total of eight unimpaired participants completed the arm-only exercise (AE) and hand-only exercise (HE) while wearing the Manumeter on the left and right arm. To explore the effects of the LP Cutoff and threshold parameters, the SDs (2 axes) and + SDs (1 axis) where defined as 5 and 2, respectively. We applied the hand count algorithm to the AE and HE data using a combination of no filtering, 2, 4, 8, and 16 Hz for the LP Filter and a 0, 2, 4, 8, and 16 to the threshold. The percentage error for AE and HE are presented for each pair of LP cutoff and threshold (Figure 6, left). As can be seen, there is a tradeoff between counting false positives during AE and miscounting during HE. In a range of LP cutoff (4 to 16 Hz) and thresholds (4 to 8 differential readings) both errors are minimized. Based on these results, we selected 8 Hz for the LP Cutoff and 8 for the threshold parameter, which corresponded to an average error of 4.14% for AE and 10.14% for HE.

Using these selected parameters, we explored the effects of SDs (2 axes) and + SDs (1 axis) on the algorithm performance. The average absolute error for the AE and HE were calculated for each combination of parameters. Smaller errors were found when SDs (2 axes) and + SDs (1 axis) added to 7 (Figure 6, right). The overall best performance was obtained with 5 and 2 for SDs (2 axes) and + SDs (1 axis), respectively. For the remainder results presented here, the parameters of the algorithm were set to LP Filter = 8 Hz, threshold = 8 differential readings, SDs (2 axes) = 5, + SDs (1 axis) = 2.

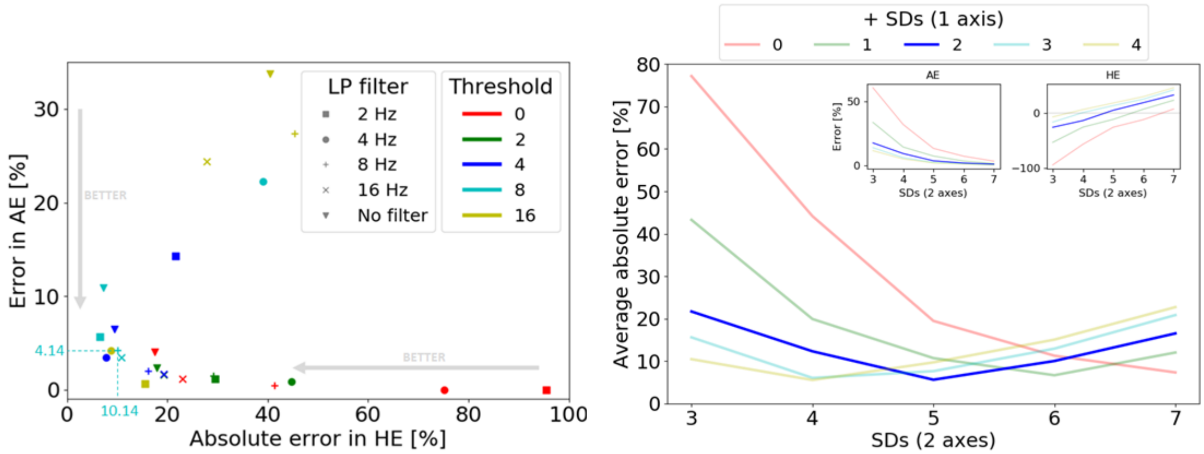


Figure 6. HAND algorithm parameter exploration. Left: Counting error for the arm-only exercise (AE) and the hand-only exercise (HE) for different thresholds (represented by the colors) and cutoffs (represented by the markers) for the low-pass filter. For AE, the error is calculated as the percentage of hand counts to the number of arm-only movements averaged across subjects. For HE, the error is calculated as the absolute difference between the number of hand counts as a percentage to the number of actual hand movements performed averaged across subjects. For both exercises, smaller errors are preferred. The errors for the selected parameters (LP filter cut-off = 8 Hz, threshold = 8) are highlighted. Right: Average error for AE and HE of the hand count algorithm for different SD parameter 2 axes (x-axis) and number of extra SD for 1 axis (represented by the color) using LP filter cut-off = 8 Hz, threshold = 8. The two inner figures show the percentage error for AE (left) and HE (right). The selected SDs are 5 for two axes plus 2 SDs for one axis.

2.4.2. ALGORITHM CHARACTERIZATION: EFFECT OF AMPLITUDE AND SPEED

To understand the effects of movement amplitude and speed on the accuracy of the HAND algorithm, we used a robotic device to emulate two types of hand movements: wrist flexion/extension and finger flexion/ extension. Both types of movements were executed ranging from 5 to 90 degrees in amplitude and 20 to 600 degrees/second for absolute peak angular speed. The emulation started with small and slow movements, going through the range of angular velocities for each amplitude (Figure 7, bottom). Due to limits on angular acceleration, the maximum peak angular speed was reduced for smaller movement amplitudes – similar to what is seen with human wrist movement [84]. The ratio of counted wrist and finger movements to the number of known movements for was calculated for three different hand sizes (Figure 7, top). A line of unity slope was expected if all movements were counted. Instead, the slope is reduced for movements smaller than 20 degrees of amplitude. There are also ripples when peak movement speeds are reset, showing the algorithm misses counts for slow movements. Both effects are more prominent in larger hands. The final accuracy for wrist flexion and extension was 87%, 93%, and 83% and for finger flexion and extension was 94%, 84%, and 70% for small, medium, and large hand, respectively (out of a total of 986 movements for each emulated movement and hand size). Note that, even though there is a decline in accuracy with increase in hand size, the hand sizes emulated here are on the extremes expected for humans (large hand in the 95th percentile for men), so this error can be seen as a worst-case estimate for the algorithm performance.

We analyzed the counting probability for slow, medium, and fast movements separately (Figure 8). For slow movements, and in particular, for finger flexion and extension, increases in hand size decreased the algorithm's performance. That is likely due to the smaller total distance travelled by the magnetic ring for the finger movement compared to wrist movement. For all cases, lower probabilities were found during slow movements with steady decrease for slower movements (below 20% in the worst-case scenario). Due to physical constraints of the emulation system, movement amplitudes were limited to 90 degrees; however, for all movement types, movement speed, and hand sizes (with the exception of large hand, slow movements for finger flexion and extension) the algorithm accurately counted all the movements for the largest amplitudes (75 to 90 degrees) indicating that the same would be true for larger movements. For large hand and slow movements of the finger, the algorithm had a counting probability of 78% for the largest amplitudes.

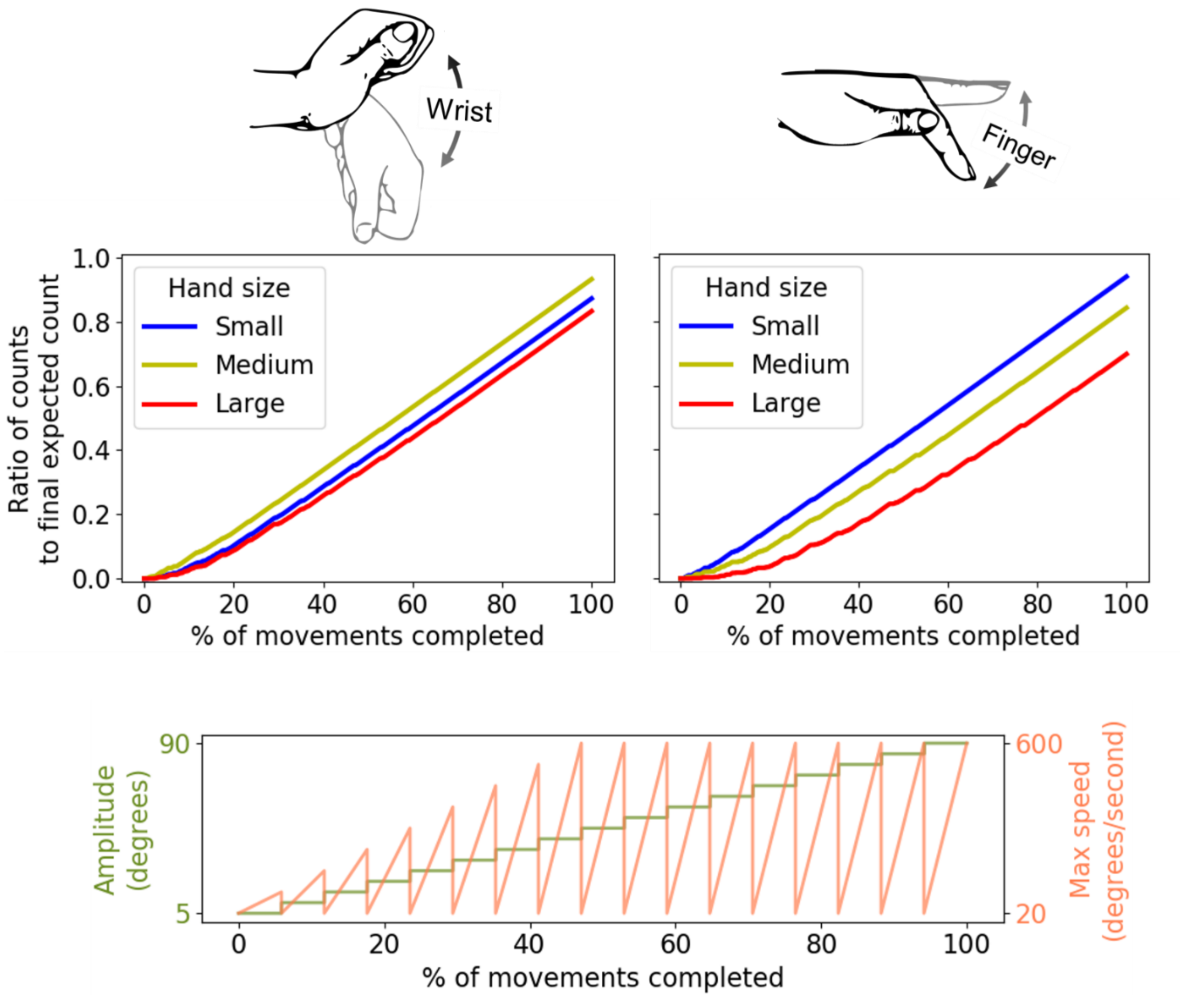


Figure 7. Progression of hand counts for the emulated movements. Top plots show the number of counts over the total expected counts for wrist flexion and extension (left) and finger flexion and extension (right) using emulated data. The bottom figure shows the progression of the emulated movements that increased in amplitude over time sweeping through a range of speeds each amplitude. The range of speeds changes for the different amplitudes due to limitations on the maximum angular acceleration of the motor.

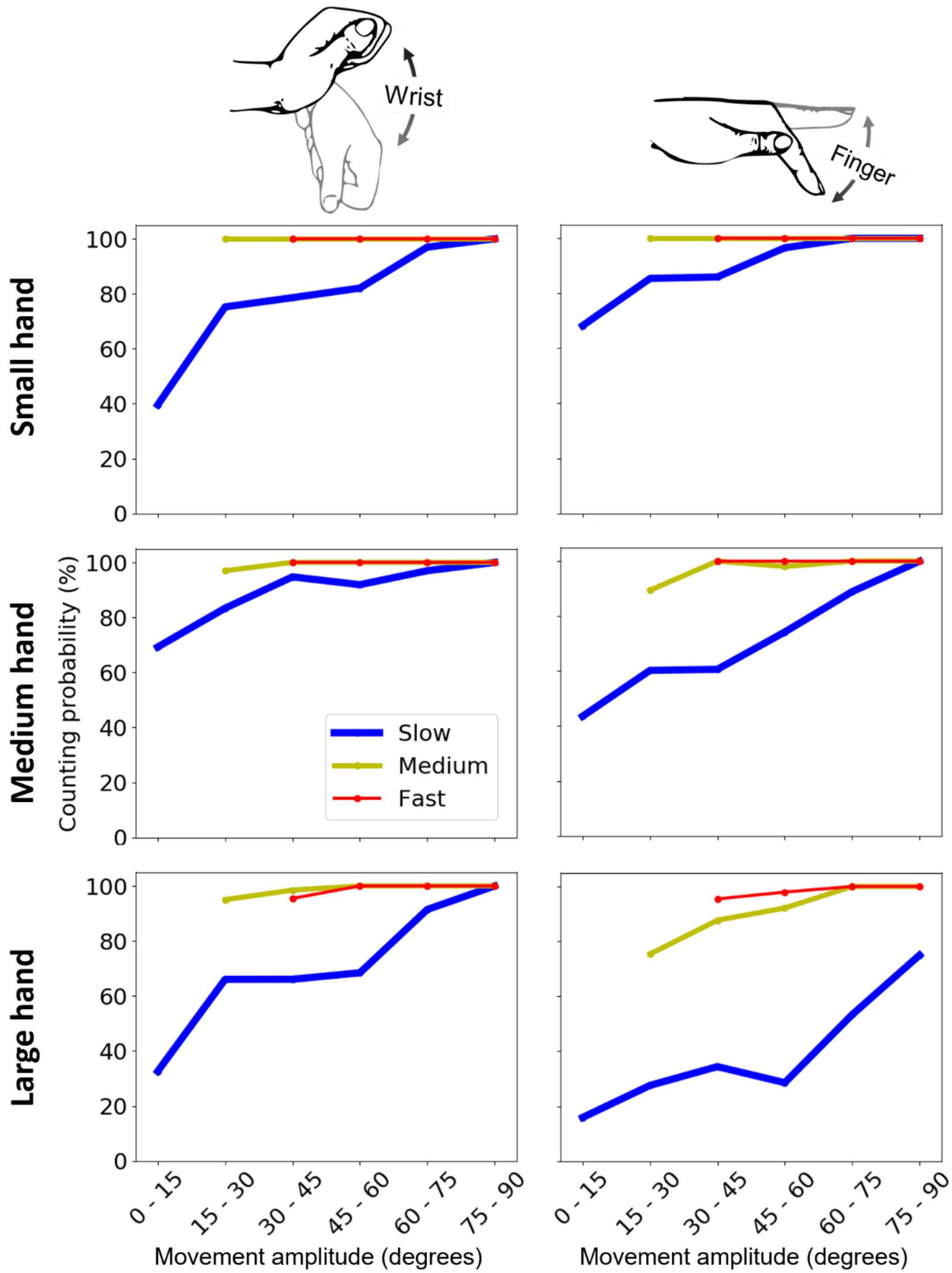


Figure 8. Probability of counting for small, medium, and large hands (top to bottom) for wrist flexion and extension and finger flexion and extension (right to left) using emulated data. For each hand size and exercise type, absolute maximum angular speed of the movement was used to classify it as slow, medium, and fast movement. The probabilities were calculated as the number of hand counts over the number of movements.

2.4.3. LABORATORY-BASED VALIDATION

A total of 8 unimpaired participants and 9 stroke survivors performed the hand-only exercise (HE) with a total of 50 hand movements. Stroke survivors performed the exercise only with their impaired hand. Two of the stroke survivors could not perform the exercise without assistance and were allowed to use their unimpaired hand to help complete the movements. Unimpaired participants performed the exercise twice, one with each hand. Unimpaired participants performed the arm-only exercise (AE) with both arms using a splint -- similar results would be expected for impaired participants, as this exercise is mainly concerned with analyzing the effect of general movements across the local magnetic field, which would be expected to not depend on impairment. For the HE, in which 50 hand movements were expected, the stroke survivors had an average hand count of 60.9 ± 11.1 for the participants who could perform the movements with no assistance and 61 and 57 for the two subjects that self-assisted their hand movement. The unimpaired participants had on average 52.4 ± 4.9 hand counts, a significantly smaller number (t-test, $p=0.03$). This is likely because, during the HE, for some exercises some stroke survivors struggled to change smoothly from one indicated posture to the next, performing the hand posture using two separate movements, which were both counted, increasing the HE count.

For the AE, in which no hand counts were expected, participants had an average of 6.8 ± 8.8 hand counts after 200 arm-only movements (Figure 9).

Twenty stroke survivors wore the Manumeter on their impaired arm while performing the Box and Blocks Test (BBT) and the Fugl-Meyer Upper Extremity Assessment (FMUE) up to three times (separate visits), and during a one-minute walk test (Figure 10). We analyzed how the participants’ clinical scores on these tests related to the hand counts obtained during the test, as well as the “activity counts” obtained from the accelerometers in the Manumeter, using a conventional arm accelerometry algorithm. For this analysis, we computed “hand use intensity” and “activity intensity” as the hand (or activity) counts per minute the participant was active performing the test.

For BBT, there was a strong correlation between BBT score and the hand use intensity ($r = 0.67$, $p < 0.01$) and activity intensity ($r = 0.64$, $p < 0.01$). If the participants with BBT = 0 were ignored, the slope for hand counts and activity counts with respect to BBT score were 0.9 and 1.8, respectively. This was expected, as for each block transferred, participants needed two movements of the arm and one of the hand (releasing the block can usually be done with a small movement that the Manumeter did not count) and the test takes 1-minute. The ratio of hand to activity was approximately constant (0.37 for all participants, 0.5 for participants with BBT>0) across the different levels of impairment ($r = 0.20$, $p = 0.06$).

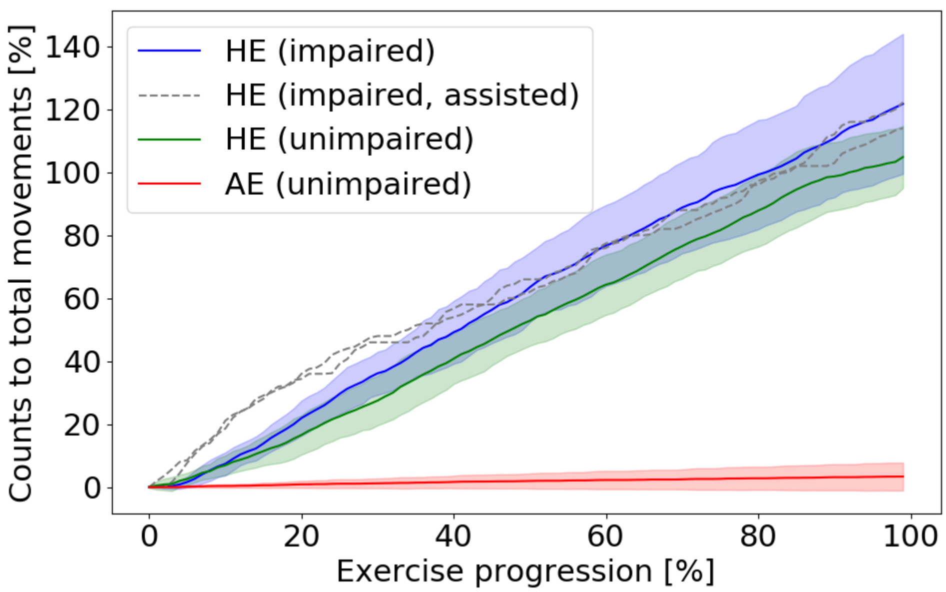


Figure 9. Hand counts for hand-only and arm-only exercises performed in the laboratory, plotted as a function of exercise progression. Subjects were divided into impaired and unimpaired. Two subjects in the impaired group could not perform the HE without assistance of their unimpaired hand and are presented with the dashed lines. The impaired, assisted subjects had an average count accuracy of 82% for HE. The remainder of the impaired subjects (N = 7) performed the exercise without assistance and had an accuracy of 78% for HE. Unimpaired subjects (N=8) had a count accuracy of 95% for HE. Perfect counting for HE would be a line with a slope of 1. Only unimpaired subjects performed AE with 96% of crosstalk. Shaded areas show 1 SD.

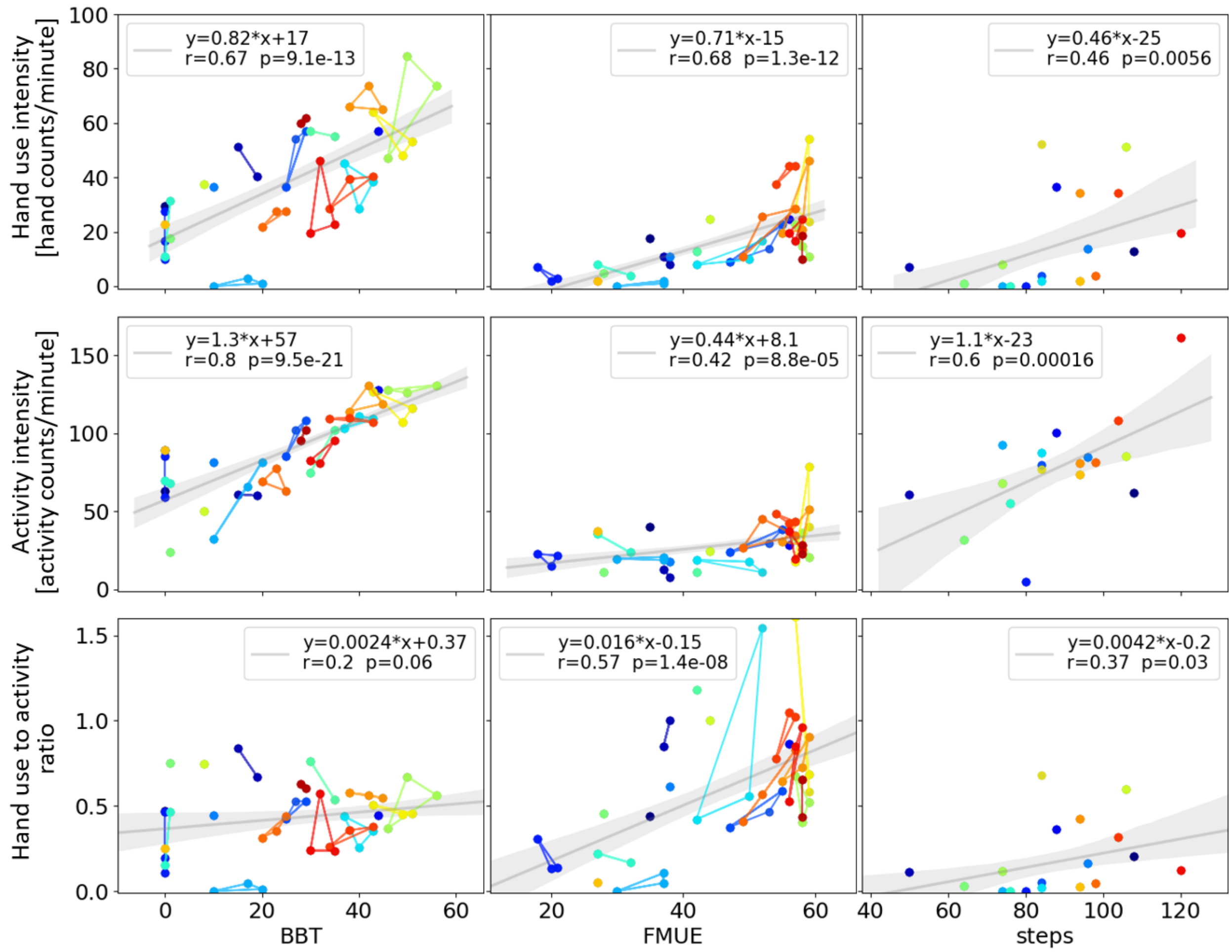


Figure 10. Hand use intensity, activity intensity, and hand use to activity ratio (from top to bottom) during BBT, FMUE, and 1-minute walking test (from right to left) performed in the lab. Linear fit is presented with the shaded area showing the 95% confidence interval. Each color (connected by lines) represents one subject, and each subject can have one to three samples for each test.

