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Investigation of different stimulation patterns with doublet pulses to reduce muscle fatigue

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Abstract

Introduction: Functional electrical stimulation is a common technique used in the rehabilitation of individuals with a spinal cord injury to produce functional movement of paralysed muscles. However, it is often associated with rapid muscle fatigue which limits its applications. **Methods:** The objective of this study is to investigate the effects on the onset of fatigue of different multi-electrode patterns of stimulation via multiple pairs of electrodes using doublet pulses: Synchronous stimulation is compared to asynchronous stimulation patterns which are activated sequentially (AsynS) or randomly (AsynR), mimicking voluntary muscle activation by targeting different motor units. We investigated these three different approaches by applying stimulation to the gastrocnemius muscle repeatedly for 10 min (300 ms stimulation followed by 700 ms of no-stimulation) with 40 Hz effective frequency for all protocols and doublet pulses with an inter-pulse-interval of 6 ms. Eleven able-bodied volunteers (28 ± 3 years old) participated in this study. Ultrasound videos were recorded during stimulation to allow evaluation of changes in muscle morphology. The main fatigue indicators we focused on were the normalised fatigue index, fatigue time interval and pre-post twitch–tetanus ratio. **Results:** The results demonstrate that asynchronous stimulation with doublet pulses gives a higher normalised fatigue index (0.80 ± 0.08 and 0.87 ± 0.08) for AsynS and AsynR, respectively, than synchronous stimulation (0.62 ± 0.06). Furthermore, a longer fatigue time interval for AsynS (302.2 ± 230.9 s) and AsynR (384.4 ± 279.0 s) compared to synchronous stimulation (68.0 ± 30.5 s) indicates that fatigue occurs later during asynchronous stimulation; however, this was only found to be statistically significant for one of two methods used to calculate the group mean. Although no significant difference was found in pre-post twitch–tetanus ratio, there was a trend towards these effects. **Conclusion:** In this study, we proposed an asynchronous stimulation pattern for the application of functional electrical stimulation and investigated its suitability for reducing muscle fatigue compared to previous methods. The results show that asynchronous multi-electrode stimulation patterns with doublet pulses may improve fatigue resistance in functional electrical stimulation applications in some conditions.

Keywords

Pattern stimulation, asynchronous stimulation, muscle fatigue, functional electrical stimulation, doublet pulses

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Introduction

Functional electrical stimulation (FES) systems are being investigated for a variety of applications, ranging from assistance in cardiovascular disease[1] to motor recovery[2] and muscle strengthening after spinal cord injury (SCI).[3–5] FES is commonly used in rehabilitation of individuals with SCI to produce functional movement of paralysed muscles (see Ragnarsson[6] for a review). However, FES is often associated with rapid muscle fatigue which becomes the main limiting factor in its application.[7]

The rapid onset of FES-induced muscle fatigue has motivated researchers to study the underlying

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mechanism and develop strategies to minimise fatigue.[8,9] Modulating the FES parameters remains the main approach to reduce muscle fatigue and maximise muscle performance.[7] Several studies have shown that the pattern of stimulation will affect muscle fatigue.[10,11]

Current implementations of FES systems typically use a constant stimulation frequency. Instead of using a constant frequency during stimulation, several studies have shown that frequency modulation can delay the onset of muscle fatigue.[12–15] The use of stimulation containing trains of doublet pulses is a promising strategy to overcome the various mechanisms of muscle fatigue, compared to single pulse stimulation trains, as doublets are associated with potentiation.[16] Deley et al.[17] suggest combining constant frequency trains with a variable frequency train at the beginning of the stimulation in order to improve muscle performance.

FES is usually delivered for one muscle group via a pair of stimulation electrodes, where all recruited motor units are activated simultaneously. Multi-electrode setups, which allow stimulation patterns to target different motor units, show some advantages in reducing muscle fatigue.[8,18,19] Bergquist et al.[20] study aggregated distributed stimulation where the stimulation covers several different motor points of the muscle with sequential activation. In these studies, stimulation is delivered to the multiple electrodes in a pre-defined sequence ('sequential stimulation'). Delivering stimulation patterns in a random order to the multiple electrodes ('random stimulation') might affect the fatigue characteristics. To our knowledge, this has not been investigated before.

