Design of a parallel-group balanced controlled trial to test the effects of assist-as-needed robotic therapy

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***Abstract*— In this methods paper, we report on the design of a clinical study testing the efficacy of a newly developed control scheme for robot-aided rehabilitation. To measure the value added by a new control scheme, we pursued a parallel-group controlled clinical study design. This approach enables comparing the effects of the novel scheme, based on the Assist-As-Needed (AAN) paradigm, with those of a less sophisticated, fixed gain, Subject-Triggered (ST) controller. We describe the steps followed in the design of this clinical study, including details on the implementation of the two control modes, and a power analysis to determine the required number of subjects to test a clinically significant difference hypothesis. Finally, we present a method for sequential group assignment with co-variates minimization, capable of guaranteeing a desired level of balance of prognostic factors in the two study groups, a crucial requisite for small-scale clinical studies in rehabilitation. To the best of our knowledge, the study presented is the first one testing, in a controlled fashion, the differential effects of a specific control mode in upper extremity rehabilitation after incomplete spinal cord injury.**

I. INTRODUCTION

The annual incidence of spinal cord injury (SCI), not including those who die at the scene of injury, is approximately 40 cases per million population in the U.S. or approximately 12,000 new cases each year [1]. The average yearly expenses for patients with SCI vary according to severity of injury. For patients with high tetraplegia (C1-4) the average yearly cost due to injury is $1,023,924 for the first year and $177,808 each subsequent year [1], excluding indirect costs such as losses in wages, fringe benefits and productivity, which sum to multi-million dollar figures of estimated per-capita lifetime costs.

Neurologically-induced deficits in motor function are common following complete and incomplete tetraplegia, and result from partial or complete paralysis of muscles. Complete paralysis results in the inability to activate muscles below the level of injury. Partial paralysis occurs from disruption to some but not all neural pathways innervating muscles. As a result of the injury, two thirds of SCI survivors are left with some functional deficit to the upper extremity, which contributes to reduced independence in most daily living activities [1].

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It has recently been suggested that repetitive movement exercise can support recovery by enhancing some form of plasticity intrinsic in the central nervous system [2], [3]. Given the strong relationship between treatment intensity and potential for motor recovery, robotic technologies have been used to automate repetitive movement exercise after incomplete spinal cord injury lesions. Most of the existing research efforts have addressed gait training [4], whereas robotic training of upper-extremity function after SCI is much less developed, with only a few case studies presented so far [5], [6]. This is in contrast to the field of robot-assisted stroke rehabilitation, where large-scale trials have shown that robotic intervention can safely and effectively induce some amount of motor recovery after stroke [7].

A distinguishing feature of rehabilitation robots is that they can implement several different control strategies during interaction with humans [8]. For stroke rehabilitation, it has become more or less clear which interaction modalities do and do not contribute to recovery [9], [10]. However, for SCI this problem is still far from being definitively answered. Despite preliminary studies on animal models suggesting that rehabilitation should leverage plasticity through stimuli similar to those tested for stroke rehabilitation [2], [11], this question still remains to be tested in a clinical study.

This lack of knowledge is surprising, especially if we consider the continuously increasing efforts that roboticists are devoting to the formalization and implementation of shared control modes to facilitate robot-assisted rehabilitation protocols [12]–[14]. A necessary condition for such research efforts to have translational significance is to test their effects in a clinical population. Especially in rehabilitation after incomplete SCI, a field still much in its infancy, such early stage trials should be aimed at giving inputs for further refinement of robot-assisted therapeutic protocols.

A. Developing clinical trials to evaluate robot controllers

Parallel-group controlled trials (PGCT) are particularly useful for determining optimal controllers and interaction schemes to promote recovery. In a PGCT, the specific effect of a treatment modality is assessed by measuring a variable (outcome measure) in a group undergoing treatment, and comparing the outcome measure with the one obtained in a parallel group, where the treatment is withheld. If a clinical study intends to evaluate the specific effects of a novel controller, it should compare the effects of this controller not to the absence of (robotic) rehabilitation, but instead to a different, *gold standard* form of robotic rehabilitation, i.e.

an active control condition. Through this methodology, it is possible to isolate the differential effects of the active treatment, and control for a wide variety of other factors that might have an effect in recovery. In fields where there is a gold standard, this is usually done by comparing the results achievable through a new treatment with literature data. However, application of this approach is made difficult by the fact that there is no robust reference data for robot-assisted upper extremity training after SCI.