For the FMUE tests, there were strong correlations between hand use intensity and FMUE score ($r = 0.68$, $p < 0.01$), and hand to activity ratio and FMUE score ($r = 0.57$, $p < 0.01$). In particular, there was a sharp increase in hand counts after FMUE score of 40. Activity intensity had a weaker, yet significant, correlation with the FMUE score ($r = 0.42$, $p < 0.01$).

For the 1-minute walk test, there was a stronger correlation activity intensity and step counts ($r = 0.6$, $p < 0.01$) than hand intensity and step counts ($r = 0.37$, $p = 0.03$). This shows that the HAND algorithm is less affected by walking than accelerometry alone.

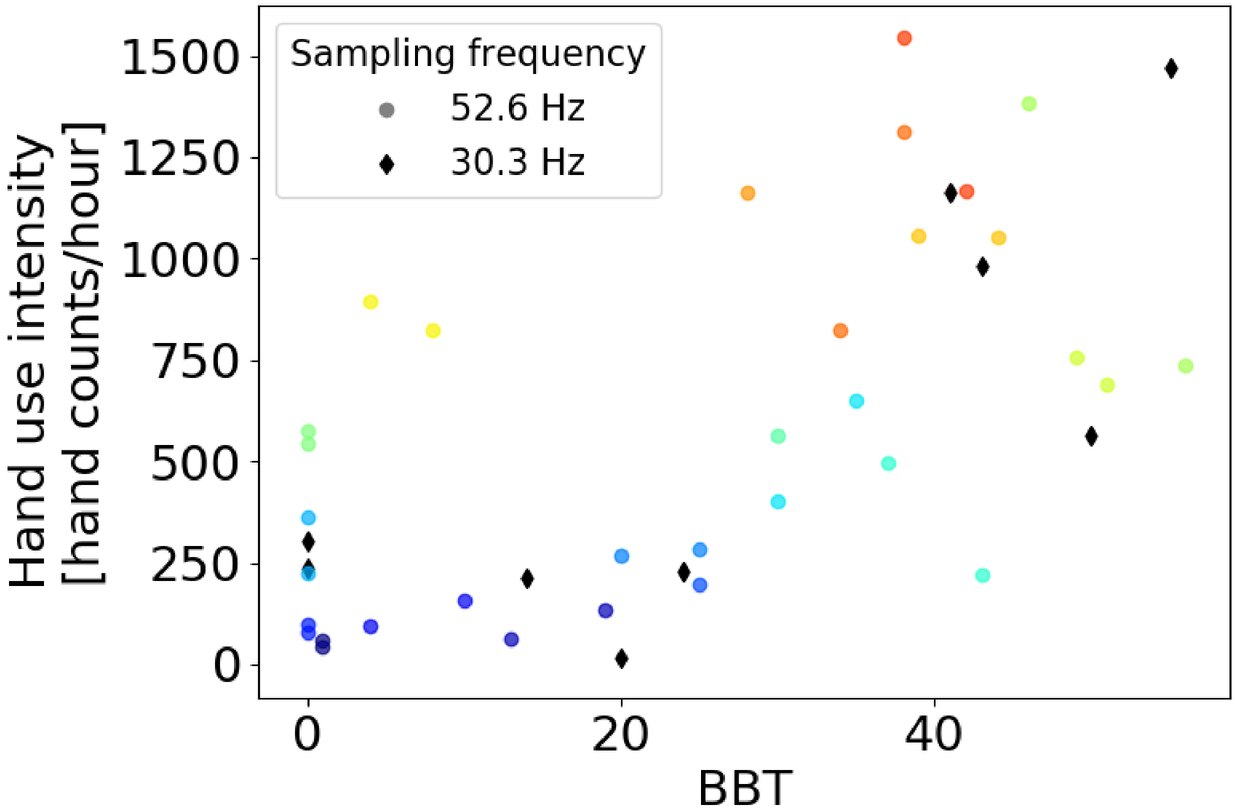


Figure 11. Hand use intensity at home for different levels of impairment using two sampling rates for the Manumeter. Parameters for the 30.3 Hz rate were obtained in a similar manner as presented in this paper for the 52.6 Hz rate.

2.4.4. AT-HOME VALIDATION

A total of 29 stroke survivors wore the Manumeter at home during their daily activities. The first 9 participants wore a previous version of the Manumeter in which data was sampled at 30.3 Hz; however, the same algorithm was used, and selection of parameters was performed in a similar fashion presented here. These participants only wore the Manumeter for one day, for 9.21 ± 1.75 hours. The remainder 20 stroke survivors wore the Manumeter twice, first for 5.88 ± 2.41 hours and then for 6.85 ± 1.98 hours. Data was lost for three participants in their first visit due to technical problems with the device. Intensity of hand use, given as hand counts/hour, were calculated for all participants (Figure 11), and we found a significant correlation between hand intensity of hand use, and BBT score ($r = 0.64$, $p < 0.01$). Participants with low clinical hand function (i.e. low BBT's) generated lower hand counts during spontaneous movement at home. There was a nonlinearity in this relationship, such that there was a sharp increase in hand activity for participants with BBT > 30 (Figure 16).

One participant (BBT = 40) wore the Manumeter at home for 15 days with the magnetic ring and 6 days without the magnetic ring (Figure 12). The amount of hand counts without the magnetic ring was on average 18% of the hand counts during the days with the ring (similar level of activity was seen on both periods). These counts come from distortion in the Earth's magnetic field caused by ferrous metal object or local magnetic field from electronic devices (e.g. cell phones).

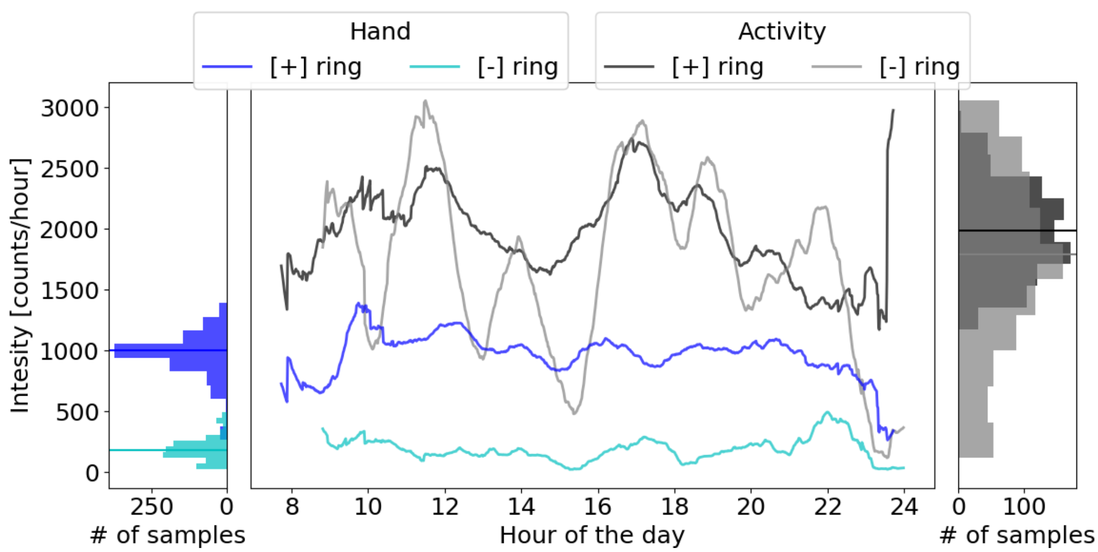


Figure 12. Data for one subject (BBT = 40) using the Manumeter for 21 days. The subject wore the Manumeter without the magnetic ring ([-] ring) for 6 out of the 21 days and with the ring ([+] ring) for the remainder days. The hand and activity counts were smoothed using a 1-hour running window average and presented in the middle plot as the average across the days with and without the ring. The left and right plots show the distribution of hand and activity counts per hour with a line representing the average intensity.

We compared hand use intensity as a function of level of impairment for people with impairment on the dominant side (before stroke) versus those with impairment on the non-dominant side (Figure 13). BBT and hand use intensity were averaged for those with multiple data points to remove dependency. Strong, significant correlations were observed for both cases ($r = 0.78$, $p < 0.01$ for impairment on dominant side and $r = 0.58$, $p = 0.04$ for impairment on non-dominant side). The linear model $hand\ use\ intensity \sim BBT * ImpairedIsDominant$ (where $ImpairedIsDominant$ is a categorial variable determining if the impaired side is the dominant side) showed no significant difference for the intercept or interaction between BBT and $ImpairedIsDominant$ (p=0.35 and p=0.50, respectively). This shows that the hand use intensity as measured with the HAND algorithm was a strong predictor of clinical hand function, independent of impaired to dominant side interaction.

2.5. Discussion

This paper describes and characterizes a calibration-free, computationally simple algorithm for measuring hand activity with the Manumeter, a wearable sensor that looks like jewelry. We optimized the parameters for the algorithm to simultaneously reduce errors in counting hand movement in a laboratory-based exercise, and spurious hand counts from arm-only exercise. We characterized the algorithm performance using a robotic device that emulated wrist and finger movement, and using in-laboratory movement exercises performed by unimpaired participants and stroke survivors. Stroke survivors also wore the Manumeter during a 1-minute walking test and during standard clinical tests (BBT and FMUE). We showed that the Manumeter was less affected by walking than accelerometry alone, and that the hand counts obtained during these tests were strongly correlated with the scores in the BBT and FMUE. Finally, stroke survivors wore the Manumeter at home during their daily activities. We showed that for a range of hand impaired level (BBT score < 30), they exhibited a low level of hand use intensity. Hand use rose quickly for participants with BBT score > 40.

2.5.1. RATIONALE FOR THE HAND ALGORITHM

Previous versions of the Manumeter have successfully measured total distance traveled by the finger and was validated for multiple days with no recalibration. However, it required user-specific calibration, which was sensitive to the positioning of the device on the wrist, and orientation of the ring. The algorithm was computationally complex, and even though it had the potential to be embedded in a wrist-worn device, the power requirements would be elevated.

A computationally simple thresholding approach has been used for wrist accelerometry to measure upper extremity activity out of the clinic and the same technique could be applied to the Manumeter data. However, we have observed lower signal-to-noise ratio with the Manumeter compared to wrist-accelerometry and setting the appropriate threshold for different movements speeds and hand sizes would be challenging. Moreover, even though it has been successful in estimating upper-extremity activity, the counts obtained with the stand thresholding approach for wrist accelerometry were not relatable to the user.

2.5.2. ALGORITHM ACCURACY

We first investigated the Manumeter accuracy through a hand and wrist emulated system with accuracies from 70 to 93%. However, some of the emulated movements were well below human average speeds. Hoffman and Strick asked unimpaired participants to step-track angles with their wrist. In movements of 20 degrees, participants had a peak velocity of 200 degrees/second when asked to move at "half natural" speed [84]. In our analysis, movements with peak velocity below 200 degrees/second (down to 20 degrees/second) were classified as slow movements and were the main source of inaccuracy.

We further investigated the algorithm accuracy through in-lab experiments. An average of 90% accuracy for unimpaired participants and 80% for stroke survivors was found. In both cases the Manumeter tended to overestimate the counts. We attributed some of the inaccuracy to participants doing multiple movements when changing from one posture to the next. This was particularly prominent for stroke survivors who decomposed movements into segments. Pedometers have been reported to have similar accuracy (70% - 90%) when measuring distance traveled outside of the clinic [85]; therefore, there is utility for wearable devices at this level of accuracy. For wrist accelerometry with stroke survivors, the variability in the test-retest has been shown as 39% for raw counts and 3% for threshold-filtered counting [41]. However, these algorithms cannot report metrics of accuracy on number of movements as they are not counting individual movements.

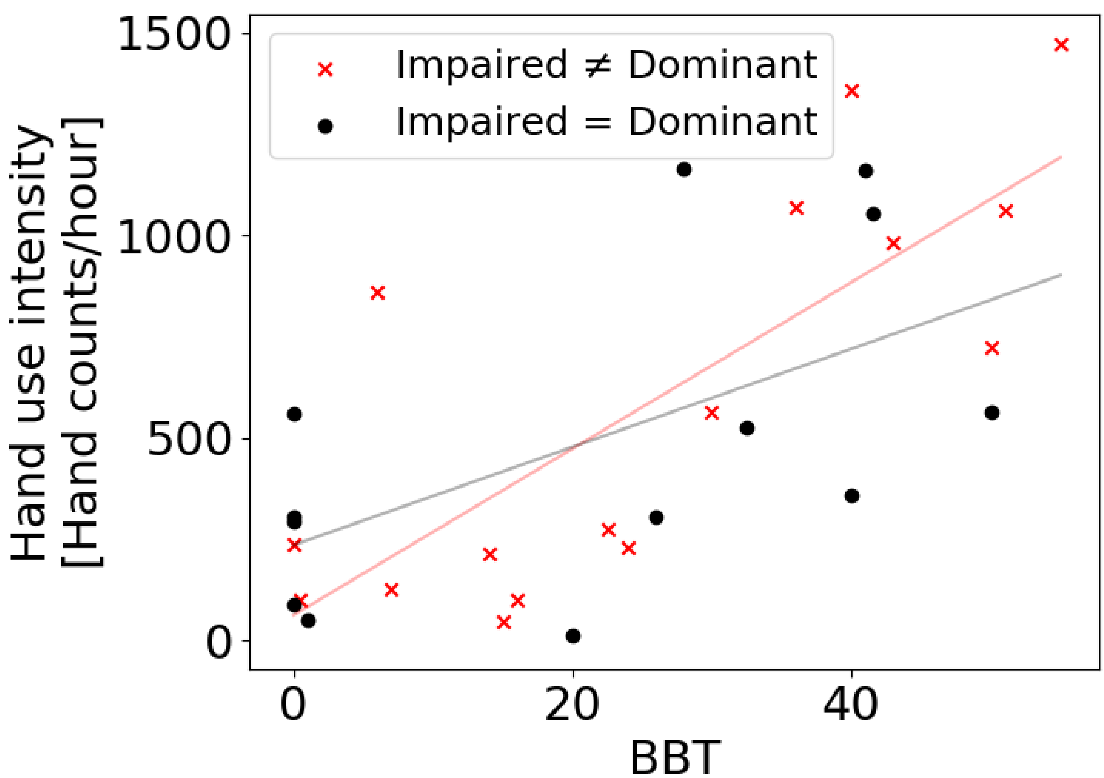


Figure 13. Interaction between handedness and stroke impairment side for hand use intensity versus impairment level. Participants with multiple data points were averaged (both BBT and hand use intensity). Both linear models are significant: ($r = 0.78$, $p < 0.01$) for impairment on dominant side and ($r = 0.58$, $p = 0.039$) for impairment on non-dominant side. The intercept and interaction between BBT and the relation impaired to dominant side were not significant (p=0.35 and p=0.50, respectively).

2.5.3. HAND COUNTS OUTSIDE OF THE CLINIC

Twenty-nine stroke survivors wore the Manumeter at home for one or two days (4 months apart). Intensity of hand use, given as hand counts/hour, was significantly correlated with BBT score (r = 0.64). Two of the low-level stroke survivors (yellow and green on the left of Figure 11) were much younger than the remaining participants (18 and 24 years old compared to an average of 63 years old) and still going to school, which might help them get more hand counts than expected at that level of motor capacity. The remaining participants with BBT < 30 were approximately constant in hand use intensity at around 200 hand counts/hour (similar to the intensity measured when one subject did not wear the magnetic ring for several days). There was a sharp increase in hand use intensity as participants BBT score increased beyond 30. This is consistent with results presented in [86], in which sixty-seven stroke survivors performed several clinical assessments and were classified into low, moderate, and high level of upper limb function using a clustering algorithm across the clinical assessments. A similar threshold of 30 blocks in the BBT was observed to split between high and moderate function levels. The main difference between the moderate and high-level groups was possession (or lack of) fine manual dexterity. Even though similar gross function (e.g. range of motion, speed, and strength) can be observed in both groups, it is the hand dexterity ability of the high-level participants that make the difference when performing everyday tasks [86].

We also analyzed the effects of impairment on dominant and nondominant side. Several studies have investigated these effects on wrist accelerometry [43], [47], [87], with a general agreement that unilateral wrist accelerometry is affected by impairment and dominance side. In [20], it was suggested that unilateral wrist accelerometry might not be useful for measuring arm activity out of the clinic as no significant correlation with clinical assessment (BBT, FMUE, and ARAT) was found. However, the accelerometer was only used for 3 hours each day. In [47], [87] showed similar results for larger populations, in which unimanual and bimanual (ratio of impaired to unimpaired) accelerometry had weak correlation with self-assessed amount of arm use (MAL-AS) when the impaired and dominant side were different (r=0.28 and r=0.32 for [47], [87], respectively) than when they were the same (r=0.56 and r=0.72 for [47], [87]) . These differences were not observed with the HAND algorithm, where hand use intensity was strongly, significantly correlated with BBT for both groups (impairment and dominance on the same or different sides, r=0.58 and r=0.78, respectively). One could suppose that this difference relates to the perception of limb use (MAL) versus capacity, however we see similar correlations for both groups for the subset of participants that took the assessment (r=0.54 for impairment on the nondominant side (N=9) and r=0.52 for impairment on the dominant side (N=11)) An explanation could be that the hand movements measured here are more functional and therefore more connected to actual use of the arm rather than general movements of the limb.

2.5.4. LIMITATIONS AND FUTURE WORK

Even though the HAND algorithm had low crosstalk when arm-only exercises and the walking test were performed, more advanced data processing techniques could be applied to further reduced these erroneous counts. Accelerometry data could be incorporated to support distinguishing hand movements from walking and arm movements. Slow hand movements were the other source of problem. It is not known the amount of slow, small hand movements participants were performing at home. It is possible that the HAND algorithm is undercounting movements for those with lower motor capacity and further investigation would be needed to understand the magnitude of this error.

In an ongoing randomized controlled trial, we are investigating the effects of giving real-time feedback on hand activity to stroke survivors. We hypothesize that quantitative, real-time, relatable feedback on amount of hand use can increase hand activity at home and promote motor recovery. We also aim to explore the HAND algorithm and the Manumeter to quantify hand use outside of the clinic for aged matched control participants.

CHAPTER 3. EFFECTS OF HAND COUNT FEEDBACK ON RECOVERY

3.1. Contributions

In CHAPTER 2, we introduced, characterized, and tested the HAND algorithm. In this chapter, we use the HAND algorithm to test, in a randomized controlled trial, whether providing a daily goal and real-time feedback on amount hand use to stroke survivors can increase their hand activity and drive recovery. **Background:** Quantitative real-time feedback can modulate health-related activity; for example, pedometers are effective in increasing walking activity and overall health. Here, we report the results of a randomized controlled trial of a “Pedometer for the Fingers”, the Manumeter, designed for home use by people with hemiparesis following a stroke. The Manumeter is a wristwatch-like device that senses the magnetic field of a small magnet ring worn on the index finger. We use the HAND (Hand Activity estimated by Nonlinear Detection) algorithm, a calibration-free, computationally simple algorithm that uses the direction of the magnetic field to count hand movements, enabling real-time feedback on the number of hand movements using a built-in display. **Study design:** Assessor-blinded, parallel-group, randomized controlled trial. **Objective:** To test whether real-time feedback on amount of hand use can help people with a chronic stroke increase hand use at home and improve clinical hand function. **Methods:** Twenty participants with a chronic stroke wore the Manumeter for one day (baseline, no feedback) and then for three weeks (with or without feedback). Subjects in the experimental group received a daily goal based on their baseline Box and Blocks Test (BBT) score and real-time feedback on the number of hand movements performed while wearing the Manumeter. Subjects in the control group used the device as a wristwatch. Both groups also received a book of upper extremity exercises tailored by a blinded physical therapist. Participants returned for a follow-up visit three months after the end of the intervention, when they wore the Manumeter for another day (follow-up, no feedback). The primary outcome was the BBT score at 3 months. **Results:** The experimental group wore the Manumeter significantly longer (11.2±1.3 hours per day) compared to the control group (10.1±1.1 hours per day), but did not detectably increase their hand use intensity, as measured with the device. BBT and Motor Activity Log score did not improve significantly at 3 months, although the scores on the Fugl-Meyer Upper Extremity Scale and the Action Research Arm Test did, for both groups. There were no significant differences between groups for any of the clinical outcomes, although there was a trend toward improved clinical hand function for the experimental group in multiple outcome measures. There was a nonlinear relationship between clinical hand function and intensity of hand use, where people with BBT score up to ~25 did not use their hand at home. **Conclusions:** Interactive feedback from a wearable device that senses hand movement was ineffective in increasing hand use intensity and improving hand function. At-home hand use after a stroke is very low even for people with a moderate level of clinical hand function, consistent with the concept of learned non-use.

3.2. Introduction

It is estimated that one person will suffer a stroke every 40 seconds with more than 7 million stroke survivors currently living in the United States alone [2]. More than 50% have long-term upper extremity (UE) motor deficits, reducing their independence and capacity to perform daily activities [5], [6]. These limitations lead to compensatory behavior with the unimpaired limb and reduced use of the impaired limb, which further reduces their performance on daily tasks driving a vicious cycle called learned non-use [17].

Wearable technologies have already proven useful for reversing disuse and promoting health and function of people without disabilities [88], [89]. For example, a recent review in the Journal of the American Medical Association indicated that daily pedometer feedback is an effective way to increase walking activity for people without disabilities and thereby improve difficult-to-change health outcomes such as body mass index and blood pressure [54]. Wearable sensing has the potential to help stroke survivors out of the learned non-use cycle. However, it requires a device capable of giving real-time, relatable feedback about the amount of hand use.

Wrist-worn accelerometers have been increasingly used to measure out-of-the-clinic UE spontaneous activity after stroke. Studies have shown a strong correlation between clinical assessments (e.g. Fugl-Meyer Upper Extremity Scale, Action Research Arm Test, Box and Blocks Test) and UE activity using threshold-based algorithms applied to wrist accelerometry, which validates their ability to continuously assess UE impairment in community living. However, even though extrinsic feedback using wearable sensors has the potential to benefit stroke survivors [56], most studies have applied it to the lower extremity [90]–[92]. Only three trials have given feedback about the upper extremity, with only one of them giving real-time feedback to the subjects.