The effects of muscle fatigue are usually studied by measuring the force output over time.[12] In addition, the neuromuscular activation can be taken into account by measuring electromyography (EMG).[21] When used in combination with FES, it is not clear whether evoked EMG is a useful measurement to predict muscle fatigue.[22] To study the effect of stimulation on the muscle contraction directly, ultrasound imaging of muscle (sonomyography) can be used: ultrasound imaging can be used to describe how the morphology of the muscle varies over time. This non-invasive imaging technique uses the behaviour of high-frequency sound waves travelling through tissue to visualise internal structures. Musculoskeletal ultrasound is a well-established technique which can measure both static and dynamic parameters of the muscle.[23] Static parameters describe the morphology of the muscle in terms of size, shape and structure (e.g. thickness, fibre length and pennation angle). Dynamic parameters are the changes in these measurements which occur during muscle contraction. Several studies have found that a relationship exists between the architectural parameters of the muscle and measurements of torque produced by joints and EMG recordings of muscle activity.[23–25] Building on this premise, Shi et al.[26] investigated the use of ultrasound imaging as a tool to detect muscle fatigue and found that a change in thickness occurred which coincided with muscle's inability to maintain its force during a constant contraction. In this case, muscle fatigue was recorded during voluntary contractions, and therefore additional motor unit recruitment would occur and as a result the rate of change of muscle thickness was considered a critical factor in the development of muscle fatigue. While changes in muscle morphology during FES activation are expected to be different, ultrasound imaging can still provide valuable information about the behaviour of the fatigue characteristics of muscle. In our study, muscle thickness was measured using tracking software based on Darby et al.,[27] providing data on the behaviour of the muscle during different stimulation patterns. As the intermittent stimulation generated very fast, short muscle contractions artificially, additional motor unit recruitment was not expected to occur and so only the maximum thickness of the muscle was used to relate morphology to fatigue.

The aim of this study is to investigate how different stimulation patterns affect muscle fatigue in able-bodied participants. With additional information about the changes in muscle thickness which will be recorded using ultrasound imaging, perhaps the structural muscle changes could be related to the effect of the onset of muscle fatigue during FES applications of the different stimulation patterns. Stimulation with doublet pulses will be delivered via different multi-electrode patterns: Synchronous stimulation (SS), where all electrodes are activated *synchronously*, is compared to *asynchronous* stimulation patterns where the electrodes are activated *sequentially* (AsynS) or *randomly* (AsynR).

Methods

Participants and protocol

Eleven able-bodied volunteers (three male, eight female, age 28.3 ± 3.2 years (mean $\pm$ SD)) participated in this study which was approved by the Ethics Committee of the College of Science and Engineering, University of Glasgow. All participants gave written informed consent. Ten participants completed the study, while one participant withdrew after the first session due to hyper-sensitivity to stimulation.

Each participant was asked to attend three sessions in total. During each session, one of the stimulation patterns (SS, AsynS, AsynR, in randomised order) was applied, using the procedures described below. Sessions were separated by at least 20 h to ensure that

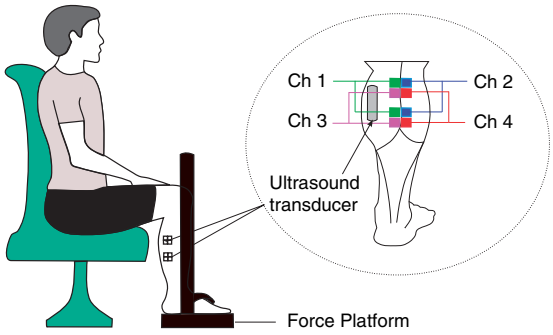

Figure 1. Subject in sitting position with knee at an angle of 90° and four pairs of surface electrodes placed over the gastrocnemius muscle. The ultrasound transducer is placed over the medial gastrocnemius in order to record muscle movement during FES (Ch 1, 2, 3, 4: Channels 1, 2, 3, 4).

fatigue from the previous session did not affect the next session.

Apparatus and data acquisition

Figure 1 shows the setup used in this study. Biphasic current controlled stimulation pulses were delivered using the RehaStim v1 device (Hasomed GmbH, Germany), controlled by a PC via a Universal Serial Bus (USB) interface. Four pairs of 2.5 × 4.5 cm electrodes (PALS Platinum Axelgaard, USA, cut to custom size) were placed over the gastrocnemius muscle. A custom-made force platform was used to measure the ankle torque which was recorded via a data acquisition board (DAQ-6024E, National Instruments, USA) with 20 Hz sampling frequency and 12 bit resolution. Muscle morphology was recorded using a 60-mm long linear probe connected to a portable ultrasound system (LV7.5/60/128 Z-2 with Echo Blaster LS128-CEXT, Telemed Medical Systems, Italy).