In general, testing the efficacy of rehabilitation paradigms is complicated by the large variability of patient populations, both in terms of baseline motor functionality and in terms of pre vs. post improvement of motor function. Moreover, there is evidence that motor recovery after nervous system injuries is highly dependent on some prognostic variables, such as baseline motor function, age, and time since injury [15]. Both factors complicate proper design of clinical trials investigating the effect of a specific feature of the robotic treatment on recovery, requiring potentially high number of subjects to test specific hypotheses. This in turn leads to demand for multicentric studies, especially in SCI rehabilitation, where low prevalence provides challenges even in large cities[1]. Increasing the number of subjects raises the statistical power of the clinical study, and the chance of an imbalance in the distribution of prognostic variables in the population decreases due to the central limit theorem.

Unfortunately, the possibility of implementing such large-scale clinical studies is a luxury that only a handful of research groups can afford, due to the cost of developing and replicating robotic rehabilitation devices and due to time constraints involved in multicentric studies. Also, large-scale clinical studies are not appropriate for early stage trials in which it is desired to test a particular aspect of a therapeutic protocol (e.g. the robot control mode), whose validity can be tested for later inclusion in larger phase-II or phase-III randomized controlled trials. This scheme is in agreement with the framework for staging motor intervention studies, recently proposed in [17]. From the consideration above, it is indeed not a surprise that most of the large-scale clinical investigations of rehabilitation robotics could only test the feasibility of robotic rehabilitation, and could not go in more depth assessing the differential effects of a specific control mode [18].

Based on current models of robotic rehabilitation clinical studies, it is unlikely that clinical evaluations can keep up with the pace of a flourishing literature reporting on the development of novel robotic interaction modes intended for rehabilitation therapy. To allow for small scale yet rigorous evaluation of the effects of such rapidly evolving controllers, this paper presents the design of a clinical study testing the efficacy of a novel controller in upper limb rehabilitation following incomplete SCI and proposes this as a model for early phase robotic rehabilitation clinical studies.

[1]Prevalence of incomplete SCI is roughly 0.1% of the population, whereas in stroke it is 2.9% [16]

II. CONTROL MODES

Two control modes are implemented in the MAHI EXO II [19], a four Degrees Of Freedom (DOFs) exoskeleton used for isolated rehabilitation of the elbow (flexion/extension) and the wrist (pronation/supination, radial-ulnar deviation, flexion/extension). The two control modes, the Assist-As-Needed (AAN) controller, and the Subject-Triggered (ST) controller, are described in the following sections.

A. AAN controller

For the AAN controller (Fig. 1), we adapt the controller proposed in [14], which consists of three main components: subject ability estimation, feedback gain modification, and on-line trajectory recalculation. The subject ability estimation algorithm employed in this study is based on the adaptive controller [20], using the following adaptation law:

$$\dot{\hat{\theta}} = -\Gamma^{-1} Y(x)^T r \tag{1}$$

where Γ is an $n \times n$ constant, positive definite, symmetric matrix; Y is a matrix of regressors which contains known functions of x, which is the task space pose of the end-effector; $\hat{\theta}$ is the vector containing estimates of unknown system parameters; and r is a weighted sum of position and velocity error, defined as

$$r = \dot{\tilde{x}} + \Lambda \tilde{x} = (\dot{x} - \dot{x_d}) + \Lambda(x - x_d) \tag{2}$$

where Λ is a weighting constant. For this study, we extend our previous formulation by introducing direction dependency on the regressor matrix $Y = Y(x, \dot{x})$, considering that an impaired subject might have different levels of disability on their agonist and antagonist muscles. As in [14], we use Gaussian Radial Basis Functions (RBFs) as known functions included in the regressor matrix, but we doubled the set of RBFs for each DOF to account for direction dependence. Another modification over [14] involves the feedback gain modification logic, a component required for modulating the amount of motion assistance in a performance-adaptive way.

For this study, we discretely update the change of the feedback gain, ΔK_D, based on the measured error in the previous task. ΔK_D is defined as

$$\Delta K_D = \Delta K_{D,max} \frac{(r_{avg} - r^*)}{(r^* - r_{min})}, \tag{3}$$

where $\Delta K_{D,max}$ is a bound on the magnitude of change of the feedback gain, r_{avg} is the average error for the previous task, and r_{min} defines the slope of the gain update curve. We use the gain update law shown in (3) rather than directly assigning a feedback gain value for a given subject error performance, as done in [14]. In this way we are able to introduce an error characteristic term, r^*, an upper bound to the allowable error. This term is introduced because even healthy subjects' movement contains natural variability and providing force support to minimize error beyond such variability might be detrimental to motor learning [21].