In [61], chronic stroke survivors wore accelerometers on both wrists and received feedback in terms of amount of use and disparity of use between arms, which was given twice a week by a therapist. Although the feedback increased participants perception of paretic UE use, no change on actual use of the arm (as measured using the accelerometers) or in functional outcomes were found. A different approach was taken in [62], where subacute stroke survivors wore an accelerometer on the paretic wrist for three continuous hours a day. Participants were prompted to move their arm every five minutes. A significant increase in some of the clinical outcomes and a significant difference in amount of arm use between groups were observed, however baseline data for amount of arm use were not collected and there is no evidence that groups were balanced at baseline. The WAVES feasibility study has been the only one to give continuous feedback on amount of UE use after stroke, in which light feedback and vibrotactile reminders on a wrist worn device were used in a multicenter pilot-controlled trial for acute stroke survivors. Amount of arm use as measured with the wrist-worn accelerometer were not presented and no comparative statistical analysis was performed [63].

All the aforementioned studies used wrist worn accelerometers to measure activity; however, in-lab experiments have shown that UE activity counts obtained using wrist-accelerometry measures accelerations from the whole body as a combination of wrist, arm, trunk and lower extremity movements rather than isolated, and more functional, hand and wrist movements. The accelerometry counts are also not relatable to the user (compared to the “steps” measured by a pedometer). To overcome these issues, we have previously developed the Manumeter [39], [52], [53] in which we use changes in the magnetic field caused by a magnetic ring to measure hand and wrist activity, using a wrist-watch-like sensing unit worn at the wrist. We also previously developed and validated an algorithm (Hand Activity based on Nonlinear Detection (HAND)) for counting hand movements with the Manumeter.

The primary goal of this study was to investigate the efficacy of providing real-time feedback on hand function and hand activity after stroke using the Manumeter. We hypothesized that participants who received feedback would significantly improve their hand use intensity, and, consequently, the motor ability of the affected arm.

3.3. Methods

3.3.1. THE MANUMETER

The Manumeter (Figure 14) is a non-obtrusive, jewelry-like device for monitoring wrist and finger movement. Four magnetometers on the edges of a watch-like device measure changes in the magnetic field produced by the movements of the magnetic ring worn on the index finger. Wrist and finger movements are counted using the HAND algorithm, which uses a thresholding approach based on magnetic field changes to count movements (as shown in CHAPTER 2). Wrist accelerometry is obtained using a 6 DOF IMU and an OLED display allows real-time feedback on amount of hand use. A button on the side of the Manumeter changes the information on the screen when that function is enabled.

3.3.2. PARTICIPANTS

Twenty-two chronic stroke survivors were recruited for this parallel-group, assessor-blinded, randomized control trial. Participants in the study met the following criteria: (1) 18 to 80 years of age, (2) experienced one or multiple strokes at least six months previously, (3) Fugl-Meyer Upper Extremity Score < 60, (4) Absence of moderate to severe upper limb pain (< 3 on the 10 point visual-analog pain scale), and (5) Ability to understand the instructions to operate the device. Participants with implanted pacemakers were not allowed in the study for safety reasons concerning the magnetic ring.

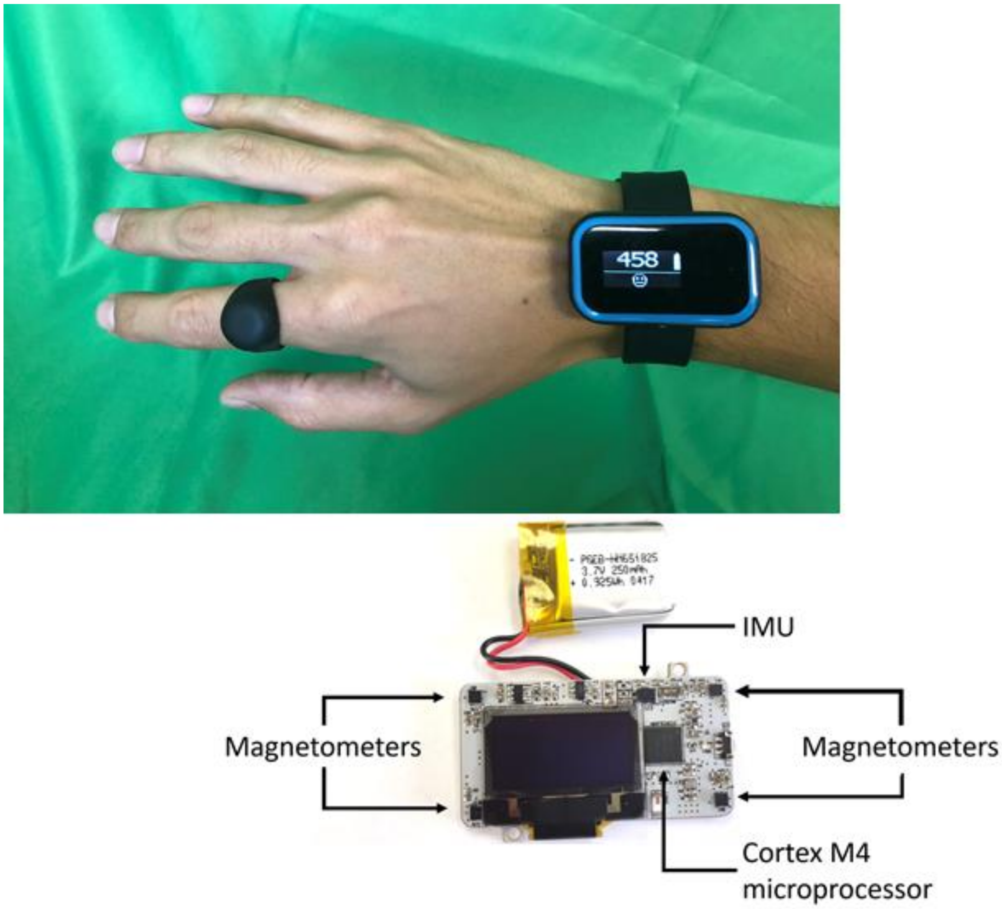


Figure 14. The Manumeter. TOP the Manumeter in the plastic enclosure with the companion magnetic ring. BOTTOM the Manumeter board, with four magnetometers position on the edges of the board, an IMU with 6 degrees of freedom, an OLED display, and the non-ferromagnetic battery. All controlled by a Cortex M4 microcontroller.

We limited the number of participants who scored zero in the Box and Blocks Test at baseline to 6. We instructed these participants to increase hand activity and function through passive movements (e.g. by helping move the impaired hand with the unimpaired hand). Participants were recruited through our database of volunteers from previous studies, the out-patient clinic at the U.C. Irvine Douglas Hospital, and other area hospitals and stroke clubs. All trials were performed at UC Irvine, and all participants provided informed consent according to a protocol approved by the local Institutional Review Board. The study was pre-registered on ClinicalTrials.gov (NCT03084705).

3.3.3. SAMPLE SIZE

Power analysis based on our data from another study on a wearable hand training device, the MusicGlove [93], found an effect size of 1.2 for within subject improvement after three weeks. We expect the increase in activity due to continuous feedback from the Manumeter to at least match this therapeutic effect. Thus, 11 participants in each group gave us an 80% chance to demonstrate a difference between the interactive feedback and control group with a = 0.05 (one-tailed), assuming a <10% dropout rate. Based on our previous work, we expected a low dropout rate.

3.3.4. DAILY GOAL

For each participant, the daily goal was defined based on their score on the Box and Blocks Test (BBT) at the beginning of the study and not changed through the three weeks of therapy. Data from a pilot study (see CHAPTER 2) was used to set daily goals, where 9 chronic stroke survivors (6 males and 3 females) with an average age of 67.9 ± 8.8 years and BBT of 24.7 ± 20.3, five with stroke affecting their dominant side. Participants wore the Manumeter during normal daily activities for an average of 9.21 ± 1.75 hours. We aimed to make the goal particularly challenging for those who have motor capacity but are not using it for daily activities. Participants that had at least 50% of hand capacity with their impaired hand (compared to the unimpaired, measured with the BBT) were set to 1200 counts/hour or 12000 for 10 hours of Manumeter use per day. This number was comparable to those of unimpaired office workers, measured in pilot testing. A linear increase from 540 to 1200 was used for those with BBT ratio from 0 to 50% (Equation 1, Figure 15).

$$Intensity\ goal\ (BBT\ ratio) = \begin{cases} 1320 * BBT\ ratio + 540, BBT\ ratio < 0.5 \\ 1200, BBT\ ratio \geq 0.5 \end{cases} \quad (1)$$

Here, BBT ratio is the ratio of BBT for the impaired and unimpaired hand and intensity goal is given in hand counts/hour. We estimated a Manumeter wear time of 10 hours per day. The daily goal was set as 10 times the intensity goal (hand counts/day).

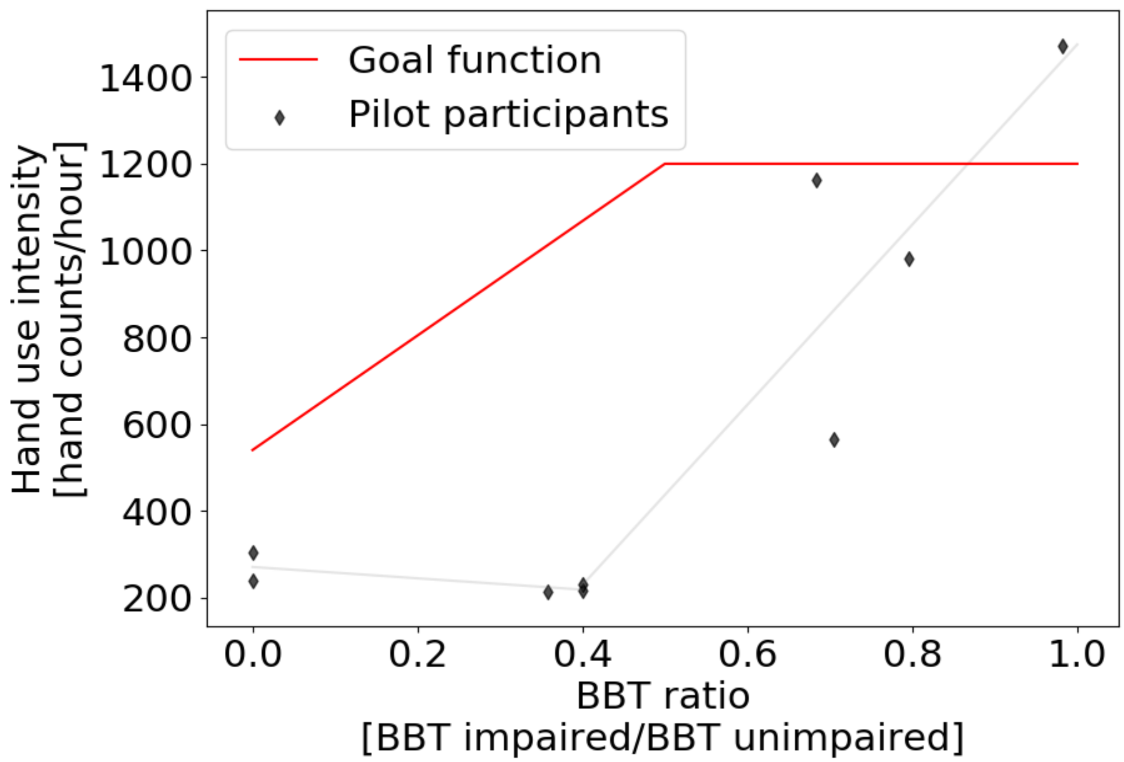


Figure 15. Intensity goal based on BBT ratio. The function was based on data from pilot participants. After intensity goal was defined, the daily goal was obtained by multiplying the intensity goal by the 10 hours of expected daily wear time.

3.3.5. THE EMOJI FEEDBACK

An emoji displayed on the watch screen was used in two different ways during the study. For the first three participants in the experimental group, the emoji represented their performance in the last 10 minutes towards the daily goal. We calculated their current hand count rate (counts/hour for the last 10 minutes) and compared to the goal count rate – the count rate needed to get to their goal at 8 pm. The goal count rate was limited to two times their hourly goal. The emoji's "happiness level" and left-right position on the screen were dependent on the goal ratio (ratio between the current count rate to the goal count rate). Goal ratios between 0 and 1 showed a frowning emoji to the left of the screen (with 0 being all the way to the left) and goal ratios greater than 1 displayed a smiley emoji to the right of the screen (with 2 being all the way to the right). The LED was also an indicator of performance and blinked at a rate inversely proportional to the goal ratio if the goal ratio was below 1 and it did not blink when goal ratio was equal or above 1. The LED only blinked if the Manumeter screen was facing the user. After the daily goal was achieved, the emoji and LED feedback were disabled.

The remaining eight participants in the experimental group had a game on the wrist implemented. The game promoted bursts of hand activity, in which participants had to get 30 hand counts in 30 seconds while the Manumeter screen was facing the user. The emoji moved from left to right and from frowny to smiley as participants increased their hand counts in 30 seconds. When brought all the way to the right (30 hand counts in 30 seconds), a celebration was displayed with a motivating, fun message. Other motivating messages were shown during the game as the user achieved the 25%, 50%, and 75% milestones. The emoji was reset if participants changed the orientation of their arm.

There were two main reasons for changing the type of feedback with the emoji. First, based on feedback from the initial users, we wanted to explore the game-on-the-wrist concept to make the Manumeter more engaging. The Manumeter provides a unique opportunity that participants can exercise their hand while receiving visual feedback on their wrist (as no arm movement is required to detect hand activity). The first type of feedback was not dynamic enough to take advantage of this feature, as it considered data for the last 10 minutes. Second, the first type of feedback required an estimated time for the end of the day, which could vary drastically for out-of-the-clinic use of the Manumeter.

3.3.6. OUTCOMES

The primary outcome was the Box and Blocks Test (BBT) measured three months after completion of the hand training period of the study. Secondary outcomes were Fugl-Meyer Upper Extremity Scale (FMUE), Action Research Arm Test (ARAT), Motor Activity Log (MAL) and amount of upper extremity activity measured using the Manumeter. The BBT (primary outcome) and FMUE were performed at the two baselines, post-therapy, and follow up. The remainder secondary outcomes and other relevant clinical tests were performed at the first baseline, post-training, and at the three-month follow-up.

3.3.7. STUDY DESIGN

The trial was composed of two baselines (three to ten days apart), a post-therapy examination after the three weeks of the hand training interventions, and a follow-up assessment three months after the end of the hand training interventions.

The first baseline consisted of acquiring demographic information, stroke details, hand dominance, and clinical testing: BBT (primary outcome), FMUE, ARAT, MAL, NIH Stroke Scale (NIH SS), grasp and grip strength, Mini-Mental State Exam (MMSE), Modified Ashworth Scale, and Visual Analog of Pain scale. All the clinical data were collected by a blinded physical therapist. During clinical testing, participants wore Manumeters (with the screens turned off) on both wrists, and the magnetic ring on the index finger of the impaired hand (only for BBT of the unimpaired hand was the magnetic ring switched to the index finger of the unimpaired hand). Before leaving the lab, participants were fitted with another Manumeter on their unimpaired ankle and asked to keep the Manumeters and ring on for the remainder of the day during their normal daily activities (other than showering, bathing or swimming). These data were used as baseline to analyze increase of amount of hand use for each participant once they started the hand training intervention. The first baseline was performed primarily in the morning to allow more hours of baseline activity. Participants were asked to ship the Manumeters and the ring back using a prepaid shipping box.

On the second baseline, performed three to ten days after the first baseline, participants played a grip strength tracking game [94] and used the FINGER robot to measure finger proprioception [95]. BBT and FMUE were performed again to establish a steady baseline. Participants then received a book of tabletop exercises tailored to them by a blinded physical therapist and were instructed to practice the exercises for a total of three hours per week.

At the end of the second baseline, participants were randomized into experimental and control group with a 1:1 ratio and balanced for BBT with separated randomizations for participants with BBT > 0 and those with BBT = 0. All participants were asked to wear the Manumeter for the next three weeks on their paretic arm and the magnetic ring on the index finger of that hand, keeping the magnet facing upwards. They were also instructed to orient the screen such that the text was readable from their perspective. The Manumeter is water-resistant, but not waterproof, so participants were instructed to take the device off when showering, bathing, or swimming.

Participants randomized to the experimental group were taught to read each of the three available screens for the Manumeter: the counts screen, the goal screen, and the time screen. The counts screen showed their current number of hand movement performed during the day, battery indicator, and the feedback emoji. The goal screen showed their daily goal of hand counts, number of sprints performed that day, and daily goal of sprints. The time screen showed the current time as well as the emoji feedback (Figure 16). To change screens, participants had to push the button on the side of the device.

Participants randomized to the control group received sham Manumeters that still recorded activity but showed only the time screen (with no emoji feedback). All the participants received a binder with their tailored tabletop book of exercises, instructions on how and when to use and charge the Manumeter.

As an important safety consideration, participants were instructed to remove the magnetic ring when cooking or working with hot metal or in proximity to sharp ferrous objects or MRI machines.

Even though the Manumeter's battery lasted for more than two full days of use, participants were asked to charge the device every night, while sleeping. A binder with this information and instructions on how to charge the device was provided to each participant.

3.3.8. DATA ANALYSIS

For evaluating changes in clinical scores, the average between baseline 1 and baseline 2 was used for BBT (primary outcome) and FMUE, baseline 1 was used for the remaining outcomes. We used a linear mixed-effect model to test significance of time, group (intervention vs control), and time and group interaction on all clinical outcomes. The model allowed random intercept and slope for each participant. All statistical analyses were performed in R with significance level was set to 0.05. Correlations are defined as strong for $|r| \geq 0.50$, moderate for $0.25 \leq |r| < 0.50$, and no correlation for $|r| < 0.25$.

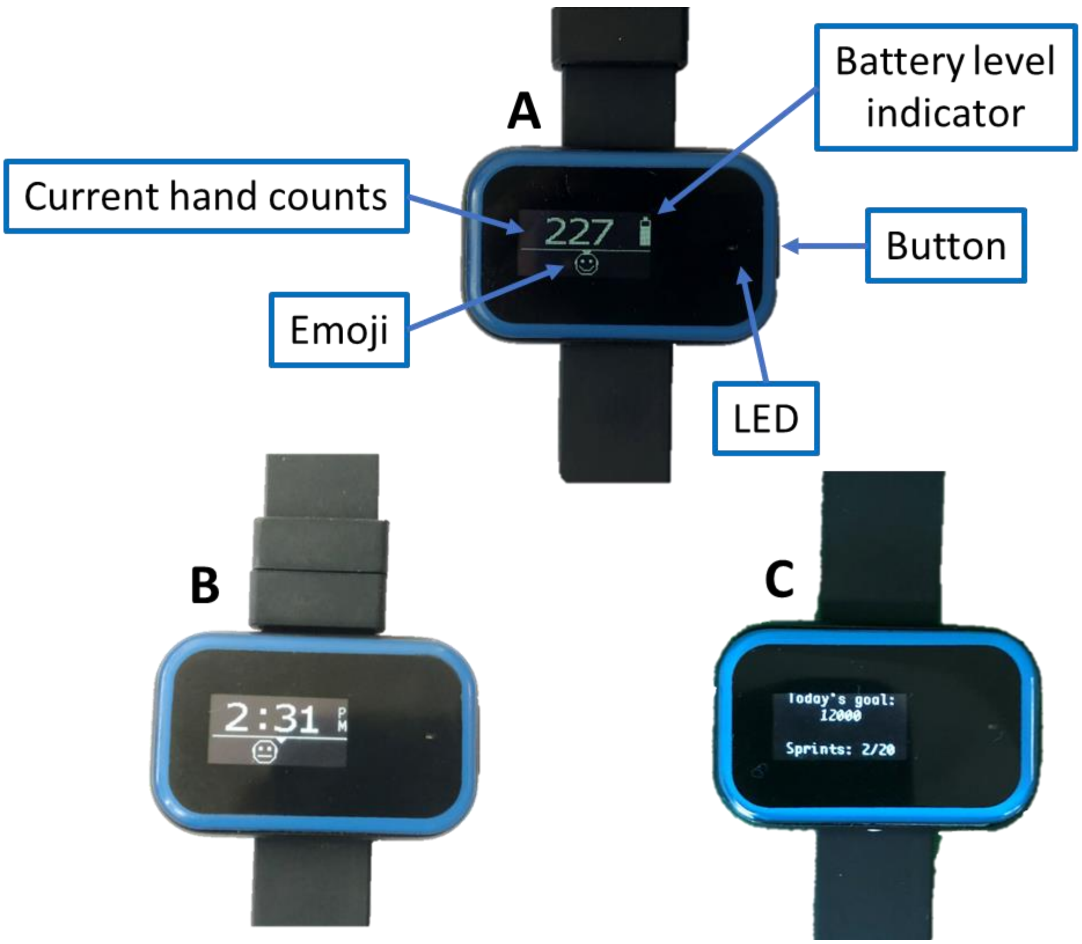


Figure 16. Manumeter screens available for the participants in the experimental group. The counts screen showed their current number of hand movement performed during the day, battery indicator, and the feedback emoji. The goal screen showed their daily goal of hand counts, number of sprints performed that day, and daily goal of sprints. And the time screen showed the current time as well as the emoji feedback.

3.4. Results

A total of 25 stroke survivors were screened for this study; 22 participants met the inclusion criteria and were successfully recruited. Half of them were randomized into the control group and the other half into the experimental group. Two participants dropped out during the three weeks of intervention - one due to a family emergency and another due to sickness (Figure 17). Table 2 shows the demographic data and key baseline clinical outcomes for the participants included in the data analysis. Some of the Manumeter data was lost during the intervention period:

- Total data loss (n=2, experimental group): technical problems when downloading the data from the device
- Partial data loss (n=2, one in each group) due to technical problems when downloading the data from the device
- Partial loss (n=1, experimental group): device was stolen from car two weeks into the intervention. Device was promptly replaced
- Partial data removal (n=1, experimental group): lost the magnetic ring. Ring was replaced after 6 days. Participant kept using the Manumeter without the ring during that period
- Total data removal (n=1, control group): participant wore the Manumeter on the unimpaired hand

Clinical data was kept for all participants with Manumeter data loss or data removal, as these technical problems did not affect the Manumeter functionalities during the study.

Table 2. Demographic data and key baseline clinical outcomes for RCT

	All (n=22)	Control (n=11)	Experimental (n=11)
Age	57 ± 14	58 ± 12	56 ± 17
Gender (Male [M]/Female [F])	18 M/4 F	10 M/1 F	8 M/3 F
Time since stroke (monts)	40 ± 33	48 ± 45	32 ± 14
Side of hemiparesis (Right [R]/Left [L])	12 R/10 L	8 R/3 L	9 R/2 L
Type of stroke (Ischemic [I]/Hemorrhagic [H])	12 I/10 H	6 I/5 H	6 I/5 H
BBT	20 ± 17	18 ± 18	22 ± 17
FMUE	40 ± 13	41 ± 16	40 ± 10
ARAT	34 ± 20	34 ± 21	34 ± 18

± standard deviation.