Stimulation patterns

Each of the three different stimulation patterns were delivered in separate sessions, carried out in a random order. Doublet pulses with 6 ms intervals were delivered to the four stimulation channels in different patterns as shown in Figure 2. The effective stimulation frequency (40 Hz) was the same for all three protocols, i.e. a doublet pulse was delivered on at least one of the channels every 25 ms. For the SS protocol, all four channels were activated synchronously every 25 ms, whereas for the AsynS and AsynR protocols, only one of the four channels was activated every 25 ms. In the AsynS protocol, the four channels were activated in a sequential order, while the sequence in which channels were activated was randomised for the AsynR protocol. The stimulation pulsewidth was 300 μs throughout.

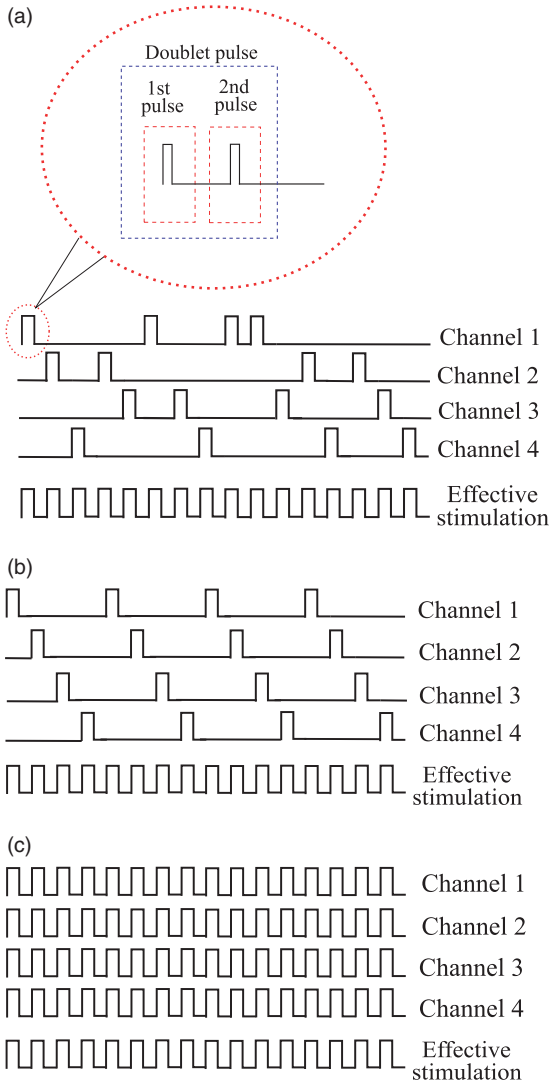

Figure 2. Doublet pulses are delivered in three different stimulation patterns: (a) asynchronous random stimulation (AsynR) where channels are stimulated asynchronously in a random order; (b) asynchronous sequential stimulation (AsynS) where channels are stimulated asynchronously in a sequential order and (c) synchronous stimulation (SS) where all channels are stimulated synchronously. The effective stimulation frequency was 40 Hz for all three patterns.

Procedures

Each session was divided into four sub-sessions: current intensity selection, pre-fatigue test, fatigue trial and post-fatigue test:

(i) *Intensity selection*: The current intensity was increased from a minimum value (10 mA) in steps of 2 mA until the maximum torque or maximum tolerable stimulation intensity was reached. The torque was considered as the maximum when it no longer increased with the increasing intensity.

(ii) *Pre-fatigue test*: A single stimulation pulse followed 10 s later by a short burst of stimulation (5 s duration, frequency 40 Hz) were delivered to determine the twitch–tetanus ratio (TTR).
(iii) *Fatigue trial*: Stimulation trains of 300 ms duration were applied intermittently at 1 s intervals, for a total of 600 s.[20]
(iv) *Post-fatigue test*: To assess fatigue recovery, the same procedure as described in the pre-fatigue test was repeated three times. The first post-fatigue test was delivered immediately after the end of the fatigue trial, while a rest period of 5 min was applied between the first and second, and between the second and third post-fatigue tests.