The generation of the desired trajectory for this controller is handled by a two-part algorithm. The first part assigns an

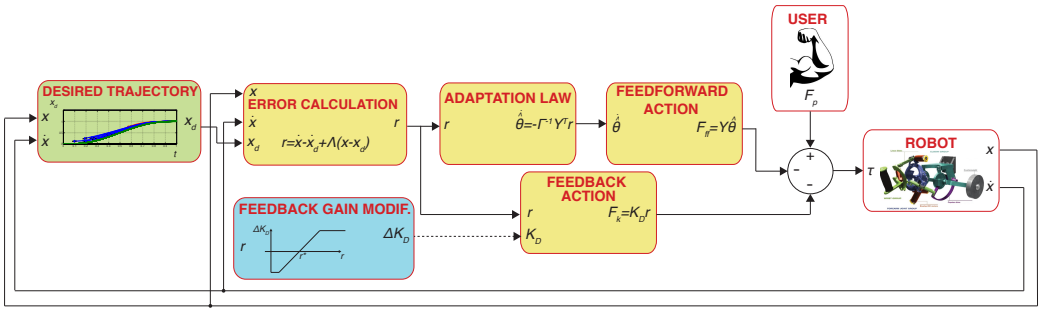

Fig. 1. Block diagram of the AAN controller implemented in this paper. Blocks with a yellow background include components of the adaptive controller [20]. The dashed line refers to a discontinuous update of signal variables, i.e. the feedback gain is changed on a task-by-task basis.

allocated time T_{end} and constructs a nominal desired trajectory based on a physiologically optimal and experimentally validated joint movement profile. The second part of the algorithm implements a conditional trajectory recalculation (CTR), so that when the position of the subject is ahead of the nominal desired trajectory, a new desired trajectory is computed as a piecewise polynomial function. After each recalculation, T_{end} is reduced until the current movement is completed and the updated value of T_{end} is passed for the next task. In an attempt to differentiate between intentional subject involvement and unintentional elastic return due to muscle stretching, the CTR is enabled only if the subject is able to be ahead of the nominal desired trajectory in both previous center-to-periphery and periphery-to-center directions for a percentage (10%) of the last movement when CTR was disabled. This helps guarantee active subject input because the elastic return of stretched muscles typically only aids movement from periphery-to-center. If the CTR is not activated for a given task, the algorithm will increase T_{end} until the subject is able to beat the nominal desired trajectory. During the CTR "off" phase, a ghost cursor following the nominal desired trajectory is displayed to the subject in the GUI in order to motivate the subject to beat the nominal trajectory (see Fig. 2(A) and supplementary video).

Since a lead-type error is not possible when the trajectory recalculation mode is switched on, the RBF amplitude estimates are mostly non-decreasing (in absolute value), in such condition, resulting in an over-estimate of the feedforward assistance. To avoid this problem, the adaptation law in (1) is modified to include a first-order decay of the RBF amplitude estimates only when the error drops below the value r_{min}.

B. ST controller

The ST controller is implemented as a two-state machine. In the first state, the robot is position controlled to keep the the start position (center or periphery), and the subject is visually cued to apply a force towards the direction of the target position (periphery or center). When the force applied by the subject exceeds a threshold F_{th}, and is sufficient to break through the virtual wall along the desired direction, the controller switches to the second state. In this phase, the robot is position-controlled to reach the target through a minimum-jerk trajectory with duration t_{ST}. Although subject input is required to trigger the switch to the movement mode, subjects are not involved in controlling their movements during target reaching. The values of F_{th} are increased by the therapist an a session-to-session, based on subject ability and comfort (pain and fatigue are recorded before and after each session to ensure excessive levels of each are avoided). This is done is to progressively increase the challenge to the subject to encourage active involvement throughout the course of training.

III. STUDY DESIGN

The null hypothesis tested in this study states that the change in motor function for subjects assigned to treatment following the Assist-As-Needed (AAN) paradigm is not different than that the one obtained through treatment following the Subject-Triggered (ST) paradigm.