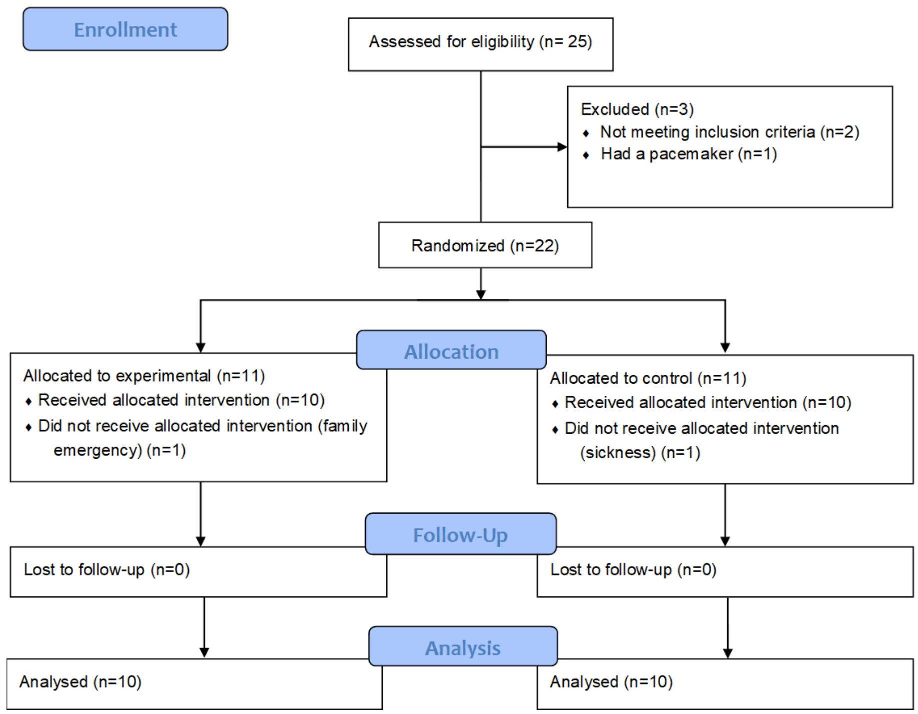


Figure 17. CONSORT flow diagram.

3.4.1. *EFFECTS OF FEEDBACK ON HAND ACTIVITY*

Participants in the experimental and control group wore the Manumeter for 17.2 ± 4.4 and 16.1 ± 3.9 days, respectively – a nonsignificant difference (t-test, p=0.66). However, those in the experimental group wore the Manumeter significantly longer each day compared to the control group across the three weeks of therapy with averages of 11.2 ± 1.3 and 10.1 ± 1.1 hours/day (t-test, p=0.005) for the experimental and control groups, respectively. Comparing the wear time for the two halves of the therapy period (Figure 18A), we found no difference between groups for the first half (t-test, p=0.238) but a significant difference for the second half (t-test, p=0.002), suggesting more compliance in the experimental group even after the novelty effect.

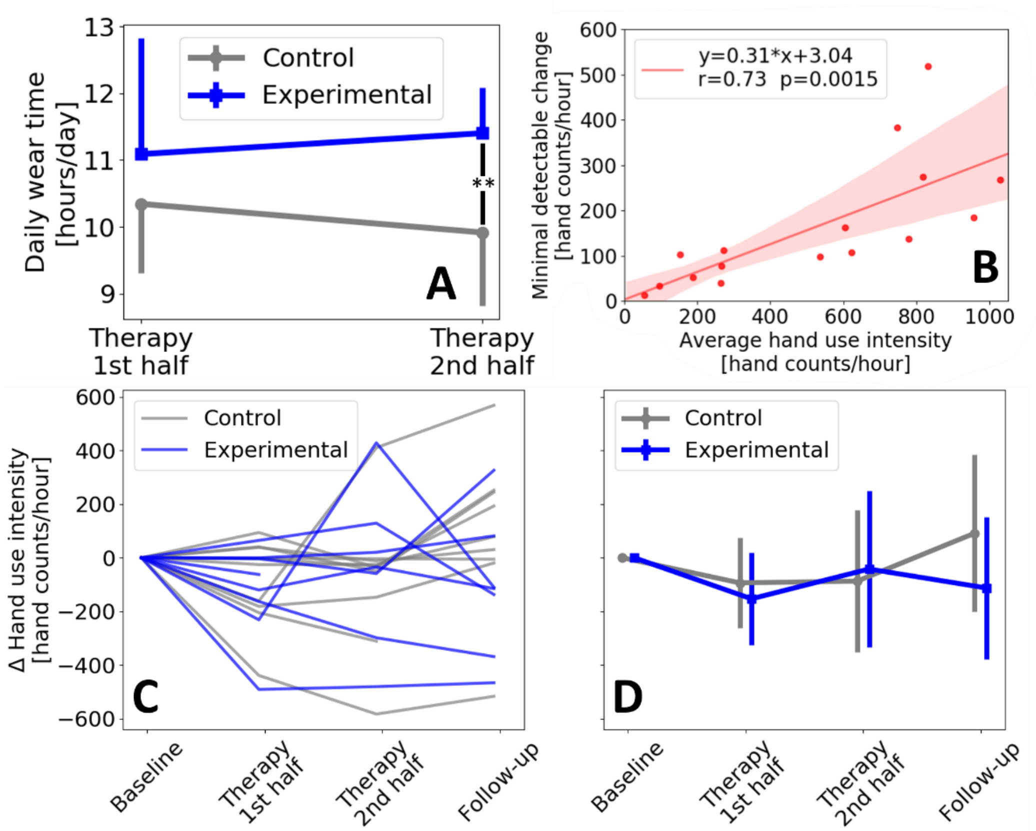


Figure 18. Manumeter compliance and change in hand use intensity. (A) Average daily wear time of the Manumeter with significant difference between groups (t-test, p=0.002) during the second half of the three weeks of therapy. (B) Minimal hand use intensity change that can be detected based on daily hand use intensity variability versus average use intensity across the three weeks of therapy. (C) Individual change in hand use intensity from baseline. Changes were only calculated for periods of the day that baseline data was available. (D) Average change in hand use intensity across participants in each group. Error bars show ± 1 standard deviation.

Change in hand use intensity was calculated for each participant as the difference to the baseline. The difference was first calculated in a minute by minute basis, only using the periods of the day that baseline data were available. No significant difference was found between groups or over time. The individual change in the average hand use intensity is presented in Figure 18C. It shows that some of the decrease in average hand use intensity in the first half of therapy was mainly driven by two participants (one in each group); however, there was no clear increase in hand use intensity even for the other participants.

3.4.2. CLINICAL OUTCOMES

Providing hand feedback with a daily goal caused a trend toward improved clinical hand function with better retention at the 3-month follow-up (Figure 19), however there was no significant difference between experimental between groups. FMUE, ARAT and MAL HW improved significantly over time (Table 3).

Table 3. Changes in clinical score in the RCT

	Significance (p value)			Delta PT		Delta FU	
Outcome	Group	Time	Group:Time	Control	Experimental	Control	Experimental
BBT	0.608	0.116	0.353	1.2±2.7	2±4.1	0.44±4.4	3.2±2.8
FMUE	0.94	<0.001***	0.454	3±2.5	4.4±2.3	3.7±3.5	5.1±3.2
ARAT	0.83	0.002**	0.416	2.1±3.4	2.7±3.3	1.8±1.5	3.8±3.8
NIHSS	0.259	0.555	0.564	-0.2±0.98	-0.1±0.54	0±0.94	-0.33±0.47
Gross grasp [kg]	0.717	0.654	0.629	-1.3±2	-0.4±0.92	-1.1±1.7	-0.78±1.5
Lateral pinch [kg]	0.275	0.616	0.334	-1.1±1.8	-0.35±1.8	-0.89±1.4	-0.61±2.4
MAL AS	0.969	0.065	0.917	0.62±0.66	0.44±1.4	0.69±0.73	0.68±1.4
MAL HW	0.884	0.017*	0.788	0.56±0.75	0.35±0.52	0.58±0.8	0.44±0.7
MMSE	0.065	0.662	0.567	0.4±1.7	-0.2±1.1	-0.11±0.74	-0.33±0.47

± standard deviation
Delta PT = change from baseline to post-therapy evaluation
Delta FU = change from baseline to follow-up evaluation
N = 10 for each group (note: missing 1 participant in each group for FU evaluation)
Significance level: * p<0.5; ** p<0.01; *** p<0.001.

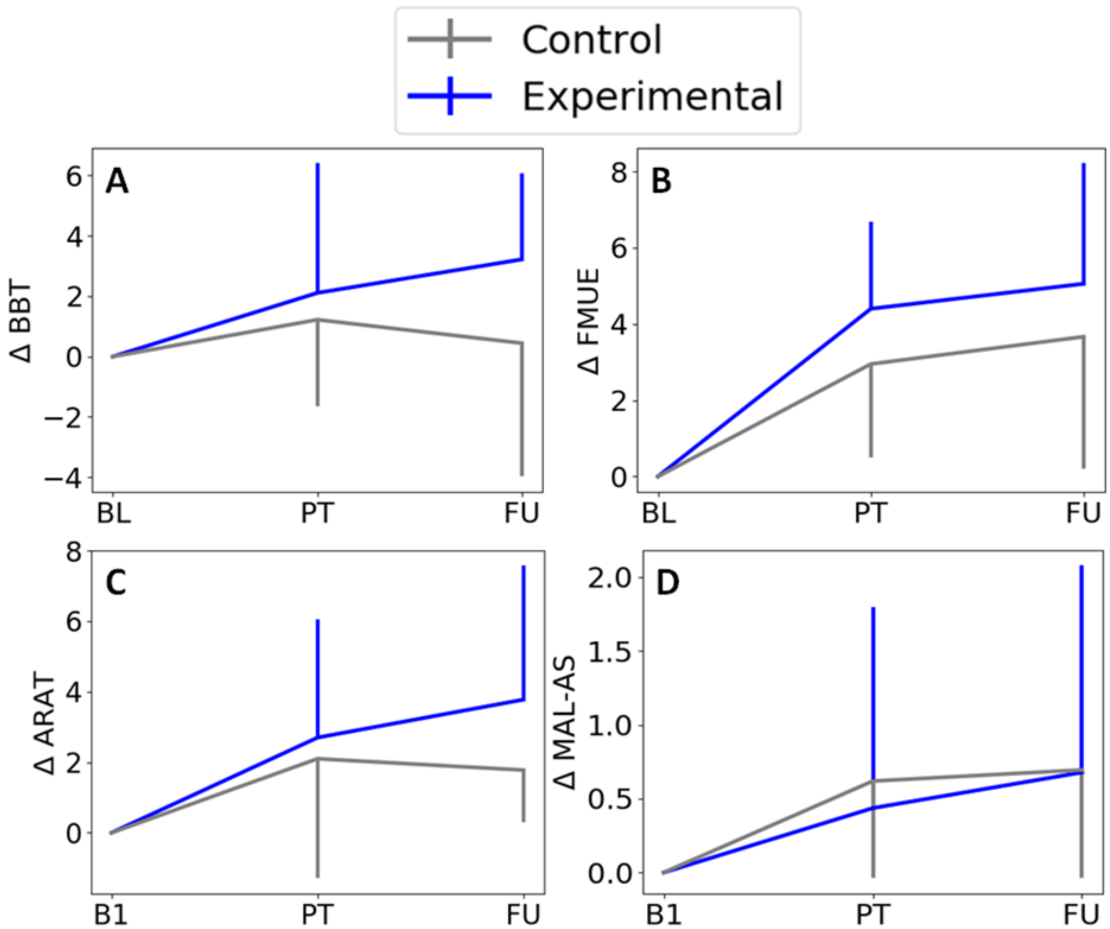


Figure 19. Change in clinical scores from baseline. For BBT and FMUE, BL is the average for the scores in baseline 1 and baseline 2. Bars represent ± 1 standard deviation. Time points are BL = baseline, B1 = baseline 1, PT = post-therapy, FU = Follow-up. Clinical assessments are BBT = Box and Blocks Test, FMUE = Fugl-Meyer Upper Extremity Scale, ARAT = Action Research Arm Test, MAL-AS = Motor Activity Log – Amount Scale.

3.4.3. RELATIONSHIP BETWEEN CLINICAL SCORES AND HAND USE

There was a nonlinear relationship between clinical score (BBT) and hand use intensity (Figure 20). Participants with BBT up to 25 did not use their hand at home, even though they had moderate levels of hand function measured with the BBT. Two exceptions were participants E1 and E3. These participants are significantly younger (18 and 29 years old) than the remaining participants (averaging 60±10 years old).

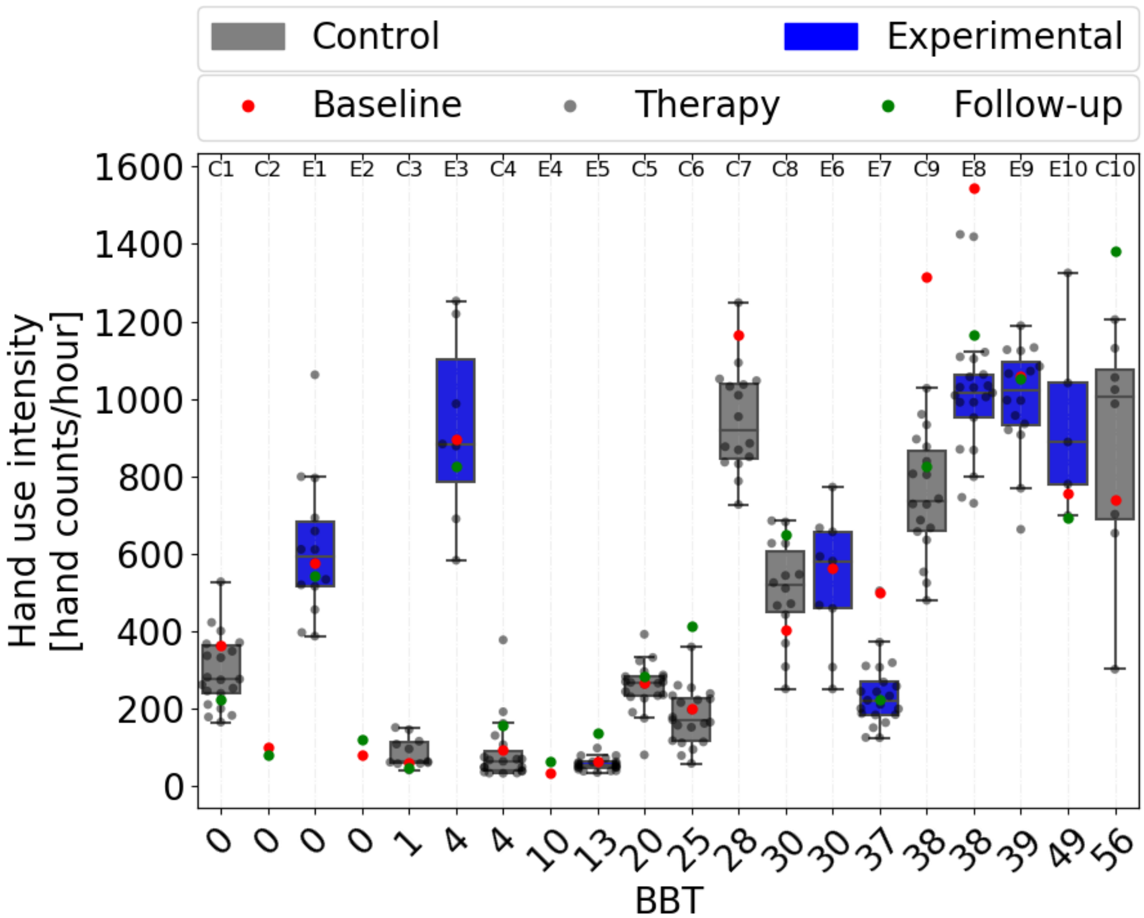


Figure 20. Nonlinear relationship between hand use intensity and impairment level. Each circle represents the average hourly count for one day. Participants were ordered by BBT and then by FMUE. The box and whisker plots represent the individual distribution of daily hand use intensity across the three weeks of therapy for participants in both groups (control in gray, experimental in blue). Box and whisker plots do not include baseline and follow-up data. Subject identification is presented on the top, with E's for participants in the experimental group and C's for participants in the control group. Note that x-axis equally spaced and not scaled to BBT. BBT=Box and Blocks Test, FMUE=Fugl-Meyer Upper Extremity Scale.

3.4.4. NOVELTY EFFECTS AND MINIMAL DETECTABLE CHANGE

In Figure 20 we can identify the two participants (C9 and E8) who had unusual hand use intensity at baseline. When we compared baseline hand use intensity with daily hand use intensity during the three weeks of therapy using a one sample t-test, we observed a significant difference (significance level set to 0.05) for 6 out of 17 subjects. If this difference were simply random, the odds that it would occur for 6 out of 17 subjects for baseline hand use is ~1e-8 (0.05 to the 6^{th} power). We conclude that baseline hand use was influenced by some factor.

We expanded this approach to calculate the minimal detectable change based on the daily hand use intensity across the three weeks of therapy. We calculated the minimal detectable change using a one sample t-test with significance level set to 0.05 for each participant (Figure 18B). A strong, significant correlation ($r=0.73$, $p=0.0015$) was found between the minimal detectable change and the daily average of hand use intensity across the weeks of therapy. It showed that, in average, a change of 31% from the daily average of hand use intensity was necessary for significance.

3.5. Discussion

The goal of this study was to investigate the efficacy of real-time feedback of hand movements in increasing hand activity and motor recovery. Participants showed a significant increase in the clinical outcomes FMUE, ARAT, and MAL-HW as a function of time. Both groups showed a non-significant increase in BBT from baseline to post-therapy, which was sustained (also not significant) at 3-month follow-up only by the experimental group. There was no significant difference between groups in number of days wearing the Manumeter, however participants in the experimental group wore the Manumeter for significantly longer each day. Continuous feedback did not significantly increase hand movement intensity.

3.5.1. THE NONLINEAR RELATIONSHIP BETWEEN HAND CAPACITY AND HAND USE

It is not surprising that stroke survivors with lower hand function have a reduced use their impaired hand outside the clinic. Several studies have correlated amount of upper extremity use with clinical assessments [96], [97]. However, from learned non-use phenomenon it is expected that this relationship is not linear. A threshold at which stroke survivors have enough function to perform daily activities and leave the learn non-use vicious cycle is expected [17], [98]. Here, we show that participants that scored up to 25 in the BBT did not use their hand at home. A sharp increase in hand use intensity was observed for participants with higher motor capacity. This is consistent with results presented in [86], in which sixty-seven stroke survivors performed several clinical assessments and were classified into low, moderate, and high level of upper limb function. A similar threshold between 20 and 30 blocks in the BBT was found to split between high and moderate function levels. The main difference between the moderate and high-level groups was possession (or lack of) fine manual dexterity. Even though similar gross function (e.g. range of motion, speed, and strength) can be observed in both groups, it is the hand dexterity ability of the high-level participants that make the difference when performing everyday tasks [86].

3.5.2. HAND USE COUNTS FOR FUNCTION RECOVERY

Providing hand feedback with a daily goal caused a trend toward improved clinical hand function, even though there was no detectable change in amount of hand use. One explanation may be that participants receiving feedback paid more attention to their impaired hand. For example, in [62], subacute stroke survivors wore an accelerometer on the impaired wrist for three continuous hours per day for four weeks. No feedback on amount of upper extremity use was given, but participants were prompted with a vibrotactile reminders about their impaired arm every five minutes. The vibrotactile feedback brought attention to the impaired experienced significant increase in clinical outcomes (FMUE and ARAT).

Changes in hand function with no increase in upper extremity activity were also observed in [99], in which 60 stroke survivors wore wrist accelerometer on both wrists for 3 days on admission to rehabilitation and for 3 days before discharge (3 weeks apart). Even though participants significantly improved hand function, there was no change in amount of upper extremity use as measured with the wrist accelerometers.

A possible explanation is that the variability in hand use is too high and inducing significant changes in hand use is therefore more challenging than expected. Here, we showed that the necessary increase in hand activity for a detectable change is about 31% of the daily average across the three weeks of therapy. For someone with 1000 hand counts per hour, that is an extra 300 counts per hour or 3000 counts for the average 10 hours of Manumeter use. Comparing to steps, it would take an adult 30 minutes of moderate intensity walk to take 3000 steps [100]. However, there is no comparable activity for increasing upper extremity repetitions at the same proportion. Hand exercise, particularly that requiring repetitive finger extension, is slow and fatiguing, relative to the same number of repetitions of walking. Could it be that the smaller, more fatigable nature of hand extensor muscle limits hand exercise to levels lower than needed to make a change? If so, finding ways to encourage exercise while limiting fatigue are important.

3.5.3. LIMITATIONS

One limitation was regarding the baseline, in which portions of the hand activity seemed incompatible with what was observed during the weeks of intervention. Using as baseline the hours immediately after a visit to lab produced a highly unusual number of outlier days – 6 out of 17 subjects, in which 4 of them had unusually high hand activity levels, but 2 had unusually low hand activity levels. We attributed these anomalies to the disruption of daily routine and motivation from meeting with the therapist. For accelerometry, it is recommended to use at least 3 days of monitoring to estimate habitual physical activity [101].

A second limitation is the high variation in age of the participants. The two younger participants (both on the control group) had unusually high counts for their impairment level. This suggests that age can have a large effect on amount of hand use. Age can also influence engagement with new technologies, such as the Manumeter.

Another limitation of this study was the goal setting strategy. With the high variability observed across and within participants, a goal based on hand capacity as measured in the clinic may not ideal. A possible solution is to use an adaptive goal, updated based on the average hand use across several days.

CHAPTER 4. UNIQUE OUTCOMES DERIVED FROM WEARABLE SENSING

4.1. Contributions

In CHAPTER 3, we showed that providing a daily goal and real-time feedback on amount of hand use did not increase hand activity and did not significantly change functional outcomes in stroke survivors. Here, we further explore the use of wearable sensing technologies to introduce new accelerometry metrics related to quality of movement. These metrics could be used as alternatives to quantity of movement when providing feedback on upper extremity movement after stroke. **Background**: Wearable sensing is a new tool for quantifying upper extremity (UE) rehabilitation after stroke. However, it is unclear whether it provides information beyond what is available through standard clinical assessments. **Methods**: To investigate this question, people with a chronic stroke (n=9) wore accelerometers on both wrists for 9 hours on a single day during their daily activities. We used principal components analysis (PCA) to characterize how novel kinematic measures of jerk and acceleration asymmetry, along with conventional measures of limb use asymmetry and clinical function, explained the behavioral variance of UE recovery across participants. **Results:** The first PC explained 55% of the variance and described a strong correlation between standard clinical assessments and limb use asymmetry, as has been observed previously. The second PC explained a further 31% of the variance and described a strong correlation between bimanual magnitude and jerk asymmetry. Because of the nature of PCA, this second PC is mathematically orthogonal to the first and thus uncorrelated with the clinical assessments. **Conclusions:** Therefore, kinematic metrics obtainable from bimanual accelerometry, including bimanual jerk asymmetry, encoded additional information about UE recovery. One interpretation is that the first PC relates to “functional status” and the second to “movement quality”. We also describe a new graphical format for presenting bimanual wrist accelerometry data that facilitates identification of asymmetries.