A summary of the procedures is shown in Figure 3.

Data analysis and outcome measures

The following four outcome measures were defined: normalised fatigue index (NFI), fatigue time interval (FTI), pre-post twitch–tetanus ratio (ΔTTR) and muscle deformation (x). These are described in detail below.

NFI and FTI were calculated from the torque data obtained during the *fatigue trial* and were analysed as follows: for each contraction (consisting of 300 ms stimulation and 700 ms rest), the maximum torque, τ, was obtained. The first 10 contractions were not included to avoid initial artefacts (since during these contractions, the intensity was ramping up and we are only concerned with the contractions generated by the selected intensity). The data were then averaged over 20 contractions resulting in 30 torque values, T_i,

$$T_i = \frac{1}{20}\sum_{k=20(i-1)+1}^{20i} \tau_k, \quad i = 1 \ldots 30 \tag{1}$$

An example of recording is shown in Figure 4. To allow comparison of the different torque levels between participants, the averaged torque, T_i, was normalised to the average torque of the first 20 contractions, T_1,

$$T_i^n = \frac{T_i}{T_1}, \quad i = 1 \ldots 30 \tag{2}$$

The NFI. It is defined as the normalised mean torque during the final 20 contractions

$$NFI = T_{30}^n \tag{3}$$

It is a measure of how much the torque decreases over the entire length of the fatigue trial, and is normally in the range $[0 \ldots 1]$. A larger value (closer to 1) indicates less fatigue, i.e. that the torque level can be better sustained for the duration of the trial.

The FTI. It is defined as the time taken for the normalised torque amplitude (T_i^n) to decrease to 80% of its initial value ($0.8T_1^n$)

$$FTI = T_{0.8}\ (\text{s}) \tag{4}$$

The FTI is a measure of how fast fatigue occurs. A smaller value indicates that fatigue occurs quicker. If the NFI is small, it could mean that a large number of fast fatiguing fibres are recruited repeatedly, leading to a rapid early decline in torque.

In cases where the torque does not decrease to 80% of its initial value within the duration of the trial (600 s), this measure cannot be determined. In order to calculate the group mean, two approaches were applied: (i) the affected FTI value was replaced by 600 s (average reported in Table 2 as *FTI*) and (ii) the affected FTI value was excluded (average reported in Table 2 as $FTI^{\leq 600\ \text{s}}$, together with the number of affected participants, $N^{FTI>600\ \text{s}}$).

Pre-post twitch–tetanus ratio (TTR). TTR is defined as the ratio of the peak of the twitch response, Tw, over the tetanus response, Tt,

$$TTR_{\text{n}} = \frac{Tt_n}{Tw_n} \tag{5}$$

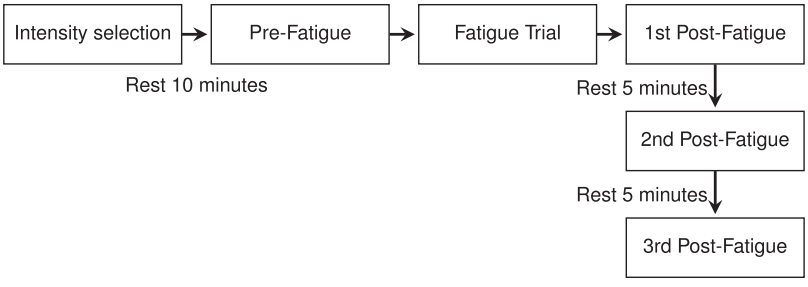

Figure 3. Flowchart of the experimental procedures.