This study uses a parallel groups design in which participants with cervical motor incomplete SCI (according to American Spinal Injury Association (ASIA) Impairment Scale (AIS) C-D levels) are assigned to either the AAN control group (group A) or to the ST control group (group B). Inclusion criteria were age (comprised between 18 and 75 years), diagnosis of chronic incomplete SCI (at least 6 months prior to enrollment), while exclusion criteria were prior enrollment in robotic rehabilitation studies for the upper arm, any planned alteration in medication for muscle tone for the duration of the study, arthritis, excessive shoulder pain, joint contracture or excessive muscle tone (Modified Ashworth Scale $>$3).

A. Outcome measures

The primary outcome measure considered for this study is the difference in upper extremity ARAT scale [22]. Secondary outcomes of this study are the Graded Redefined Assessment of Strength, Sensibility and Prehension test (GRASSP) [23], the Modified Ashworth Scale [24], and robotic data assessment measures that extract changes in smoothness or directionality of the movement profiles [25].

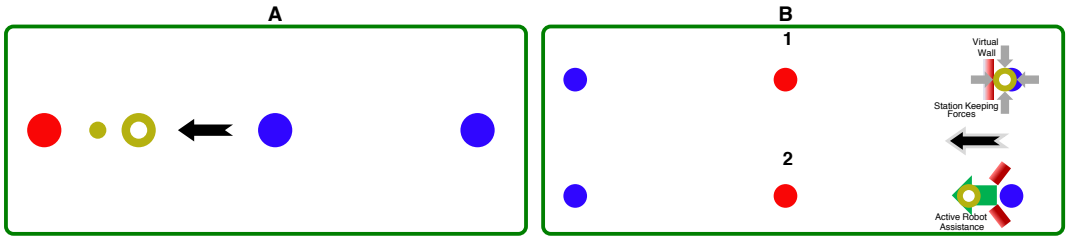

Fig. 2. (A) GUI used in the AAN controller, during the on-line recalculation "off" phase. The red circle corresponds to the active target, the blue circles are the other targets (center and periphery). The current subject position is displayed with the yellow ring, while the ghost cursor is the smaller yellow cursor leading the subject in this center-to-periphery movement (black arrow). (B) Sequence of the two modes of the ST controller. (1) A virtual wall is implemented, and the force required to keep the desired position (blue circle) is continuously measured. When the force exceeds F_{th}, the system switches to mode (2), where the robot implements position control towards the target (red circle).

An additional secondary outcome of this study is assessment of the overall benefits of robotic rehabilitation in subjects with incomplete SCI, obtained by measuring the pre-post change in motor function scores in the entire subject population. The functional outcome measures are evaluated by a trained occupational therapist blind to the assignment of subjects to treatment groups. To avoid inter-rater variability, the same therapist performs the entire set of assessments for a given subject.

B. Study methods

1) Power analysis: The trial is designed to test for significant differences between the change in functional measures obtained through AAN control and the one obtained through ST control. Thus, a 2-sided type I error of 0.05 is used for the primary treatment comparison. Sample size is calculated for a 2-sample t test assuming a common standard deviation of 2 (calculated from the results of a previous study with 8 SCI survivors undergoing resistance training [26]), 90% power, a mean difference of 3 points in the ARAT scale (see outcome measures section below), and a loss rate of 20%[2]. A sample size of 24 admitted participants is required to detect the hypothesized 3-points difference in the two treatment groups, resulting in a final population of 10 subjects per group completing the study (20 subjects in total), given the 20% loss rate foreseen. When merged together in a comparison of the overall effects of both rehabilitation modes, the resulting 1-sample t test with the 20 participants has 90% of power to test significant differences in the increase in ARAT score of 1.5, with $p < 0.05$.

2) Treatment regimens: Each subject participates to a total of fifteen visits. The first two visits involve screening for inclusion and exclusion criteria and baseline assessment on primary and secondary outcome measures, in addition to the ASIA upper extremity scale to verify the diagnosis. During the second baseline visit, each subject undergoes a robotic evaluation session, in which he is asked to perform sixty point-to-point isolated reaching movements for each of four the MAHI Exo-II DOFs enabling measurement of timing, smoothness and directionality measures [25]. Within one week after the last baseline visit, subjects start a program of robotic training, in ten 90-minute long sessions, spread over a period of three to four weeks. At the beginning of each robotic training session, subjects execute an evaluation session, then undergo robotic training, which takes the form of p repetitions per DOF, with p adapted to result in sessions of the prescribed duration. Through this design, we can evaluate whether a specific controller implementation is capable of maximizing the number of repetitions in a given maximum allowed session time, a measure of interest for a rehabilitation trial design. For the AAN controller, both force and timing parameters estimated from the previous sessions are retained as initial guess in the subject-adaptive therapy mode, whereas for the ST controller, the therapist manually sets the challenge parameters (i.e. force threshold F_{th} and time allowed for a movement T_{ST}) on a session-by-session basis, based on subjects qualitative assessment. After the last training session, three post-treatment clinical assessment sessions (one week, two weeks, and two months after treatment) are completed with the therapist, in addition to the robotic evaluations.