4.2. Introduction

More than 50% of people who have had a stroke exhibit long-term upper extremity (UE) deficits, including decreased use of the affected limb for activities of daily living [3]. Since most of our daily activities involve the use of both of our hands [46], [102], understanding bilateral use of the UEs after stroke is paramount for understanding decreased use of the limb.

Advances in miniaturization and processing speed have allowed development of wearable sensing systems for real-world, or out-of-the-clinic, monitoring of human activity [37]. For rehabilitation after stroke, the use of wrist-worn accelerometers as a means of quantifying UE use in the community living environment has been increasing [37], [39], [40]. This approach can quantify people's actual use of their UE as opposed to their capability, which is what is measured by standard clinical assessments such as the Fugl-Meyer Assessment (FMA) or Box and Blocks Test (BBT), and as opposed to subjectively perceived use of the UE, which is what self-assessment questionnaires such as the Motor Assessment Log (MAL) measure.

An increasing number of studies have evaluated the viability of applying wrist-worn accelerometry to measure UE use after stroke [39], [41], [44], [77] [45]–[47]. The majority found strong correlations between accelerometry metrics and clinical assessments, including the FMA, BBT, and MAL, among others (see reviews [40], [77]). These findings validate the ability of wrist accelerometry to continuously assess UE impairment in community living. However, paradoxically, they raise the question of whether wrist accelerometry provides additional information beyond what can be obtained with standard clinical assessments. It seems reasonable to expect that bimanual wrist accelerometry carries additional information since it collects extended amounts of bimanual, kinematic data during daily living activities, as opposed to simply scoring or timing a fixed set of movements, as standard clinical assessments typically do. However, the additional information that accelerometry might convey remains relatively unexplored.

Lang and her group have showed compelling results using accelerometers to quantify bilateral, real-world, UE activity after stroke [45]–[47]. They developed new ways to interpret bimanual accelerometry data and to extract relevant information from it, including bimanual activity asymmetry, a measure that strongly correlates with clinical assessments. However, partly due to software limitations on commercial wrist accelerometers, most of these studies have focused on activity counts rather than kinematics.

Aiming to extract additional kinematic information from bimanual wrist accelerometry, we propose two new metrics. The first, jerk asymmetry, is based on the physical quantity of jerk, which has been suggested to reflect fundamental kinematic building blocks or subunits of movement and exhibits significant differences for the affected and non-affected arm after stroke [103], [104] (NOTE: we will use the terms "non-affected" and "affected" for simplicity although we understand that the "non-affected" limb is somewhat affected [105]). Jerk has also been shown to contain unique information about movement recovery after stroke [106] and to predict disease onset in Huntington's Disease [107]. With bimanual accelerometry, it is possible to calculate jerk asymmetry between the two limbs during daily life. The second, acceleration magnitude asymmetry, is based on the concept that the brain specializes the control of each limb for either control or for posture [108]. Thus, one might expect differences in the profiles of the peak accelerations experienced throughout the day, depending on how individuals re-specialize hand roles after neural injury.

The first goal of this study was to address the question of what new information accelerometry can provide that is distinct from clinical measurements. To this end, we used principal component analysis (PCA), an exploratory data analysis technique suited for characterizing patterns of variance in data [109]. A secondary goal was to develop an alternative method of data representation that highlights the asymmetries in bimanual UE activity after stroke.

4.3. Methods

4.3.1. PARTICIPANTS

Participants were nine males, seven right-handed, and six with stroke affecting their dominant side. Table 4 summarizes the population. All participants provided informed consent and were compensated for their time.

Table 4. Participants' demographic and clinical information for bimanual wrist accelerometry

	Average	SD
Age	56.1	14.9
Days Post-Stroke	749	577
BBT Affected	25.8	18.9
BBT Non-Affected	55.4	8.2
NHPT Affected	51.7	14.1
NHPT Non-Affected	23.1	3.9
MAL-AS	2.4	1.5
MAL-HWS	2.5	1.4

BBT: Box and Blocks Test; NHPT: Nine Hole Peg Test; MAL: Motor Activity Log; AS/HS – Amount of Use / How Well Score.

4.3.2. PROCEDURE

Participants first completed a visit to the laboratory, in which UE assessments (BBT, NHPT, and MAL) were performed by a trained therapist and demographic information was collected. The therapist helped the participants don an accelerometer on each wrist. Both the devices were started simultaneously using serial interfaces with a computer. The participants were instructed to wear the devices throughout their day and continue with their normal daily routine until going to take a shower or turning in to sleep, when they were instructed to remove the device. They brought the device back the next day. We chose to avoid asking the participants to don and doff the devices to ensure that they did not swap hands or misplace the device during the data collection. The participants were also asked to log their activities during the day and the time they removed the device, which was used to validate the time stamping of the data.

4.3.3. ACCELEROMETRY

A system consisting of a LSM9DS0 9DOF IMU (with ranges of ±6 g for the accelerometer, ±4 Gauss for the magnetometer, and ±500 DPS for the gyroscope), an Arduino Pro Mini with real time clock, a 400 mAh battery, and a micro-SD card socket for data logging (Figure 21) was assembled for this study. The IMU data were read and stored at 30 Hz into the micro-SD card, and later transferred to a computer by the therapist.

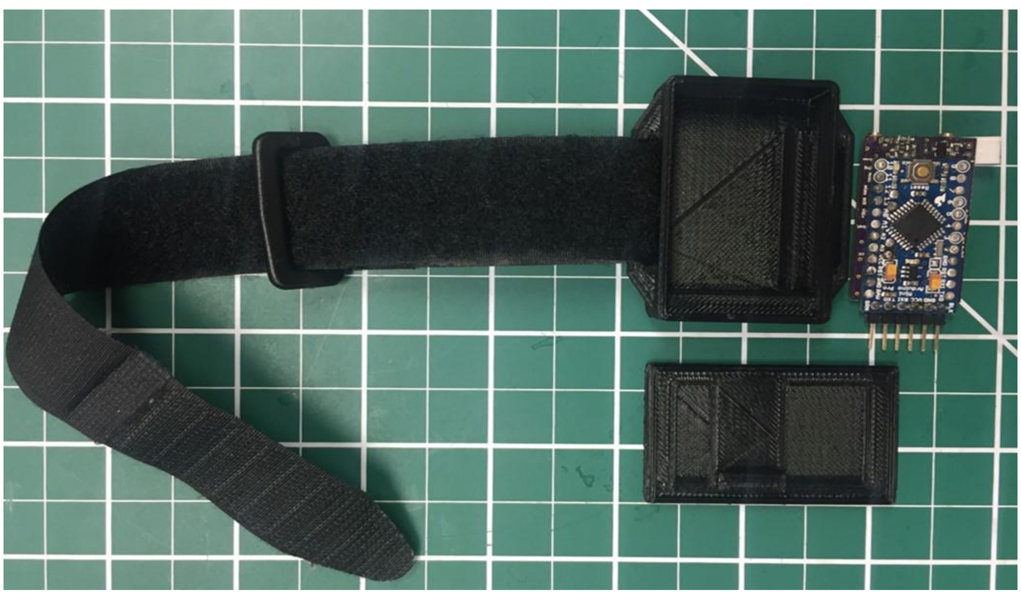


Figure 21. Wrist accelerometer. Electronics, enclosure and wristband used in the study.

4.3.4. DATA PROCESSING

To process the accelerometer data, a similar approach to the already established and well tested method presented in [46], [80], [110] was used. First, the recordings were clipped to remove data from before and after participants wore the device. Gravity direction was estimated using the 9DOF data of the IMU with Mahony's Algorithm [111]. The effects of gravity were then removed from the acceleration vector and its magnitude calculated. A band-pass filter in the frequencies of 0.25 Hz to 2.5 Hz was applied to the magnitude of the acceleration and the data were down sampled to 1 Hz (taking the average value for every 1 second bin). The resulting down-sampled acceleration was converted into activity counts, where 1 activity count = 0.017 g and values below 1 activity count were set to 0. Walking artifacts were not removed, however [79] has shown that bimanual wrist accelerometry is not significantly affected by ambulatory movement after stroke.

To calculate the laterality of the movements, one established method [110] uses the log-ratio of the counts for each arm. However, this method breaks down when either of the two counts is 0. In [110], when that happens values are set to -7 or +7, for the affected or non-affected side, respectively. To avoid that problem, in this study we used a different laterality equation:

$$laterality = \frac{counts_{aff} - counts_{non-aff}}{counts_{aff} + counts_{non-aff}} \quad (2)$$

where $counts_{aff}$ and $counts_{non-aff}$ are the vectors representing the counts on the affected side and non-affected side, respectively. The result, $laterality$, is bounded from -1 to +1, where values closer to 0 mean a bimanual activity, values near -1 represent larger activity on the affected side, and values closer to +1 denote higher activity on the affected side. Values of -1 and +1 are unilateral activities in the affected and non-affected side, respectively. When both counts are 0, the sample is counted as resting. A laterality index was calculated as the mean of the laterality vector.

Using the laterality vector and the resting samples, the data were divided into four different categories: "resting" (both counts equal to 0), "unimanual movement of the affected side" (defined as $laterality < -0.95$; results were similar with $laterality < -0.90$), "unimanual movement of the non-affected side" ($laterality > 0.95$), and "bimanual" (when $-0.95 \leq laterality \leq 0.95$). The number of samples in each of these groups divided by the total number of samples was used to calculate the ratio, with respect to total worn time, of each category.

Two new metrics were also calculated: the magnitude asymmetry and the jerk asymmetry. The magnitude asymmetry index was calculated using the accelerometer magnitude, before converting to activity counts, as in

$$acc\_asymm = \frac{acc_{uni\_aff} - acc_{uni\_non-aff}}{acc_{uni\_aff} + acc_{uni\_non-aff}} \quad (3)$$

where acc_{uni_aff} and $acc_{uni\_non-aff}$ are the average magnitude of the acceleration for unimanual samples in the affected side and unimanual samples in the non-affected side, respectively. Similar to laterality, the index acc_asymm is bounded from -1 to +1. Values close to 0 represent symmetrical average acceleration magnitude for both UE, and values close to -1 or +1 represent higher average acceleration magnitude on the affected side or non-affected side, respectively. This metric is a modified version of the magnitude ratio proposed in [13], the differences being that in [13] the median of the log ratio of the magnitude of the acceleration was used instead, and magnitudes in the both bimanual and unimanual samples were considered. The rationale behind only using accelerations of unimanual movements is that in bimanual movement there might be a coupling of the acceleration of the two limbs (for instance, when manipulating an object with both hands). Therefore, using only unimanual samples guarantees that one limb is not interfering with the other.

The jerk asymmetry was calculated in a similar fashion, except that the magnitude of the differential of the acceleration vector was used instead of the magnitude of the acceleration:

$$jerk\_asymm = \frac{jerk_{uni\_aff} - jerk_{uni\_non-aff}}{jerk_{uni\_aff} + jerk_{uni\_non-aff}} \quad (4)$$

where $jerk_{uni\_aff}$ and $jerk_{uni\_non-aff}$ are the average magnitude of the jerk for unimanual samples in the affected side and unimanual samples in the non-affected side, respectively.

The $jerk\_asymm$ metric should be read in the same way as acc_asymm, but using average jerk magnitude instead of average acceleration magnitude.

4.3.5. STATISTICAL ANALYSIS

Paired t-tests were performed to evaluate the difference between the affected side and the non-affected side in the acceleration magnitude and the jerk. To study the interrelation of the standard clinical assessments and bimanual wrist accelerometry metrics, PCA was applied. PCA aims to reduce dimensionality, by transforming the data into a new set of variables using principal components (PCs), which are orthogonal to each other and ordered by the amount of data variance they can explain.

In [109], the PCA method is explained in detail, and to provide a brief conceptual overview useful for interpreting the analysis to follow, we now summarize one example given in this source. Specifically, the size of the hand, wrist, height, forearm, head, chest, and waist were measured for a sample of men and then PCA was applied. The analysis showed that the first PC, which explained 60% of the variation, was characterized by an overall correlation in size (all the variables were strongly correlated), which means that the first PC accounted for the fact that when one of the size measures increases, the other ones also tend to increase. The second PC, which explained less than 20% of the variation, showed that the main source of variation, after the overall size was accounted for, was the contrast of hand and wrist size to height. It is important to highlight that the second PC only accounts for new information that was not varying in the direction of the first PC. This is an important concept to understand the contribution of this study.

The methodology for calculating each metric is presented in Figure 22.

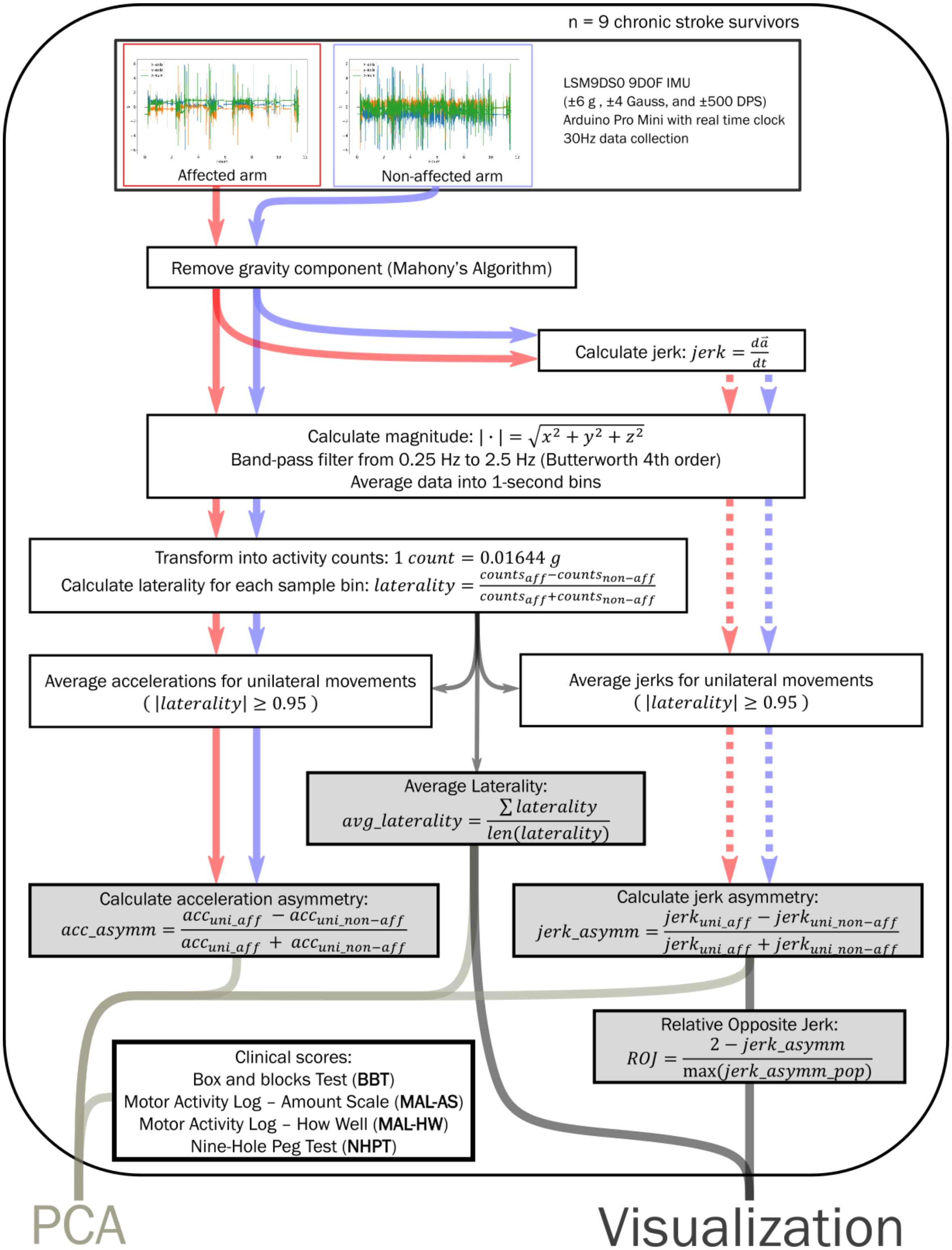


Figure 22. Data processing methodology. Dashed lines carry jerk data and full lines carry acceleration data.

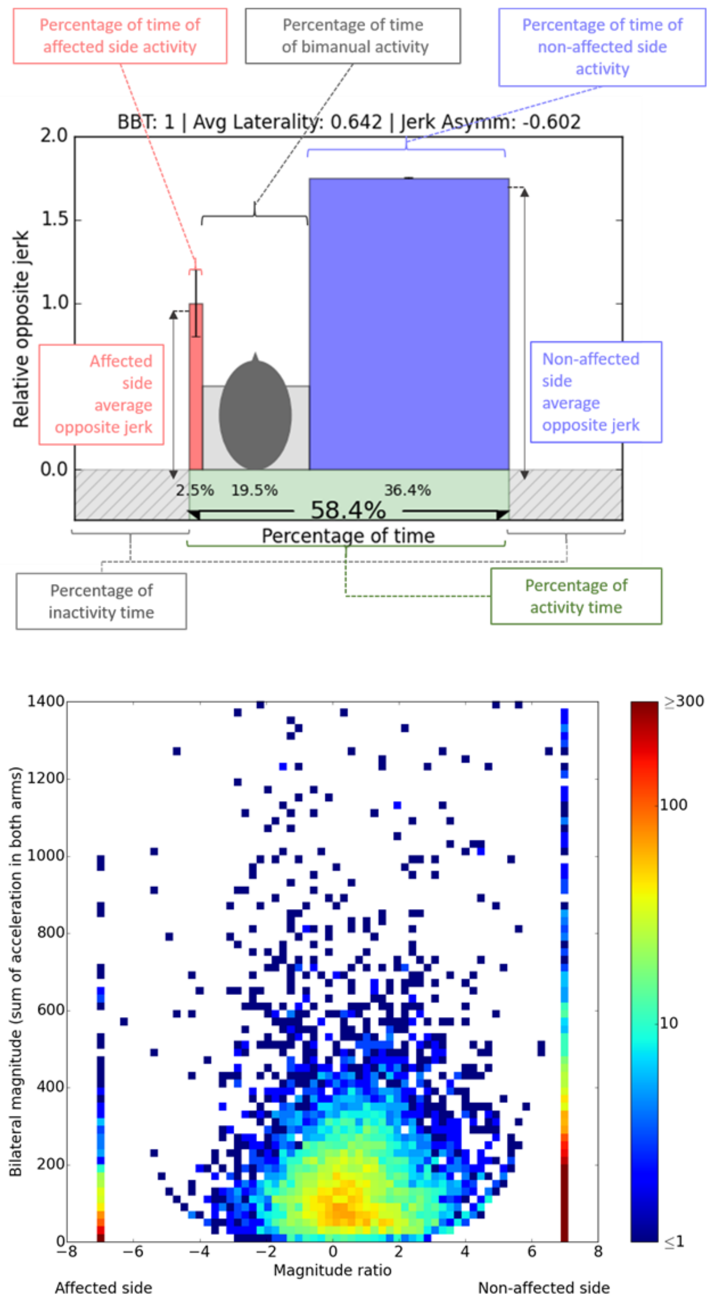


Figure 23. Example of two types of data representation for a participant with Box and Blocks Test score equal to 1. The top plot is proposed in this study. The upper part of the plot shows the percentage of activity time for unimanual, bimanual movements, and inactivity in the x-axis. In the y-axis is presented the average relative opposite jerk for unimanual movements. The bottom plot was proposed in [46] and shows the histogram of number of activity counts in terms of magnitude ratio and bilateral magnitude (BBT = Box and Blocks Test Score) for the same subject.

4.4. Results

4.4.1. VISUALIZING BIMANUAL WRIST ACCELEROMETRY DATA

Participants wore the device for 9.1 ± 2.6 continuous hours on average. One of our goals was to develop a graphical means to summarize the data. Figure 23 compares two approaches for visualizing the large amount of data obtained from one participant in this relatively short period. The bottom approach to plotting the data was developed in [46] and the top one is a complementary approach proposed here that makes certain relationships more explicit. Both plots show data from the same subject.

The bottom plot shows a 2D histogram of number of activity counts, plotted in terms of magnitude ratio on the x-axis (comparable to the laterality index defined above), and bilateral magnitude on the y-axis (which is the sum of the acceleration magnitude for both accelerometers). This type of plot makes clear through its heat map the overall statistical distribution of movements in terms of laterality and bilateral magnitude. However, its use of a color-map histogram makes it difficult to perceive the quantitative relationship of total bimanual to total unimanual activity, and the amount of rest (inactivity of both limbs) is not explicit. Judging asymmetry requires judging color gradients, and one would in fact have to sum colors in the bimanual regime to precisely quantify amount of bimanual activity. An advantage of this plot, however, is that it makes explicit that, during bimanual activities, there is more use of the non-affected side, clear from the skewing of color to the right side of the plot.

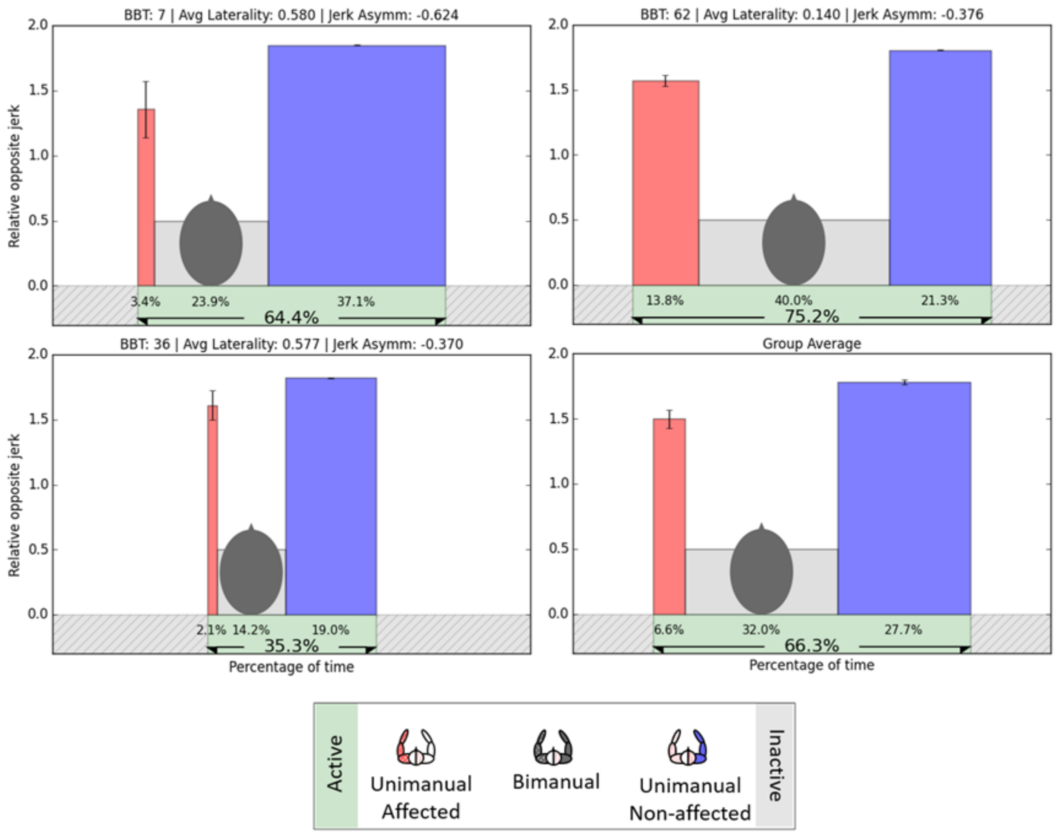


Figure 24. Sample plots for three participants and group average. The top two plots and the bottom left plot show inactivity and inactivity percentage of time, and average relative opposite jerk for three participants in order of Box and Blocks score. Bottom right plot shows the average for all 9 participants. Error bars represent standard error (BBT = Box and Blocks Test Score).