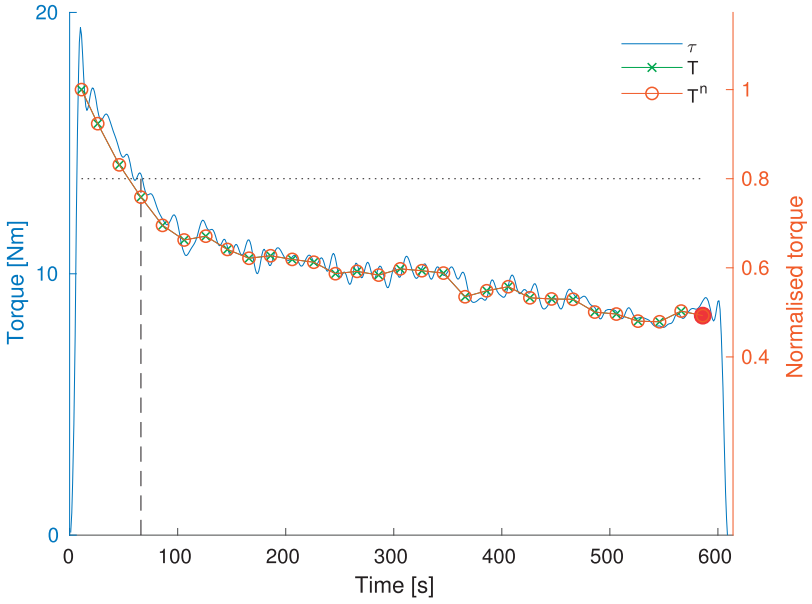

Figure 4. Example of an individual torque recording. The blue line shows the absolute torque, τ, while the green line indicates the torque averaged over 20 contractions, T (both left-side scale). The red line shows the normalised torque, T^n (right-side scale). The red solid marker indicates the NFI, while the dashed line shows the FTI.

where $n \in$ [Pre,Post1,Post2,Post3] indicates the twitch–tetanus test (cf. *Procedures*). A larger TTR is an indication that more muscle fibres are involved in the contraction.[28]

The ratio of the post-fatigue TTR to pre-fatigue TTR is the ΔTTR

$$\Delta TTR_{np} = \frac{TTR_{n_p}}{TTR_{\text{pre}}} \tag{6}$$

where $n_p \in$ [Post1,Post2,Post3]. The overall ΔTTR is the average of the ΔTTR values from the three tests. The ΔTTR is a measure of the change in muscle fibre activation, with a smaller value indicating a larger decrease in fibre activation.

Muscle deformation. The ultrasound recordings were processed with custom tracking software[27] which used automatic segmentation to define anatomically distinct regions of the muscle, i.e. it separates the upper and lower aponeuroses and the muscle tissue itself. This is done by manually labelling frames with 19 marker points along each of the upper and lower boundaries of the deep and superficial aponeuroses to create a point distribution model (PDM). This PDM captures variations in shape and is used to create an active shape model (ASM). The ASM is a widely used algorithm for shape detection which performs a probabilistic search for known shapes in new images and iteratively deforms to fit the new image of an object. It is fitted to new image frames by adjusting the PDM landmarks after being initialised from its mean shape hypothesis. The thickness of the muscle can be obtained from the output of the tracking software and is defined as the average distance between the superficial and deep aponeuroses as shown in Figure 5. Muscle deformation (x) is defined as the percentage change of muscle thickness (ΔT) relative to the muscle thickness at rest (T_0)

$$x = \frac{\Delta T}{T_0} \times 100 \tag{7}$$

The amount of muscle deformation, x, is related to how much the muscle is contracting. A larger value indicates a higher level of contraction, while a smaller value of muscle deformation, x, indicates a less contraction (more fatigue).

Group analysis. Data were averaged over all participants, and the mean and SD were calculated. For all test conditions, the significant differences were tested using one way analysis of variance with the p-value set at 0.05. Multiple group comparisons were then tested in additional analysis using Tukey–Kramer's method.

Results and discussion

The current used for each of the three stimulation patterns is summarised in Table 1, showing that the current selected for the each protocol is very similar, with the SS current being slightly larger on average than that

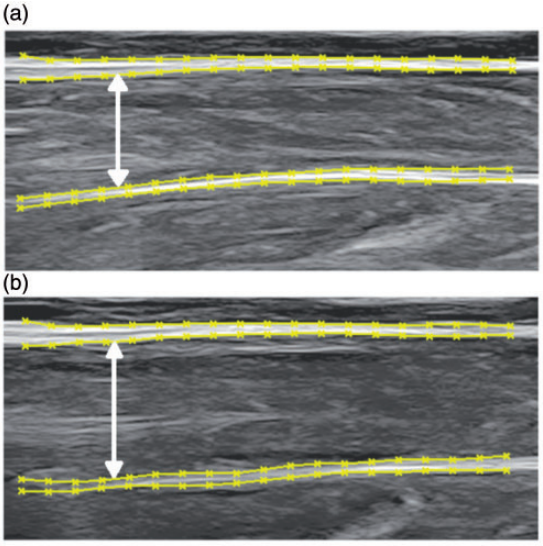

Figure 5. Example of ultrasound image of medial gastrocnemius muscle showing the thickness when stimulation is off (a) and stimulation is on (b).