3) Sequential group assignment with co-variates minimization: Several variables such as baseline motor function and age can predict part of the potential of recovery after a neurological injury [15], called co-variates for a specific outcome measure. Proper design of rehabilitation trials should achieve balancing the distribution of the most important co-variates [15]. It is possible to guarantee balancing of co-variates without excessive increase in the number of subjects required for the study by adopting techniques such as minimization [27], and its later adaptations [28].

For this study, we developed a group assignment technique that approximates the minimization procedure of [27], and guarantees the equinumerosity of the two groups. As this appears to be the first time that minimization-like assignment schemes are used in clinical trials of robotic rehabilitation, we report the details of our assignment schemes, highlighting the benefits introduced in minimizing imbalances of co-variates using the presented clinical study as a case study, where $N = 20$ and two uniformly distributed co-variates are

[2]The software STPLAN, University of Texas M. D. Anderson Cancer Center, Houston TX was used for the power analysis

considered for minimization.

We first describe the procedure for the simpler case of a single co-variate k. We define $A(i)$ as the set of subjects assigned to group A after i subjects have been recruited for the study, and

$$A(i)_{i+1} = A(i) \bigcup s_{i+1} \tag{4}$$

as the set resulting from having assigned subject $i+1$ to group A. Further, we introduce the operator $\text{mean}_k(\cdot)$ that, when applied to a group, produces as output the mean value of the co-variate k of subjects in the group, and the operator $\Delta m_k(\cdot)$:

$$\Delta m_k(A_{i+1}) = |\text{mean}_k(A(i)_{i+1}) - \text{mean}_k(B(i))|. \tag{5}$$

$\Delta m_k(A_{i+1})$ is the difference in the means of the co-variate k resulting from the assignment of subject $i+1$ to group A. Subject $i+1$ is assigned to group A if the difference of the mean of k between groups A and B, resulting from the assignment of subject $i+1$ to group A is smaller than the difference of the mean of k, resulting from the assignment of subject $i+1$ to group B. Under these definitions, the assignment logic is defined as

$$A(i+1) = \begin{cases} A(i) & \text{if } \Delta m_k(A_{i+1}) - \Delta m_k(B_{i+1}) > 0 \\ A(i)_{i+1} & \text{otherwise.} \end{cases} \tag{6}$$

This assignment method does not guarantee equinumerosity of the two groups after N assignments. An obvious adaption of this simple method consists in ceasing assignment of subjects to group A (or B), when the number of subjects already assigned to group A (or B) equals $N/2$. Simple implementation of this method, to which we will refer to as *sequential assignment*, has drawbacks. In fact, in some cases, for a slight improvement in the difference between the means generated by several consecutive assignments to group A (i.e. $0 < \Delta m_k(A)_{i+1} - \Delta m_k(B)_{i+1} < |\epsilon|$, for several consecutive i, and with ϵ small), group A will be populated rapidly, reaching size of $N/2$ with several subjects to be assigned. At that time, no possible choice on the remaining subjects is possible, potentially leading to a distribution imbalance. To address this problem, we sequentially assign subjects to the two groups by taking into account both needs: i.e. the one of minimizing co-variate imbalance within the population of subjects, and the one of resulting in a desired ratio in the number of subjects between the two groups. This choice can be made by combining the following conditions:

$$\begin{aligned} C_1 &:= |\Delta m_k(A)_{i+1} - \Delta m_k(B)_{i+1}| < |\epsilon| \\ C_2 &:= \Delta m_k(A)_{i+1} - \Delta m_k(B)_{i+1} < 0 \\ C_3 &:= \text{no}[A(i)] < \text{no}[B(i)] \\ C_4 &:= \text{no}[A(i)] = \text{no}[B(i)], \end{aligned}$$

using the assignment logic defined by

$$A(i+1) = \begin{cases} A(i)_{i+1} & \text{if } C_1C_3 + \bar{C_1}C_2 + C_1C_2C_4 = true \\ A(i)_i & \text{otherwise} \end{cases} \tag{7}$$

It is then guaranteed that assignment to group A occurs only if the difference in the mean in the co-variates is substantial. Otherwise, the new subject is added to the least sized group. By defining the threshold ϵ as a linear function of the difference of number of subjects recruited in the two groups (i.e. $\epsilon = \epsilon_0(\text{no}[A] - \text{no}[B])$), it is guaranteed that subject number imbalance is more compensated when it is more needed.