The top plot is an alternative presentation of the same data from the same participant that averages the total activity in each category of limb use (unimanual, bimanual, and inactivity) and shows the ratio with respect to total recording time, making the asymmetry as well as the amount of inactivity explicit. Specifically, the x-axis quantifies the percentage of time for each of the different types of activities is presented: non-affected and affected unimanual activity, and bimanual activity. Percentage of activity time is obtained adding the three types of activity and percentage of inactivity time is represented in the remainder of the x-axis. These four percentages add up to a hundred percent, representing the full time the participant wore the devices. For the example participant shown in Figure 23, the inactivity time was about 42%, unimanual activity affected and non-affected side were around 3% and 36%, respectively, and bimanual activity was 19%.

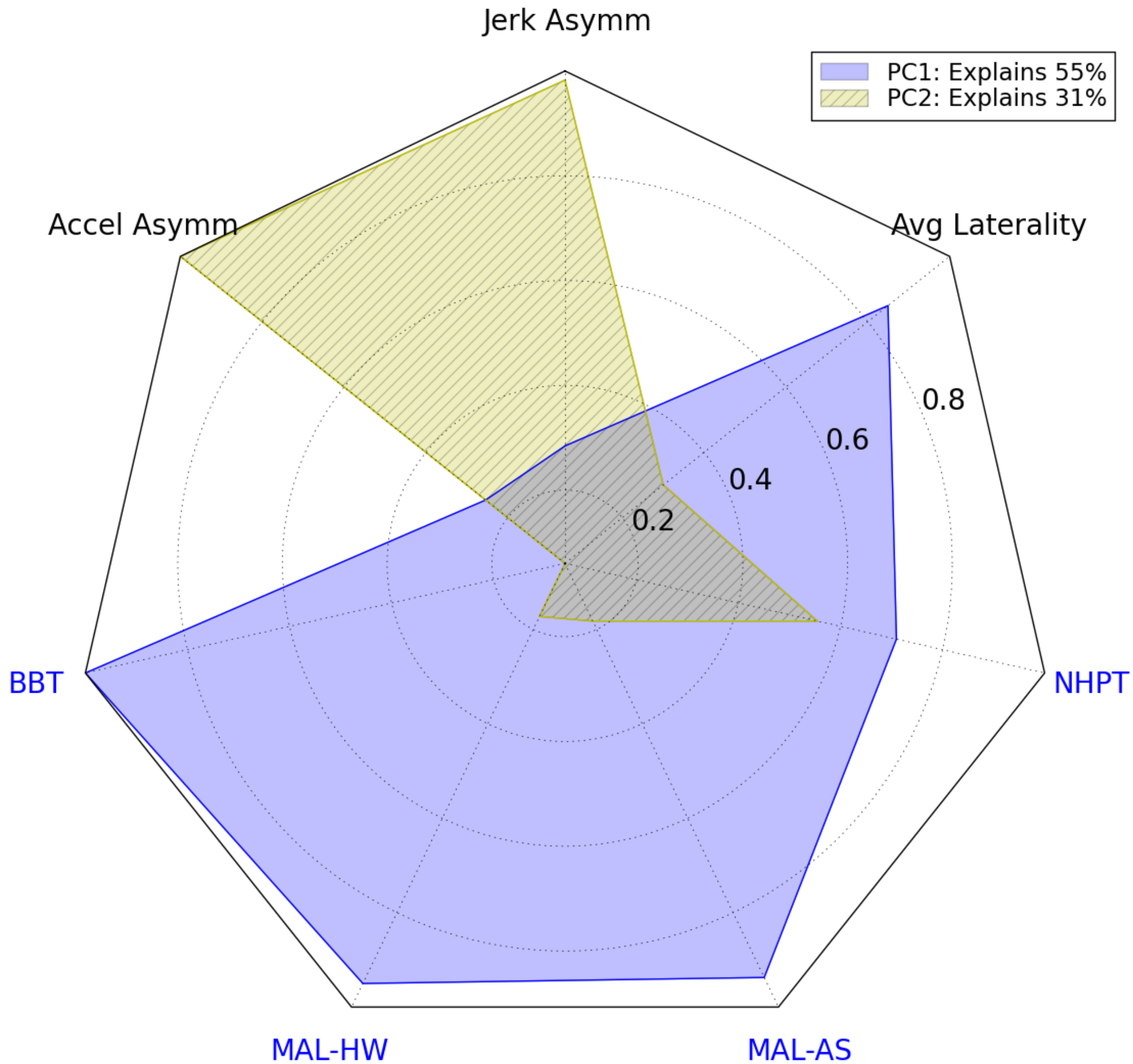


Figure 25. Weights (or "loadings") for each PC normalized to the highest weight in that PC. PC1 accounts for 55% of the variance of the data and PC2 accounts for 31% (Accel Asymm = Acceleration Asymmetry Metric, Jerk Asymm = Jerk Asymmetry Metric, Avg Laterality = Average Laterality, NHPT = Nine-Hole Peg Test Ratio (affected/non-affected), MAL-AS = Motor Activity Log – Amount Scale, MAL-HW = Motor Activity Log – How Well Scale, and BB = Box and Blocks Test Ratio (affected/non-affected)).

In the y-axis, a kinematic measure derived from the accelerometers is presented. For the purpose of presentation, the calculated jerk was normalized to the maximum jerk of the population and transformed as:

$$ROJ = 2 - \frac{jerk}{max\_average\_jerk} \quad (5)$$

where *ROJ* is the relative opposite jerk, *jerk* is the jerk calculated from the accelerometer data, and *max_average_jerk* is the maximum average jerk across all the participants.

For the participant in Figure 23, the average relative opposite jerk was 1 and 1.75, for the affected and non-affected, respectively. That is, jerk was higher for the impaired arm.

4.4.2. LIMB ASYMMETRY AFTER STROKE

Figure 24 shows three sample participants with different BBT scores, all who exhibited asymmetry of use (higher use ratio for the non-affected arm) and jerk (higher for the affected arm). The amount of rest (i.e. the pink mountains of inactivity) varied broadly across participants, which might be expected since the amount of rest would likely depend strongly on the activities the participant chose to perform in the single day that they were measured.

The average of the data from all 9 participants (Figure 24, bottom) makes the overall use and kinematic asymmetries clear. Calculating the averages across participants, the non-affected limb showed a significantly greater activity time ratio than the contralesional limb (0.39 ± 0.15 and 0.60 ± 0.14, paired t-test, $p < 0.001$). The average acceleration magnitude was, however, significantly greater on the unilateral affected limb movements compared to the non-affected limb (0.12 ± 0.047 g and 0.047 ± 0.012 g, paired t-test, $p=0.002$). Jerk magnitude average was also significantly greater for the affected limb movements compared to the unaffected limb (3.56 ± 1.45 g/s and 1.56 ± 0.38, paired t-test, $p= 0.004$).

Table 5. Types of correlation between each variable in the PCs

		PC1	PC2
Conventional Clinical Assessments	BB	+	
	MAL-AS	+	
	MAL-HW	+	
	NHPT	(-)	(+)
Accelerometry	Avg Laterality	-	
	Acc Asymm		+
	Jerk Asymm		+

"+" for strong positive correlations (≥ 0.75)
"(+)" for moderate positive correlations (≥ 0.5 & < 0.75)
"-" for strong negative correlations (≤ -0.75)
"(-)" for moderate negative correlations (≤ -0.5 & > -0.75)
NHPT is time based (lower is better).

4.4.3. VARIANCE IN UPPER EXTREMITY RECOVERY

We applied PCA to characterize the UE behavioral variance across participants, using the clinical assessments (4 values for each of the 9 participants) and accelerometry measures (3 values for each participant).

We found that two PCs were sufficient to account for 86% of the variance in the data (Figure 25). We normalized the weights (or "loadings") of each PC to the highest weight in that PC, so that values over 0.75 indicated strong correlation and values between 0.5 and 0.75 indicated moderate correlation [109] (Table 5). The first PC explained 55% of the variance and described a strong correlation between the standard clinical assessments and the conventional accelerometry measure (activity count asymmetry). The second PC explained a further 31% of the variance and described a strong correlation between acceleration asymmetry and jerk asymmetry.

4.5. Discussion

The first PC that we found is consistent with what several studies have already shown: standard clinical assessments are correlated with each other as well as limb use asymmetry quantified with accelerometry [40]. One interpretation is that this first PC relates to “functional status” of the limb, and that functional status can be reasonably well predicted using either clinical assessments, including timed tests such as the BBT and NHPT or subjective surveys, such as the MAL, or with accelerometry-based measures of use asymmetry.

In contrast, the second PC was composed solely of the new kinematic metrics proposed in this study, jerk asymmetry and acceleration asymmetry. Because of the nature of PCA, this second PC is mathematically orthogonal to the first and thus uncorrelated with clinical assessments and the average laterality. And yet, it explained 31% of the variance of the participants. Thus, this PC appears to express additional information about UE recovery variability not available in the standard clinical assessments used here.

4.5.1. INTERPRETING THE NON-CLINICAL INFORMATION

What is the nature of this non-clinical information? One interpretation is that the second PC related to “movement quality”. The clinical hand assessments we used here, the BBT and NHPT, are timed tests of hand dexterity, and are relatively “blind” to how a person achieves the targeted functional task. Further, the MAL and the use asymmetry accelerometry measure relate to subjective and objective amount of use of the limb, respectively, and again, not to the details of how the limb is being used (although the MAL “how well” scale perhaps should – this is an interesting question). The kinematic measures, in contrast, likely relate to the quality of the movement: jerk relates to smoothness [103], and acceleration magnitude possibly relates to specialization of the roles of the limbs [108], and/or relative coarseness versus fineness of the movements achieved by each UE throughout the day.

If this “movement quality” interpretation is accepted, what this analysis seems to say is that there are aspects of movement quality that are uncorrelated with functional status. Although one might expect movement quality usually to degrade with lower functional status, we speculate that people sometimes achieve higher UE function, but with low movement quality, or, conversely, exhibit lower UE function, but with higher movement quality. If quality of movement during daily life is an outcome important to people with a stroke, perhaps kinematic analysis of accelerometry provides a window to assess it.

4.5.2. VISUALIZING BIMANUAL ACCELEROMETRY DATA

A secondary goal of this work was to develop a data representation for bimanual wrist accelerometry that can simplify and complement the 2D color histograms developed in [46]. By averaging data, the “asymmetry” plots presented here better highlight the imbalance in both bilateral UE use and kinematics. Moreover, the plots illustrate inactivity ratio, a feature of limb non-use not contained in the color maps.

4.5.3. LIMITATIONS AND FUTURE DIRECTIONS

The number of participants was limited, and the results should be confirmed with a larger sample size. We only enrolled men, which had the advantage of eliminating any effects of sex in the PCA but limits the scope of interpretation. We did not analyze effects of stroke side and limb dominance. We have not yet studied age-matched controls without a stroke either and doing so would provide a deeper understanding of any non-stroke-related asymmetries in the acceleration magnitude and jerk metrics, for example. Another limitation was that the period of data collection was only one day. Recording accelerometry data for a longer period of time will be important for gaining insight into overall levels of inactivity and their relation to other limb metrics. However, we speculate that, even with relative short recordings, acceleration and jerk asymmetry estimates should be fairly accurate, since it seems unlikely that these properties change significantly on a day-to-day basis. Shorter recording times may therefore be sufficient for such kinematic measures. Finally, there are many ways to measure movement smoothness, and these should be investigated [104].

An important future direction is to incorporate measurements of wrist and finger movement with the measurements of arm movement that accelerometry provides. Our group recently developed the Manumeter, in which a wrist unit with magnetometers senses the magnetic field changes from a magnetic ring worn on a finger [39], [52], [53]. The Manumeter wrist unit also incorporates accelerometers, allowing bimanual wrist accelerometry. Combining finger movement and arm movement measurements should provide greater insight into the variability of UE recovery in individuals who have experienced a stroke [53].

CHAPTER 5. REINFORCEMENT LEARNING BASED ROBOT FOR HAND TRAINING AFTER SCI

5.1. Contributions

In previous chapters, we explored the use of wearable sensing for measuring and providing feedback on amount of hand activity after stroke. We discussed that, to increase amount of hand use, feedback needs to be paired with mechanisms for increasing hand activity. Here, we introduce a robot that aims encourage the use of the impaired hand and arm of non-human primates after a lateralized spinal cord injury. **Background**: Non-human primate studies are helping to optimize protocols for translating neuroregenerative therapies to humans. However, an unsolved need is emulating the intensive movement rehabilitation that will be provided to patients as an obligatory component of any clinical trial. Here we describe a novel robotic system for providing on-demand hand rehabilitation to rhesus macaque monkeys engaging in trials of regenerative therapies after a spinal cord injury (SCI). The SCI is lateralized, producing weakness and incoordination in one hand, similar to the effects of a stroke. Subjects with this injury use their unimpaired hand for daily activities, causing disuse of the impaired hand. **Methods**: To encourage use of the impaired hand, we designed a robot that presents a bimanual coordination task in which manipulating a hand trainer with the impaired hand causes the robot to deliver food treats to the unimpaired hand. **Results**: We show that subjects taught to interact with the robot before injury engaged with the device at a similar rate after injury across a range of hand impairment severity for durations up to 1.5 years after injury. By rewarding different arm and hand movements, we shaped relative use of the arm and hand. We found we could increase the number of exercise repetitions per reward by lowering reward probabilities or increasing task difficulty. The peak grip forces the subjects applied to the robot decreased after SCI, serving as a potential marker of recovery. **Conclusions:** These results are the first example of using a robot to deliver rehabilitative exercise in primates after spinal cord injury receiving a regenerative therapy and provide insights into how robotics technologies can advance translational science for neuroregeneration studies.

5.2. Significance

Non-human primate studies have potential to accelerate translation of neuroregenerative treatments after spinal cord injury, but a key need is providing efficient, quantifiable, intense rehabilitative movement training. This is necessary because rehabilitation is included as an obligatory component of any human clinical trial in order to maximize the potential benefit of treatment. Here, we describe a novel robotic training paradigm that promoted hand activity of monkeys receiving a stem cell therapy after a spinal cord injury.

5.3. Introduction

Regenerative rehabilitation is an emerging field that seeks to understand and optimize potential synergies between regenerative therapies and rehabilitation [64]–[66]. In the context of paralysis following neurologic injuries such as spinal cord injury (SCI), the premise is that any candidate regenerative treatment should be coupled with intensive rehabilitation because sensory motor activity shapes the structure and connectivity of neurons [67], [68]. Optimal functional outcomes will likely depend on optimal forms of movement practice that drive appropriate connectivity.

Regenerative medicine has struggled to scale treatments from rodents to humans. Inserting an intermediate step of studying non-human primates is helping to address this problem [69]–[71].

However, a key need is emulating the rehabilitative movement training that individuals with neurologic injury will receive in any clinical trial. Failing to intensively train a patient following a stem cell graft would be unethical because it would potentially reduce the chances of functional benefit from the treatment. Yet there are currently few standardized protocols or technologies for delivering intense rehabilitative movement training in large animal models. Thus, it is currently difficult to replicate the movement-related inputs that are likely to modulate the effectiveness of neuroregenerative treatments.

In the context of hand recovery, previous studies have typically used pellet retrieval tasks (such as the Brinkman or Klüver Board), to quantify and train monkey hand function (reviewed in [72]). The task requires subjects to retrieve pellets from wells of different orientations and depths. While performing this task allows hand dexterity to be quantified, it requires substantial finger dexterity to perform, and a human trainer to replenish the wells. Other studies have used sleeves that cover the hand to encourage use of the hand in hemiparetic models, but beneficial neuroplasticity still depends on active training of the hemiparetic hand [73]. One can emulate rehabilitation therapy using chair-based exercises with a human trainer, but this strategy is labor intensive and difficult to quantify.

For humans, robotics technologies have been developed to automate hand movement training following neurologic injury [74], [75]. Robotic therapy now refers to a diverse set of technologies and algorithms that can match or improve the clinical benefits achievable with conventional rehabilitation therapies [76]. Since robotic therapy has shown benefits in humans and is a vetted and increasingly used rehabilitative training strategy, we sought here to reverse-translate robotic movement therapy to a non-human primate model of SCI.

The primate model we studied uses a lateralized spinal cord injury to cause impairment in only one hand. This allows the monkey to achieve daily tasks through the use of their other hand and legs. The behavioral outcome of this model is thus similar to that following a stroke in humans in which hemiparesis causes disuse of one hand, as well as to the behavioral outcome following lateralized SCI in humans. Here, we increased activity of the impaired hand using a bimanual robotic task.

5.4. Methods

5.4.1. SUBJECTS

We studied a total of 38 adult male rhesus monkeys (Macaca mulatta) aged 8.50 +/- 1.70 years and weighing 12.20 +/- 2.25 kg. Twenty subjects received a right-side C7 spinal cord hemisection or hemicontusion lesion (as described in [69]–[71]), producing impairment of the right hand. Nineteen of the injured subjects used the robot before and after lesion and one used the robot only after lesion.

5.4.2. ROBOT DESCRIPTION

The Bimanual Vending Machine (BVM) is a novel, cage-mounted robot for semi-automated training and assessment of non-human primate hand and arm function. The BVM consists of two main subsystems: a hand trainer and a reward system. The key design concept of the BVM is that monkeys manipulate the hand trainer with one hand (the impaired, right hand) in order to bring food treats progressively closer to the other hand (the unimpaired, left hand) via the reward system (Figure 26).

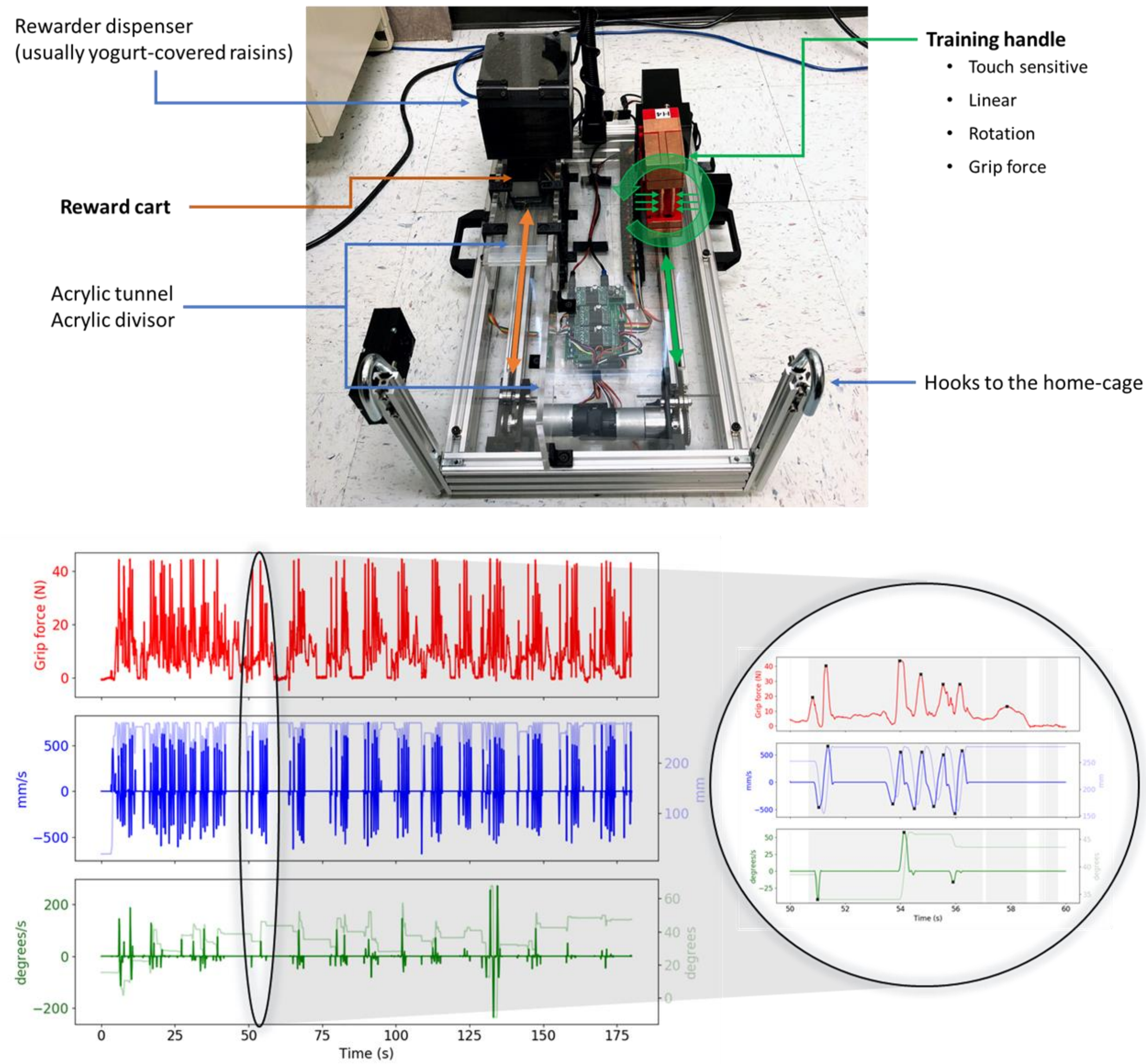


Figure 26. The Bimanual Vending Machine and sample data. Top: The Bimanual Vending Machine. Subjects manipulate the hand trainer on the right track by touching, gripping, pulling, or rotating it with their impaired, right hand. Manipulating the hand trainer causes a reward cart on the left track to progress toward them through a clear acrylic tunnel, to an opening where the subject can grasp the reward with their unimpaired, left hand. To prevent using the unimpaired hand to both manipulate the hand trainer and retrieve the reward, the reward cart is programmed to retract promptly into the tunnel if the monkey stops touching the hand trainer. A tablet computer interfacing to a microcontroller controls the hand trainer and reward subsystems. Cameras mounted on the device record data to the tablet computer. The device is hung from the front of the cage using hooks. Bottom: Sample data showing the sensed grip force, handle velocity along the track, and handle rotation speed. To count exercise repetitions (or “counts”) in each degree of freedom, we identify peaks in these sensed variables.