Table 1. Summary of stimulation currents.

Current (mA)	mean ± SD	min	max
SS	35.4 ± 8.8	24	54
AsynS	31.8 ± 6.2	24	40
AsynR	30.8 ± 8.0	20	44

SS: asynchronous stimulation; AsynS: asynchronous stimulation patterns where the electrodes are activated sequentially; AsynR: asynchronous stimulation patterns where the electrodes are activated randomly.

of the asynchronous protocols. No significant differences were found between the selected stimulation intensities, indicating that this method of selecting the stimulation intensity did not affect the results. It is expected that adjusting the intensity of each pattern to produce the same initial torque would result in similar trends.

The progression of torque during the fatigue trial is summarised in Figure 6. The absolute torque shown in Figure 6(a) indicates that it is similar for each of the different stimulation patterns. Normalised torque is shown in Figure 6(b). The two asynchronous stimulation patterns show less fatigue at the end of the trial compared to synchronous stimulation. This finding is consistent with a previous study using single pulse stimulation.[29]

The outcome measures derived from the torque are summarised in Table 2. This shows that NFI was higher and FTI was longer for asynchronous stimulation compared to synchronous stimulation. This indicates less fatigue[8,13,16,30,31] during asynchronous stimulation; however, it should be noted that the FTI was only statistically significantly longer when the time taken for fatigue to occur was assumed to be 600 s for participants whose torque did not reach the 80% fatigue threshold. For the SS protocol, this threshold was reached by all participants, whereas for AsynS and AsynR, three and six participants, respectively, did not reach the fatigue threshold within the trial duration. Together with the slightly larger NFI for AsynR compared to AsynS, this indicates that AsynR might be the more effective approach to reducing fatigue.

The ΔTTR indicates how muscle fibre recruitment has changed after the fatigue trial compared to the baseline measurement.[28] The larger values for the asynchronous stimulation protocols suggest that the fatigue trial has less effect on fibre recruitment than sequential stimulation; however, this result was not statistically significant.

An example from one subject of how muscle thickness changes throughout the trial is shown in Figure 7, where each peak represents an increase in thickness as the result of the stimulation turning on and then returning to the resting thickness when the stimulation is turned off.

The change in muscle thickness was normalised with respect to the muscle thickness at rest and is referred to as muscle deformation as described in equation (7). Group results for muscle deformation at the start and end of the fatigue trial are shown in Figure 8. Due to recording problems, these data are only available for eight of the 11 participants.

Muscle deformation had decreased at the end of all three protocols compared to the beginning. This corresponds with a reduction in torque as the muscle fatigues, suggesting that the ultrasound analysis results correspond to the fatigue behaviour of the muscle. Deformation tended to be higher for asynchronous stimulation patterns than for synchronous stimulation, both at the start and at the end of the trial, supporting the possibility of higher muscle fibre recruitment during asynchronous stimulation. This is consistent with the idea that asynchronous stimulation allows different motor units to be targeted and for the overall recruitment of muscle fibres to be more effective.[32] The variation in muscle deformation is much larger during the random asynchronous stimulation compared to both the sequential asynchronous and synchronous stimulation. As this is not seen during the sequential stimulation, it can be concluded that this is not a result of asynchronous stimulation but can be attributed to the random order of activation. However, since this study was tested on a small sample size, confirmation of these findings might be worthwhile with a larger sample size. The comfort of the stimulation patterns for participants might limit their use in FES applications. Even though