The presented approach can be easily extended to the case of two or more co-variates, creating a co-variates set $\mathbf{k} = \{k_1, k_2, ..., k_n\}$. In this case, the sequential assignment can be performed by assigning a subject to group A if, by doing so, the resulting sum of squared standardized differences SoS_{stdd} is lower than the one that would result from assigning said subject to group B, by defining

$$\text{SoS}_{stdd} = \sum_{i=1}^{n} w_i \Big(\frac{k_i - \bar{k}_i}{\sigma_i} \Big)^2 \tag{8}$$

The benefits of the reported assignment schemes are tested in a Monte Carlo simulation experiment, where recruitment of $N = 20$ subjects is simulated with the distributions of age (a) and ARAT (b) at admission modeled as uniform distributions $a = \mathcal{U}\{31, 70\}$, $b = \mathcal{U}\{1, 57\}$. In each simulated run, four different assignment schemes were compared: *a)* random assignment, *b)* ex-ante optimal assignment, *c)* sequential assignment (defined in (6)), *d)* sequential assignment with control for number of subjects, defined in (7). *Ex-ante optimal assignment* assumes knowledge of the characteristics of all 20 subjects and finds the assignment among the $\binom{N}{N/2}$ possible ones which results in the minimal SoS_{stdd}.

The histogram of the distribution of the difference in the mean value of the two co-variates in the two groups resulting from each assignment schemes is shown in Fig. 3. With sequential assignment, in about 15% of the simulated studies, the inter-group difference of the mean of at least one co-variate is higher than two times the standard deviation of that co-variate. With the modified scheme for sequential assignment, the intra-group difference of means of all co-variates can be limited to less than one standard deviation.

IV. CONCLUSION

This paper presents the design of a parallel-group controlled trial (PGCT) to test the efficacy of a novel AAN controller in robotic rehabilitation after incomplete spinal cord injury. With its design features (presence of an active control condition, blindness of the evaluator to treatment assignment, and execution of a power analysis for the primary study outcomes), this study falls within the category of stage 2, *development-of-concept* pilot studies, despite the relatively small sample size emerging as a result of the power analysis ($N = 20$). As such, to the best of our knowledge, this is the first time this type of study has been conducted in the field of robot-assisted therapy for upper extremity rehabilitation in incomplete spinal cord injury.

In an effort to enable reproducibility of the study, we have provided thorough descriptions of the controller modes and

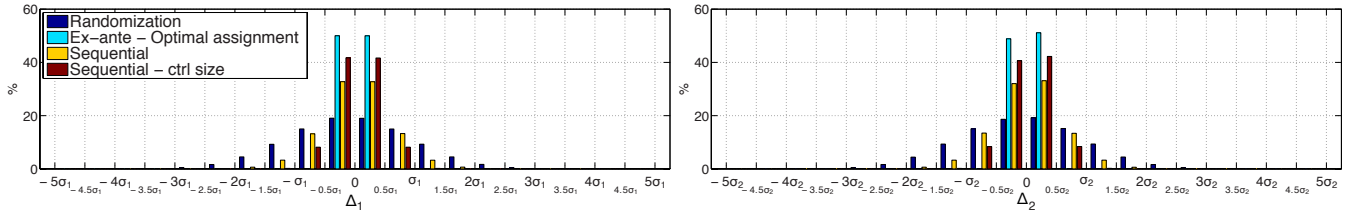

Fig. 3. Distribution of the group means difference between the two co-variates age (left) and ARAT (right) for the 10^4 simulated studies, for the four considered group assignment strategies. The horizontal axis is rescaled considering the known co-variate standard deviation.

treatment regimens. Also, we have introduced some methodological features in the study design which are of interest to the rehabilitation robotics community. In particular, the presented scheme of sequential group assignment with co-variates minimization guarantees the desired level of balance of co-variates in the two groups, a feature that cannot be reliably achieved with unrestricted randomization in studies with low ($N < 50$) sample sizes [29]. In the presence of strong correlation between the value of a prognostic factor and the study outcome, the study loses specificity and suddenly measures an already known relationship: the effect of a prognostic factor on the study outcome. This appears to be a risk that investigators should minimize, considering the rather modest efforts required to avoid it.

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