5.4.2.1. HAND TRAINER

The hand trainer consists of a 3D-printed handle mounted on a linear track of 260 mm and attached to a belt drive controlled by a motor (19:1 Metal Gearmotor 37D, Pololu) with an encoder giving displacement measurement with a resolution of 0.10 mm (Figure 1). The linear track is positioned in front of the right, impaired hand and allows four types of input: touch, hand grip, pulling and pushing along the linear track, and rotation (which can be accomplished by forearm pronation and supination, for example).

To measure hand grip force, two steel bars are connected to a load cell (TAL220, up to 98 N). The handle is enveloped in copper tape connected to a microcontroller to enable capacitive touch sensing. To allow rotation, this handle system rotates on a DC motor (50:1 Metal Gearmotor 37D, Pololu) measured with an encoder with 0.11 degree of resolution.

A custom printed circuit board with a load cell amplifier (INA125P, Texas Instrument) and a microcontroller system (Teensy 3.2) collects and transmits the data from the presence and touch sensors, load cell, and motor positions to the main controller board (Arduino) at 100 Hz using UART serial communication.

5.4.2.2. REWARD SYSTEM

The reward system is designed so that manipulating the hand trainer drives food treats (yogurt-covered raisins and/or almonds) toward the subject. A custom-designed, automatic, reward dispenser delivers the treats into a rewarding cart that rides on a track of 280 mm length aligned with the non-injured side of the subject. The system first drops 1-3 treats (the “reward”) into the cart when the cart is positioned at the farthest point away from the cage. Interaction with the hand trainer then drives the reward cart closer toward the subject. The reward cart is equipped with an array of three reflectance sensors (GP2S60, Sharp) that determine when a reward is available and when it is retrieved by the subject. To avoid subjects retrieving rewards prematurely, but to still allow them to see the reward progressing toward them, the reward cart travels inside a clear acrylic tunnel and only exits the tunnel and becomes accessible to the subject as it nears the cage. The edges of the tunnel are protected with silicone padding to avoid finger pinching when the reward cart retreats.

Software measures prevent the subject from compensating, defined as using only their non-impaired hand to operate the machine. To prevent compensation, the reward cart is programmed to promptly retract back into the tunnel if the monkey stops touching the hand trainer. Thus, the only way to retrieve a reward is for the monkey to keep the impaired hand on the hand trainer and then to use the unimpaired hand to pick up the reward from the reward cart.

5.4.3. TRAINING MODES

Three different modes can be used to train the subjects to interact with the robot and to progressively challenge hand function: 1) Touch Mode, for which the subject only needs to touch the handle with either hand to drive the reward cart closer. In this mode, bimanual activity is not required. This mode is designed for familiarization with the device and the early phases of learning; 2) Bimanual Touch Mode, in which subjects use their right (impaired) hand to interact with the hand trainer and their left hand (unimpaired) to collect rewards. This mode is used to learn the bimanual task and to promote use of the impaired limb early after SCI before a gripping motion is possible; and 3) Parallel Mode, in which, like Bimanual Touch Mode, subjects use the right hand to grip the hand trainer and the left hand to collect rewards. In this mode, monkeys drive the reward card by squeezing the handle, pushing or pulling the handle, or rotating the handle (or some combination of them, thus the name Parallel Mode).

In Parallel Mode, a “repetition” or “count” of each of the three possible exercises is defined as a peak in the linear or rotational velocity, or a peak in the derivative of the force applied to the handle (Figure 26). Peaks are detected using the peak finder function in the SciPy Python Library with prominence threshold set to 100 mm/s, 10 degrees/s, and 3 Newtons for linear motion, rotation, and gripping of the handle, respectively. Each peak corresponds to a roughly bell-shaped profile in the velocity or force (Figure 26).

For Parallel Mode, the amount of activity required to obtain a reward can be graded using the control software. Specifically, the contribution of each type of exercise to the amount the reward cart progresses along its track is graded through a software gain parameter for each exercise. Setting this gain has the effect of setting a difficulty, defined as the required amount of upper extremity activity, as measured by the hand trainer, to drive the reward cart from to the beginning of the linear track to the cage. For grip force, difficulty is specified in Newtons, for push/pull in millimeters and for rotation in degrees. Subjects can choose how to achieve the needed amount of activity, e.g. a difficulty of 200 Newtons for hand grip can be achieved by exerting four grips with peak force of 50 N or 10 grips with peak force of 20 N. The default difficulties for gripping, push/pull, and rotation were set to 200 N, 6000 mm, and 540°. When difficulty was changed, each gain was scaled by the same factor.

5.4.4. PROBABILISTIC REWARDING

A probabilistic rewarding paradigm was implemented to increase the exercise to reward ratio. Once the subject drives the reward cart to the edge of the tunnel, this paradigm allows the cart to proceed out of the tunnel on the next exercise repetition only if a computer-generated random number between 0 and 1 falls below a set value (the reward chance). For the times the reward cart is not allowed to come out of the tunnel, the reward cart returns to the beginning of the linear track, at which point the subject has to drive it forward again to the tunnel edge with impaired hand activity to have another chance at accessing the reward.

5.4.5. QUANTIFYING ENGAGEMENT

We were interested in quantifying the level of engagement with the robot when it was on their cage. Since the robot is touch sensitive, one approach for doing this is to measure the percentage of session time the subjects spend touching the robot. However, we noted that some subjects kept holding the handle when they ate the reward, while others did not. Maintaining contact with the robot while eating biases touch time in way that make it seem like these subjects had higher engagement. Therefore, to reduce this effect, we quantified engagement with the robot as the ratio of 30 second periods during which the subject touched the robot to the total number of 30 second periods when the robot was on the cage (thus allowing for eating time, with or without touching the robot). We computed this measure for different time windows and found no conceptual differences in the results for different time windows, so we present the results for the 30 second window here.

5.4.6. DATA ANALYSIS

Temporal data is presented in weeks pre- and post- SCI. For subjects with multiple training sessions in one week, the variable of interest was averaged across the sessions in that week. If a subject did not use the robot in a given week, data were interpolated from the nearest week. The same approach was used for extrapolating the data, replicating their first and last data points through prior and/or subsequent weeks to keep the number of subjects constant throughout time, in order to visualize the ensemble average over time. However, only actual data points were used for all bar plots and statistical analysis.

5.5. Results

Our primary goal in developing the BVM robot was to provide non-human primates with rehabilitative hand movement exercise after SCI. Here, we analyze data acquired with the device over 200 hours of use total among 37 subjects. During this period, the human trainers freely altered training parameters (session duration, difficulty, and reward chance) with the goal of promoting more exercise repetitions, or sometimes, to perform experiments that tested the effects of those parameters.

5.5.1. LEARNING TO USE THE BVM

A total of 37 subjects learned to use the BVM before SCI. Training sessions were offered to the subjects 1-5 times per week, for 3-60 minutes per session. Trainers started the subjects in touch mode, spending an average of 0.6 +/- 0.21 hours over 4.50 +/- 3.28 weeks in this mode before progressing to bimanual touch mode for another 1.61 +/- 2.94

hours over 6.68 +/- 5.89 weeks. A total of 27 subjects eventually learned to use the robot in parallel mode. Of these, 18 subjects received a SCI. After SCI, the trainers again progressed subjects from touch mode (0.37 +/- 0.29 hour over 2.64 +/- 1.49 weeks) to bimanual touch (2.38 +/- 2.04 hours over 9.33 +/- 8.07 weeks) to parallel mode. One subject learned to use the robot only after he had already experienced a SCI and progressed to parallel mode after 0.33 hours over 2 weeks of touch mode and 1.2 hours over 8 weeks of bimanual mode.

Two subjects found a way to partially compensate with their unimpaired hand during parallel mode. They achieved this by using the unimpaired hand (or both hands) to manipulate the hand trainer and thereby drive the reward cart forward. Then, while holding the hand trainer with the impaired hand, they reached with the unimpaired hand to obtain the treat. Even though this type of compensation still requires activity of the impaired hand, the repetitive activity that drives the cart arises primarily from the unimpaired hand. For what follows, we focus on data from subjects who used the BVM in parallel mode without such compensation both before and after SCI (n = 13). The data after SCI represents 97 hours of usage over 78 weeks and includes over 200,000 exercise repetitions.

5.5.2. ENGAGEMENT WITH THE BVM ROBOT

Figure 27 shows the means across animals of three quantitative measures of robot use – engagement, exercise rate, and grip force – before and after SCI. Also shown are the time evolution of three parameters that the trainers manipulated – session length, training difficulty, and reward chance.

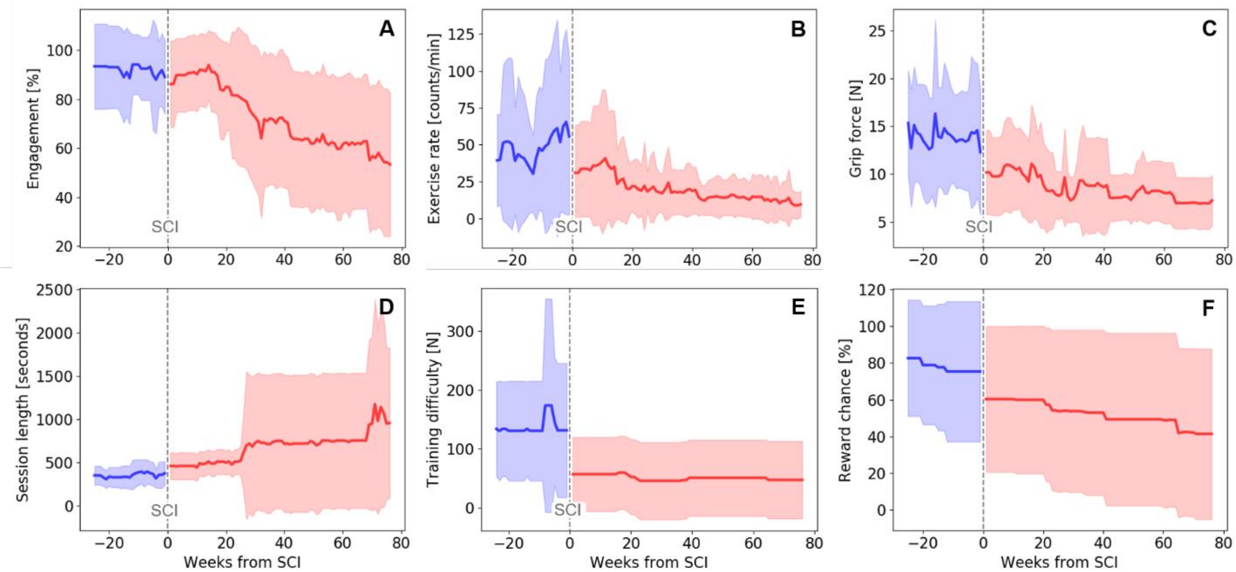


Figure 27. Overview of BVM usage in parallel mode. Usage data are shown before and after SCI (top row - engagement, exercise rate, grip), as well as robot parameters (bottom row -- session length, difficulty, and reward chance). Shown are the average +/- std for 13 subjects who used the BVM in parallel mode both before and after the SCI. This subject began using the robot one year after the SCI, when he showed some return of hand movement.

First, we focus on engagement – what percent of 30 second time periods did the subjects choose to interact with the robot while it was on the cage? Before SCI, engagement was 92% +/- 13% and after the SCI it was 88 +/- 14%, a non-significant difference (Figure 27A). Note that the trainers decreased difficulty after SCI (Figure 27E) to help the animal re-learn to operate the robot in parallel mode, and this may have helped to keep them engaged.

Engagement did then decrease steadily to about 50% over the 80 weeks of robot use after SCI (Figure 27A). However, during his period the trainers increased session length and decreased reward chance, on average, (Figure 27D and Figure 27F), which, while allowing subjects to achieve more exercise repetitions, may have decreased engagement. Indeed, engagement steadily dropped within a session for three subjects who experienced 60-minute training sessions at low reward rates (Figure 28A). Another possibility that could explain decreased engagement over the time after SCI is that subjects became less interested in the robot task the more they experienced it. However, when we divided data into sessions that occurred during the first 20 weeks versus second 20 weeks after SCI (controlling for duration and reward chance), there was not a significant drop in engagement (Figure 28B).

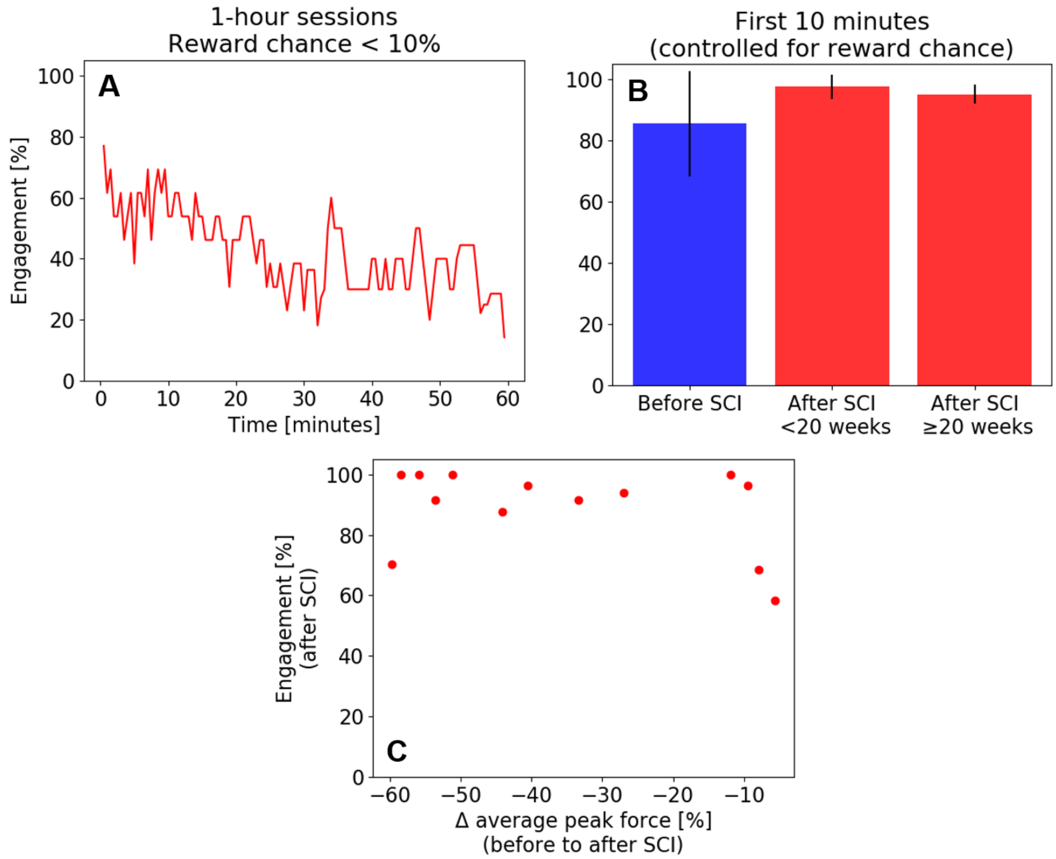


Figure 28. Quantifying Robot Engagement. A: Engagement dropped steadily during longer sessions with low reward chances. Shown is the average engagement for three subjects who trained with these parameters. B: Engagement remained high for sessions 20 weeks after the SCI. Here we selected sessions for subjects with the same reward chance before and after SCI, in both time periods (< 20 weeks, and > 20 weeks), and looked only at the first ten minutes of training C: Engagement in the first parallel session after SCI remained high for subjects with a range of hand impairment levels, quantified as the change in grip force after SCI. Each point is a subject.

A key question is whether more impaired animals were less engaged. The peak grip force used to drive the reward cart decreased significantly after SCI (Figure 27C). Using the individual decrease in hand grip force as a marker of hand impairment, we found no significant relationship with engagement. That is, subjects with a larger drop in hand force still exhibited a high engagement percentage (Figure 28C).

In summary, SCI-injured subjects with a range of hand impairment remained engaged with the robot during periods lasting up to 1.5 years. Engagement progressively decreased during longer training sessions with low reward chances.

5.5.3. EXERCISE WITH THE BVM ROBOT

Subjects achieved 57 +/- 54 exercise repetitions/minute with the BVM before SCI, and 30 +/- 22 repetitions/minute after SCI, a significant decrease (Figure 27B). Exercise rate decreased slightly over the 80-week period we monitored after SCI, possibly again due to the increased session lengths and lowered reward chances. The longest sessions that we allowed were sixty minutes, which is the length of a typical rehabilitation therapy sessions for humans. During these sessions, subjects achieved on average 1138 +/- 1096 exercise repetitions.

5.5.4. SHAPING HAND AND ARM ACTIVITY

Across all parallel mode sessions, 39% of repetitions were grips, 44% push/pull and 17% rotation of the handle (Figure 29), indicating that the subjects chose a variety of strategies to drive the reward cart, as, indeed, parallel mode was designed to allow. However, to potentially target rehabilitation to specific movement, we tested whether we could shape the relative use of these three motions. Four non-injured subjects who were experienced with parallel mode used the robot under four sequential conditions. Each condition changed how the different types of hand and arm activity contributed to the movement of the reward cart (i.e. the “difficulties” associated with each degree of freedom – DOF).

For the first eight weeks, we rewarded all activity types (i.e. gripping, push/pull, and rotation, difficulty gains were set to 200 N, 6000 mm, and 540° respectively). During this period, subjects predominantly gripped the handle to obtain rewards (Figure 29). For the next ten weeks, we removed the contribution of gripping through software and subjects therefore had to find an alternative solution to drive the reward cart. This change in gain triggered a significant increase in total exercise activity (t-test $p<0.01$) mostly through a significant increase in the two other activity types: rotation (t-test $p<0.05$), and pull/push (t-test p<0.01). However, even though animals started exploring the other types of activity, they continued to grip the handle as well (t-test p=0.25). This may have been due to the mechanical association of these two activities, as most animals would squeeze the handle while they were pulling and pushing, masking which activity was actually being rewarded.

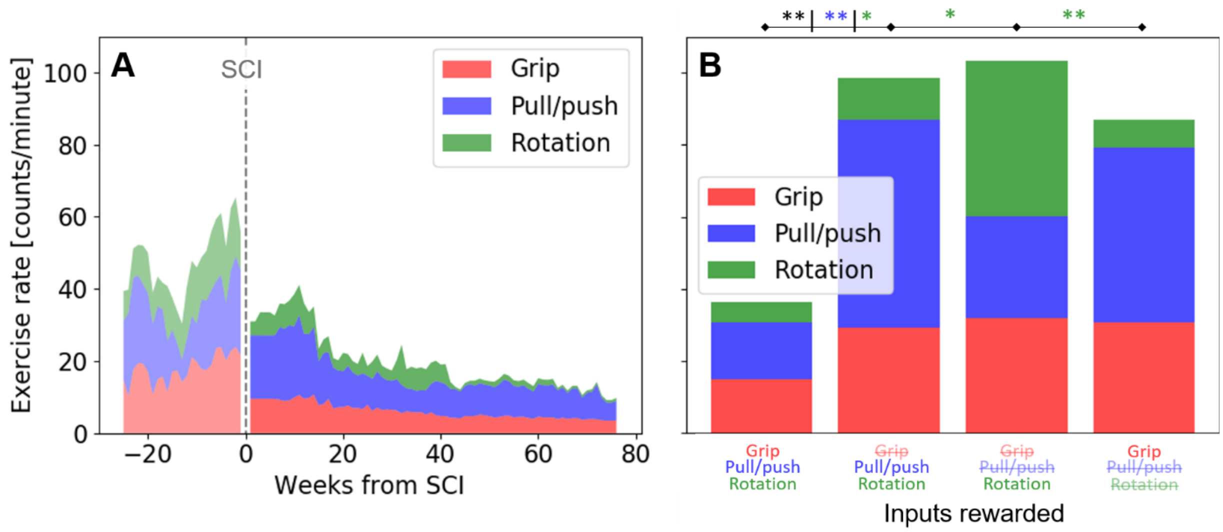


Figure 29. Shaping Exercise Motions. A: Exercise rate for each of the degrees of freedom (DOF) of the robot across all parallel mode sessions, measured in counts/minute, where a count is an exercise repetition. This is data from all 13 subjects who used the robot in parallel mode before and after SCI. B: Exercise rate for a subset of four subjects before SCI as we sequentially varied the difficulty associated with each of the three DOF. Each vertical bar summarizes data from a time period ranging from 6-8 weeks for the four subjects. A line through a DOF indicates that we removed the effect of that DOF on the reward cart during that time period. * = p < 0.05; ** p < 0.01, paired t-test.

The robot experienced a mechanical failure during the subsequent six weeks, but in a way that logically continued the experiment. Specifically, the pulley on the hand trainer track began slipping on the motor shaft causing push/pull movements to be incorrectly sensed. In this situation, even though counts remained high for push/pull, the size of each movement was largely reduced due to the slippage, causing push/pull to have little effect on the movement of the reward cart (similarly to when we made squeezing the handle have little effect through the software). This change caused animals to increase rotation activity (t-test $p<0.05$) while still squeezing and pushing/pulling.

Finally, for eight more weeks, we removed the contribution of rotation and push/pull (now through software with a repaired robot) and re-enabled the gripping gain such that gripping was the only activity that drove the reward cart forward. This re-weighting of gains caused a significant reduction in rotation activity (t-test $p<0.01$), but there was no change in push/pull or grip activity.

In summary, removing the ability of a specific movement to drive the reward card caused subjects to search for and increase other movements that worked.

5.5.5. INCREASING THE AMOUNT OF EXERCISE

A goal for the robot was to generate a large amount of hand activity, which required consideration of how to reduce the ratio of exercise repetitions to rewards. We explored two training strategies for achieving this. First, we implemented a probabilistic reward scenario in which subjects manipulated the hand trainer to bring food treats to the end of the tunnel, but the food cart emerged from the tunnel at a defined reward chance and retracted otherwise. By lowering the reward chance, we sought to drive more hand activity per reward. Indeed, counts per reward increased as we decreased reward chance (Figure 30A, $p < 0.001$ – we kept difficulty low for these sessions). Subjects who exercised at a 3% reward rate accomplished an average of 65 +/- 32 exercise repetitions per reward (n=8, 231 sessions).

The second strategy was to increase difficulty thus requiring more hand activity to drive the reward cart to the end of the tunnel. Again, counts per reward increased as we increased difficulty (Figure 30B, $p < 0.01$ – we kept reward chance high for these sessions). Subjects who exercised at the highest difficulty we tried (200 N for gripping) accomplished an average of 35 +/- 40 exercise repetitions per reward (n=5, 84 sessions).

We explored the effect of increasing session duration on the exercise repetitions achieved using these two strategies, for two subjects for each strategy. For all subjects, the number of exercise repetitions increased approximately linearly with the total training time over a 3-week period (Figure 30C). The highest slope (and therefore shortest training time to achieve a given count level) was achieved by one subject who trained with high difficulty and high reward rate.