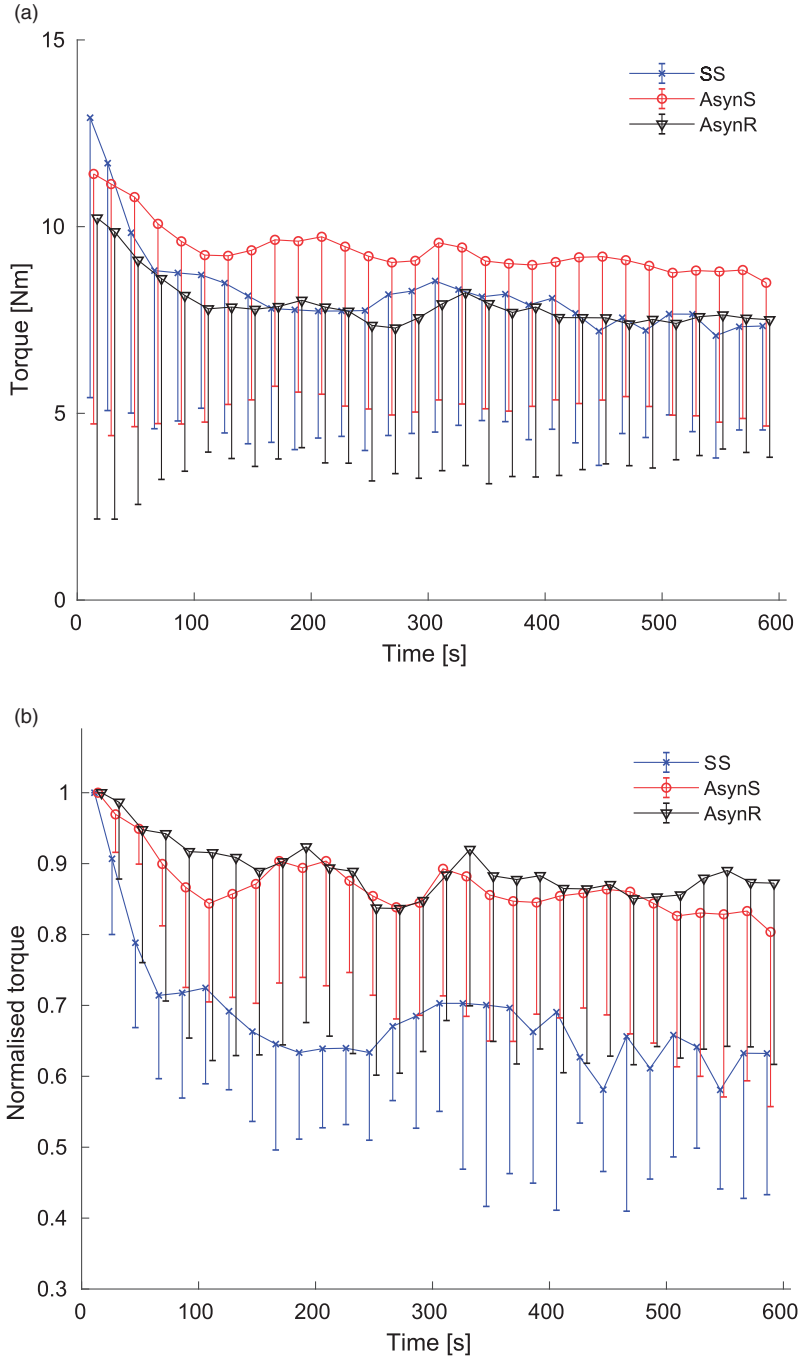

Figure 6. Measured torque along 600 s of FES, where each point represents the mean across all subjects, averaged over 20 contractions (20 s). Error bars represent the standard deviations: (a) absolute torque and (b) normalised torque.

Table 2. Values for NFI, FTI and ΔTTR.

Protocol	NFI	FTI (s)	$FTI^{\leq 600\ s}$ (s)	$N^{FTI>}600$ s	ΔTTR
SS	0.62 ± 0.06*	68.0 ± 30.5*	68.0 ± 30.5	0	0.809 ± 0.334
AsynS	0.80 ± 0.08	302.2 ± 230.9	174.6 ± 129.0	3	0.935 ± 0.335
AsynR	0.87 ± 0.08	384.4 ± 279.0	61.0 ± 34.2	6	0.885 ± 0.320

Note: All results are presented as mean ± SD for all protocols. SS: asynchronous stimulation; AsynS: asynchronous stimulation patterns where the electrodes are activated sequentially; AsynR: asynchronous stimulation patterns where the electrodes are activated randomly.
*Significantly different from AsynS and AsynR ($p < 0.05$).