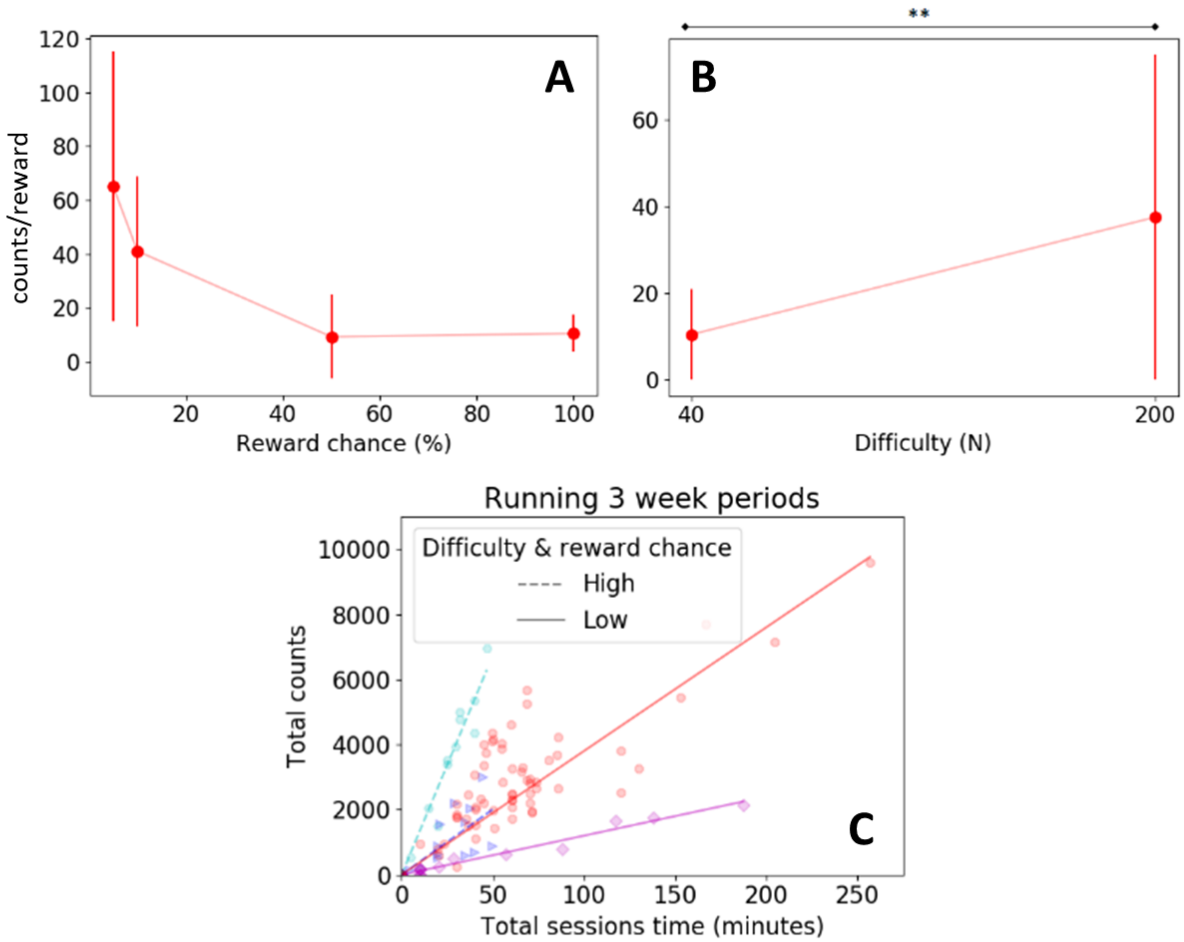


Figure 30. Strategies to increase the exercise to reward ratio. A: Low reward chance/low difficulty strategy – lowering reward chance increased exercise repetitions (counts) per reward. For this data, we held difficulty constant at a low level 40 N. B: High reward chance/high difficulty strategy – increasing difficulty increased counts per reward as well (** $p < 0.01$, t-test). For this data, we held reward chance at its maximum value, 100%. C: Using a running window of three weeks over months of data, we calculated total training time during the three weeks as we varied session length for four subjects with a SCI (each subject is a different color and marker type; each point is a three-week period). Two subjects trained with each strategy. Total counts increased approximately linearly with total training time for each subject, with the highest slope (and therefore shortest training time to achieve a given count level) associated with one of the subjects who trained with the high reward chance/high difficulty strategy.

5.6. Discussion

Robotics technologies are increasingly being developed to automate tasks that have not been previously automated, including medical rehabilitation following neurologic injury. Here, we described the development and testing of a novel robotic therapy device designed to improve the evaluation of regenerative therapies in a large animal model. Our primary design goal for the BVM was to emulate movement rehabilitation provided to neurologic patients as an obligatory component of any human clinical trial. We asked: “how can we deliver engaging, intensive, on-cage, movement training of the hand, gradable for very impaired hands up to less impaired hands, at an appropriate reward dispensing rate over rehabilitation-typical time periods?” We were constrained by the nature of the model – a hemi-injury to the spinal cord – and thus created a robotic task that senses and requires bimanual coordination.

Our key results were as follows: We were able to promote activity of the impaired hand in all animals exposed to the BVM robot, although 27% of subjects did not progress to the most challenging mode – parallel mode – and 7% of animals who progressed to parallel mode learned a strategy to partially compensate with the unimpaired hand. Subjects were highly engaged with the robot before injury and remained engaged months after injury. Engagement progressively declined during longer sessions. After SCI, subjects achieved an average exercise rate of about 30 counts/minute, through a mixture of arm and hand motions. We were able to shape activity toward gripping, push/pull, or rotation by changing the difficulty of each of these degrees of freedom, although subjects typically persisted in performing the movement that worked previously, as well as adding the new movement (a result also found in an experiment studying human motor search [112]). Decreasing reward rate or increasing difficulty increased the ratio of exercise repetitions to reward. We discuss now the potential of the BVM robot to improve translational science of regenerative rehabilitation, then limitations and directions for future research.

5.6.1. TOWARD ROBOTIC REGENERATIVE REHABILITATION SCIENCE

We developed the BVM to provide hand rehabilitation exercise for a specific model of SCI. Does the BVM drive enough hand activity to cause a rehabilitative response? Surprisingly, the adequate dose of hand rehabilitation is still debated, and the dose-response curve in the context of neuroregenerative therapy is unknown. Perhaps the best data for developing a guideline comes from a meta-analysis of a series forepaw rehabilitation experiments in a rat model of stroke [113]. These data suggested a threshold effect of rehabilitation – at least 300 reaches per day were required to see a positive effect – when training sessions were provided five days per week for three weeks. Taking three weeks as the time unit for evaluating dosage, this means we should aim to provide at least 4500 exercise repetitions over the three weeks. We achieved this for two subjects for whom we experimented with longer session times. Each subject used a different strategy – low reward rate/low difficulty or high reward rate/high difficulty. These subjects were rewarded ~51 and ~40 times per week, which meets site guidelines for calories from food rewards. Two other subjects experienced longer sessions but did not reach 4500 repetitions. However, there was a linear relationship between session duration and counts, so further increasing training time would be expected to allow these subjects to meet this criterion. If the trend apparent in Figure 30 holds for more subjects, the high reward rate/high difficulty strategy may allow this to happen with overall shorter training time.

The current standard approach for assessing and promoting hand movement practice in non-human primates are pellet retrieval tasks (such as the Brinkman or Kluver Board). The BVM fully automates training whereas a conventional pellet retrieval board approach requires a human to replace pellets in the wells. The pellet retrieval approach also has the limitation that subjects with severely impaired hands cannot retrieve treats from the slots, although this can be helped by designing wider, shallower slots. The BVM provides a means for trainers to progress subjects through varying levels of task difficulty, mimicking what commonly happens in human rehabilitation. Trainers can select one of the three training modes – touch, bimanual touch, and parallel – and, indeed, trainers had subjects spend on average approximately two months in bimanual touch mode after SCI, before progressing to parallel mode. The trainers could also vary the difficulty of parallel mode using the difficulty parameter that specified the amount of upper extremity activity needed in each DOF to drive the reward cart out of the tunnel.

Is the type of exercise activity that the robot encourages comparable to what happens in human rehabilitation? Rehabilitation therapists incorporate three main activities into therapy sessions: 1) activities aimed at helping patients learn how to achieve functional goals (in which case they often allow compensation with the unimpaired hand in persons with hemi-injuries); 2) activities aimed at improving quality of movement (in which case they discourage compensation during training); and 3) activities aimed at completing a high dose of exercise (again, typically, while discouraging compensation during this exercise). The BVM mainly focuses on the last activity - exercise dose, and like a therapist, prevents compensation. Many studies have found that achieving a high number of simple movements is rehabilitative. For example, Butefisch *et al.* found a therapeutic benefit of performing a high dose of repetitive, power grasping after stroke [114]. Robotic therapy devices that encourage a limited repertoire of stereotypical arm and hand movement have also been found to be therapeutic after stroke (see review [115]). Studies with patients who have an SCI are scarcer but also suggest efficacy (see review [116]). Thus, training with the BVM is different than what happens during training in a conventional rehabilitation program, it does replicate a beneficial component of rehabilitation.

The BVM is also potentially useful for translational science because it quantifies the amount and content of rehabilitation exercise. Thus, going forward, it will be possible to include the amount and type of rehabilitation exercise that subjects achieve as a covariate in analyzing the effects of regenerative treatments. Further, the BVM can generate novel measures of recovery. Here, for example, we found that the grip force (i.e. the peaks in hand grip pulses that subjects used to drive the robot in parallel mode) were sensitive to SCI and increased in one subject after stem cell engraftment. Other measures will likely be possible.

5.6.2. LIMITATIONS AND FUTURE DIRECTIONS

One limitation of the BVM is that 7% of subjects partially compensated with their unimpaired hand. We recently developed an algorithm using presence sensors embedded in the hand trainer to detect which hand is engaging the hand trainer, and we can now prevent partial compensation. Another limitation is that the most challenging mode – parallel mode – focuses on power grasp, which exercises gross finger flexion. Finger extension and individuation will also likely be important targets [117]. We are currently exploring a new training mode in which subjects must exert a finger extension force against a plate attached to hand trainer to drive the reward cart. It is also possible to develop other types of handles that, for example, better challenge finger dexterity. On the other hand, if it were desired to target rehabilitation of hand strength, we have developed a robotic protocol in a rat model for promoting large gripping forces with an analogous device [118]. Such a grip strength-building protocol could potentially be applied with the BVM. Further, we have not yet designed modes that train combined hand and arm coordination.

Another possibility for promoting dexterity and providing training variety is to combine training with the BVM with training in a pellet retrieval task. It is possible to achieve 500 pellet retrieval motions per day by placing a treat pellet in one of the wells and requiring the animal to clear all pellets before refilling, including another treat pellet [73]. Robotics technology could automate well refilling, and automatically quantify pellet retrieval using sensors. Implementing a hand trainer for the BVM comprised of a small set of sensorized wells is one approach that would allow further control over reward frequency.

Proprioception is another important function often compromised by neurologic injuries, and indeed, baseline finger proprioception predicts benefit from robotic hand rehabilitation after stroke [119], [120]. Regenerative therapies may form relay circuits that carry somatosensory information, including proprioception. A key direction for future research is to determine whether the BVM robot can be used to re-train and quantify somatosensation.

We developed the robot for use in a model of SCI, but, as mentioned above, this model of SCI mimics the hemiparesis of stroke. Thus, the BVM may also be useful for future research on non-human primate models of stroke.

Finally, we reverse-translated the concept of robotic therapy, which has primarily been developed for humans, to a non-human primate model of SCI. Some aspects of the BVM robot design are unique to the nature of the user, such as the use of food rewards or the requirement to prevent compensation, although the compensation prevention strategy we implemented might be useful for ensuring scientific quality of studies of home-based training of humans. Nonetheless, we expect that insights gained with the BVM will provide new directions for robotic therapy for humans. For example, with non-human primates, we could no longer verbally instruct the subject how to use the robot, and instead relied on a reinforcement learning (RL) approach, in which a scalar variable (the reward cart location) indicated to subjects that they were performing the desired movements. There have been limited attempts to implement RL-based motor training in robotic therapy for humans, perhaps precisely because therapists have a tradition of verbally instructing patients in a multitude of details about their desired and actual movement performance. However, it has recently been hypothesized that stimulating RL mechanisms may be important for promoting movement recovery, since these mechanisms are a primary way by which humans improve motor skill outside of coached training sessions. Solving a RL problem requires exploration, which may be required to identify subject-specific optimal movement strategies. What we learn about the parameters that determine the efficacy of RL-based motor rehabilitation with non-human primates will be useful for optimizing this strategy with humans.

CHAPTER 6. CONCLUSIONS AND MAIN CONTRIBUTIONS

Rehabilitation of the upper extremity is paramount to achieve independence and increase quality of life after a neurologic injury. This dissertation focused on understanding upper extremity use after neurologic injuries and developing tools to help the rehabilitative process in the living environment. We first summarize the main contributions in the areas of wearable sensing of hand function, then robotic training of hand function in non-human primates. We then discuss limitations and directions for future research.

6.1. Wearable sensing for monitoring and feedback of the upper extremity

The use of wearable sensing for health-related monitoring has vastly increased in the past few years. It allows monitoring in the “wild”, outside-of-the-clinic. Yet, it is still unclear what information, outside of that available with clinical assessments, can be gained from wearable sensing of UE movement for people after stroke, and how to use that information to promote hand movement recovery.

After reviewing the wearable sensing literature, we argued that there are limited options for non-obtrusive, out-of-the-clinic monitoring of distal movements, such as wrist and finger movements - technology that could be applied to hand rehabilitation after neurologic or orthopedic injuries the wearable sensing on upper extremity monitoring field. To tackle this problem, our lab has previously developed the Manumeter. The Manumeter is a wristwatch-like device that works in companion with a magnetic ring worn on the index finger to estimate wrist and finger angles. However, our previous approach toward quantifying hand movement with the Manumeter required subject-specific calibration and offline computation. In CHAPTER 2, we showed the development a threshold-based algorithm, HAND, to address these problems.

We first investigated the HAND algorithm accuracy through a robotic system that emulates hand and wrist movements, and found it counted emulated movements with accuracies from 70 to 93%. However, some of the emulated movements were well below human average speeds. In our analysis, movements with peak velocity below 200 degrees/second (down to 20 degrees/second) were classified as slow movements and were the main source of inaccuracy.

We further investigated the algorithm accuracy through in-lab experiments. An average of 90% accuracy for unimpaired participants and 80% for stroke survivors was found. In both cases the Manumeter tended to overestimate the counts. We attributed some of the inaccuracy to participants with stroke making multiple movements when changing from one posture to the next. Pedometers have been reported to have similar accuracy (70% - 90%) when measuring distance traveled outside of the clinic; therefore, there is utility for wearable devices at this level of accuracy.

In CHAPTER 3, we investigated the efficacy of real-time feedback on hand activity and motor recovery with 20 stroke survivors. Half of the participants received feedback and half of them did not. The goal of this study was to investigate the efficacy of real-time feedback of hand movements in increasing hand activity and motor recovery. Participants showed a significant increase in the clinical outcomes FMUE, ARAT, and MAL-HW as a function of time. Both groups showed a non-significant increase in BBT from baseline to post-therapy, which was sustained (also not significant) at 3-month follow-up only by the experimental group. There was no significant difference between groups in number of days wearing the Manumeter, however participants in the experimental group wore the Manumeter for significantly longer each day. Real-time feedback did not significantly increase hand movement intensity.

We showed for the first time the non-linear relationship between hand capacity and hand use at home. Several studies have correlated amount of upper extremity use with clinical assessments [96], [97]. However, from the learned non-use phenomenon it is expected that this relationship is nonlinear. Here, we showed that participants that scored up to 25 in the BBT did not use their hand at home. A sharp increase in hand use intensity was observed for participants with higher motor capacity.

Providing hand feedback with a daily goal caused a trend toward improved clinical hand function, even though there was no detectable change in amount of hand use. One explanation may be that participants receiving feedback paid more attention to their impaired hand, and similar effects have been previously observed [62]. Other studies have failed at correlating change in clinical outcomes and change in amount of upper extremity use at home [99]. A possible explanation is that the variability in hand use is too high and inducing significant changes in hand use is therefore more challenging than expected. Here, we showed that the necessary increase in hand activity for a detectable change is about 31% of the daily average across the three weeks of therapy. Hand exercise, particularly that requiring repetitive finger extension, is slow and fatiguing, relative to the same number of repetitions of walking. Could it be that the smaller, more fatigable nature of hand extensor muscle limits hand exercise to levels lower than needed to make a change? If so, finding ways to encourage exercise while limiting fatigue are important. Perhaps wearable hand feedback can only be effective if it is coupled with a structured plan for how to achieve higher levels of hand activity.

In CHAPTER 4, we explored the use of bimanual wrist accelerometry in the living environment with stroke survivors. Similar work has been carried out by several other groups and there is a general agreement that standard clinical assessments are correlated with each other and with accelerometry measures of limb use asymmetry [40]. However, we showed that there is additional kinematic information that can be extracted from bimanual wrist accelerometry. It makes sense that wearing sensors on both hands all day long should contain information other than that extracted from a 1-minute assessment in the laboratory.

To explore some of this available information, we proposed and tested, with a small group of 9 stroke survivors, two new metrics: jerk asymmetry and acceleration magnitude asymmetry. We applied the principal component analysis to show that these proposed metrics contain extra information (explaining 31% of the variance in the data) than clinical assessment and hand use asymmetry (that explained 55% of the variance).

We related these two new metrics to movement quality. The clinical hand assessments we used here, the BBT and NHPT, are timed tests of hand dexterity, and are relatively "blind" to how a person achieves the targeted functional task. The kinematic measures, in contrast, likely relate to the quality of the movement: jerk relates to smoothness [103], and acceleration magnitude possibly relates to specialization of the roles of the limbs [108], and/or relative coarseness versus fineness of the movements achieved by each UE throughout the day. This analysis says that there are aspects of movement quality that are uncorrelated with functional status, which has also been previously observed using a robotic therapy device [106].

If this "movement quality" interpretation is accepted, it is an important extension to bimanual wrist accelerometry. The lack of movement quality information has been one of the most challenging aspects of the clinical application of wrist accelerometry clinically [77]. These new metrics could be used as feedback in a similarly to the hand use that we explored in previous chapters.

6.2. Regenerative rehabilitation in non-human primates

In CHAPTER 5, we described the development and testing of a novel robotic therapy device designed to improve the evaluation of regenerative therapies in a large animal model. Our goal was to emulate hand rehabilitation provided as a component of any human clinical trial. The translation of this regenerative therapy to humans is the ultimate goal of this project. We asked: "how can we deliver engaging, intensive, on-cage, movement training of the hand, gradable for very impaired hands up to less impaired hands, at an appropriate reward dispensing rate over rehabilitation-typical time periods?" We were constrained by the nature of the model – a hemi-injury to the spinal cord – and thus created a robotic task that senses and requires bimanual coordination.

Our key results were as follows: We were able to promote activity of the impaired hand in all animals exposed to the BVM robot, although 27% of subjects did not progress to the most challenging mode – parallel mode – and 7% of animals who progressed to parallel mode learned a strategy to partially compensate with the unimpaired hand.

Subjects were highly engaged with the robot before injury and remained engaged months after injury. Engagement progressively declined during longer sessions. After SCI, subjects achieved an average exercise rate of about 30 counts/minute, through a mixture of arm and hand motions. We were able to shape activity toward gripping, push/pull, or rotation by changing the difficulty of each of these degrees of freedom, although subjects typically persisted in performing the movement that worked previously, as well as adding the new movement (a result also found in an experiment studying human motor search [112]). Decreasing reward rate or increasing difficulty increased the ratio of exercise repetitions to reward. The peak grip force the subjects applied to the robot decreased after SCI and recovered in a subject whose spinal cord successfully incorporated a stem cell graft. We discuss now the potential of the BVM robot to improve translational science of regenerative rehabilitation, then limitations and directions for future research.

We developed the BVM to provide hand rehabilitation exercise for a specific model of SCI. Does the BVM drive enough hand activity to cause a rehabilitative response? Surprisingly, the adequate dose of hand rehabilitation is still debated, and the dose-response curve in the context of neuroregenerative therapy is unknown. Perhaps the best data for developing a guideline comes from a meta-analysis of a series forepaw rehabilitation experiments in a rat model of stroke [113]. These data suggested a threshold effect of rehabilitation – at least 300 reaches per day were required to see a positive effect – when training sessions were provided five days per week for three weeks. Taking three weeks as the time unit for evaluating dosage, this means we should aim to provide at least 4500 exercise repetitions over the three weeks. We achieved this for two subjects for whom we experimented with longer session times. Each subject used a different strategy of low reward rate/low difficulty or high reward rate/high difficulty. These subjects were rewarded ~51 and ~40 times per week, which meets site guidelines for calories from food rewards. Two other subjects experienced longer sessions but did not reach 4500 repetitions. However, there was a linear relationship between session duration and counts, so further increasing training time would be expected to allow these subjects to meet this criterion.

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The BVM is also potentially useful for translational science because it quantifies the amount and content of rehabilitation exercise. Thus, going forward, it will be possible to include the amount and type of rehabilitation exercise that subjects achieve as a covariate in analyzing the effects of regenerative treatments. Further, the BVM can generate novel measures of recovery. Here, for example, we found that the grip force (i.e. the peaks in hand grip pulses that subjects used to drive the robot in parallel mode) were sensitive to SCI and increased in one subject after stem cell engraftment. Other measures will likely be possible.

6.3. Future directions

The Manumeter has the potential to be expanded to other target groups (e.g. children with cerebral palsy, people with Parkinson's). Studies with unimpaired, age-matched controls are need to great insight into normative amounts of hand use and hand use variability. From unpublished data, we observed that unimpaired office workers achieve around 12,000 hand movements in a day. Understanding how hand use changes across groups of people performing different daily activities will give important insights on how to more efficiently use the Manumeter to help rehabilitation.

Even though the Manumeter is nonobtrusive and participants enjoyed wearing the device, removing the need of the magnetic ring and use wrist accelerometry to count hand movements would be powerful next step. We have seen this opportunity in experiments performed in the laboratory, in which even hand-only movements caused changes in the wrist accelerometry signal through the movements of the skin, muscles, and tendons. Using wrist accelerometry opens the possibility of using smart watches and expands research to larger and more powerful studies (e.g., recruiting participants through the ResearchKit by Apple and ResearchStack by Android). It would also allow other research groups to apply the methods developed in our laboratory to their own studies, as the current design of the Manumeter requires customized hardware and firmware that makes it less accessible.

For the Bimanual Vending Machine, we will further investigate the effects of the combination of the robotic therapy and stem-cell therapy on hand recovery. There will be in total 10 robots available for training which will support increasing exercise intensity. We aim to correlate amount of hand exercise repetitions with functional recovery. Furthermore, we are investigating methods to incorporate somatosensory measurement and training into the robot as it is another important function often compromised by neurologic injuries that is currently not exploited.

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