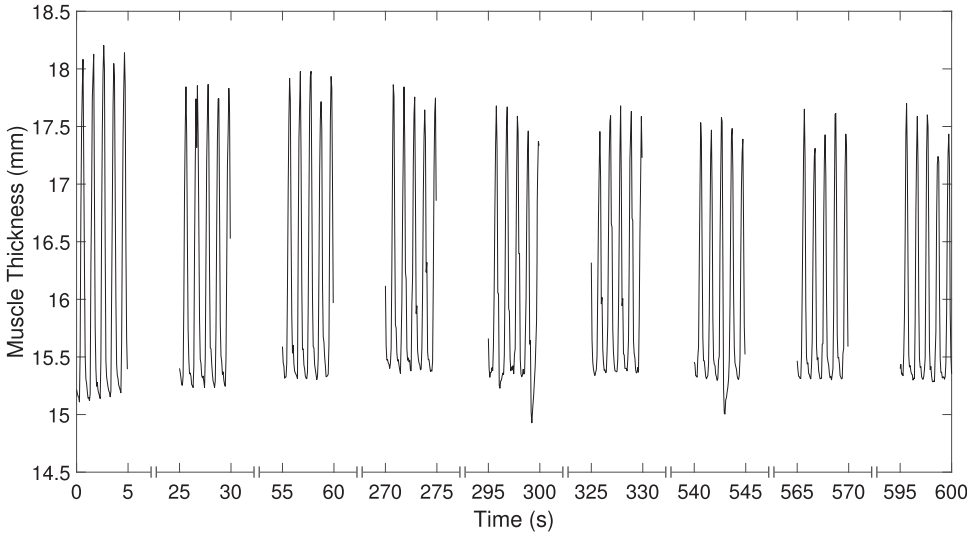

Figure 7. Muscle thickness throughout fatigue protocol. Ultrasound was recorded for 1 min at the start ($t = 0$ s), middle ($t = 270$ s) and end ($t = 540$ s). Five contractions at the start, middle and end of each video were tracked using the software.

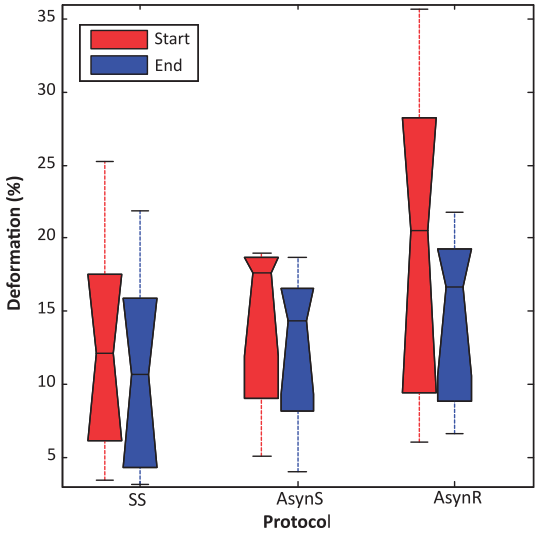

Figure 8. Muscle deformation at the start and end of each protocol. Error bars represent the distribution of muscle deformations. (Data are shown for eight subjects only).

the position of the electrodes used in this study has been reported as the most comfortable and effective,[33] some participants experienced discomfort and further research should exercise caution, particularly with those who are sensitive to electrical stimulation.

Conclusions

This study aimed to investigate the effect of different stimulation patterns on muscle fatigue and relate this to structural muscle changes observed with ultrasound imaging. We have shown that patterned stimulation with asynchronous distribution shows benefits in reducing muscle fatigue. Asynchronous stimulation with random distribution shows advantages compared to asynchronous sequential stimulation and better performance than synchronous stimulation. Hence, random distribution appears to improve performance by reducing muscle fatigue as well as increasing the time before fatigue occurs. This is consistent with the changes in muscle thickness observed from the ultrasound videos. Since this study was small in sample size, further research is needed to investigate the role which this plays to improve fatigue resistance in FES applications. In addition, different effective frequency of single and doublet pulse stimulation might be worth further research since the physiological effect on these distributions might have interesting similarities in different conditions. We believe that AsynR could have potential for clinical use, and we are planning to investigate this further in a clinical study with SCI participants.

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Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Guarantor

HG

Contributorship

RR, JM and HG researched the literature, conceived the study, and developed the protocol. RR gained ethical approval and recruited participants. RR and JM conducted the experiments, collected the data and performed data analysis. RR wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version.

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