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Automatic Determination of Parameters for Multipad Functional Electrical Stimulation: Application to Hand Opening and Closing

Ulrich Hoffmann[1], Martin Deinhofer[2], and Thierry Keller[1]

Abstract— **Transcutaneous functional electrical stimulation (FES) is a method used for rehabilitation of patients having suffered a stroke or spinal cord injury. When applying FES a common problem is that stimulation electrodes have to be placed with great care in order to avoid activation of muscles close to the target muscles. A promising approach to circumvent this problem is to employ multipad FES, i.e. to employ electrode arrays containing many small electrodes allowing selective activation of muscles. In this work an algorithm is presented which automatically determines subsets of active electrodes and stimulation currents such that movements with user-specified amplitudes are induced. Using a recently developed portable multipad FES system and a virtual reality dataglove, the algorithm was tested with seven able-bodied subjects. Stimulation with parameters determined by the algorithm led to movements with a median deviation of between 0° and 5° from the specified wrist angle and between 0% and 12% from the specified degree of finger flexion.**

I. INTRODUCTION

Stroke and spinal cord injury are injuries to the central nervous system (CNS) with dramatic consequences. Among these consequences often is compromised hand function, i.e. patients have no or only limited control over movements of wrist and fingers. Compromised hand function causes difficulties in performing daily tasks, such as grooming or eating and consequently leads to a loss of independence and the need for help from caregivers. It is widely accepted that physiotherapy or other rehabilitation treatments allow to limit the loss of independence induced by injuries to the CNS.

Transcutaneous functional electrical stimulation (FES) is a promising tool for rehabilitation and is typically used in combination with conventional rehabilitation therapies. For performing FES, electrodes are attached to the skin near the motor points of muscles and small, pulsed currents are passed between the electrodes. The currents lead to action potentials in motor nerves and consequently to muscle contractions.

While FES has been shown to be helpful for the rehabilitation of hand function [1], [2], [10], technical problems hinder the more widespread use of FES by therapists and patients. A significant problem is that stimulation electrodes have to be placed with great care because otherwise the FES-induced muscle activation "spills over" to muscles which should not be activated in a targeted functional movement. Manually finding the correct position of electrodes requires experience, can take several minutes, and might be impossible for disabled users.

A possible solution to the problem of electrode positioning is implemented in the commercially available H200 Hand Therapy system (Bioness Inc.). In this system the electrode placement is done once by a therapist and then electrodes are embedded at fixed positions in plastic shells which can be easily donned and doffed by the user. Unwanted wrist movements are avoided with a splint, fixing the wrist in a static position.

A more flexible approach, allowing easier repositioning of electrodes and dynamic changes of electrode shape and position is to use so-called multipad electrodes, i.e. arrays of small electrodes. By activating only a subset of electrodes on the array stimulation can be made highly selective and unwanted muscle activations can be avoided. Furthermore, compared to standard electrodes, donning and doffing is facilitated. This is the case because the array has to be attached to the skin only once, and then the optimal stimulation parameters can be determined.

Several groups have previously performed research concerning multipad FES systems. In [3] the multipad approach was tested by attaching four small stimulation electrodes (cathodes) to the upper (dorsal) side of the forearm near the elbow, and two return electrodes (anodes) to the upper side of the forearm near the wrist joint. An optimization algorithm performed an exhaustive search over all possible pairs of stimulation and return electrodes in order to minimize an optimization criterion. The optimization criterion was composed of the deviation of the wrist angle from a preset target angle, the degree of wrist adduction and abduction, and the degree of finger flexion. To measure movement parameters an accelerometer and flex sensors were used. The system was tested with ten able-bodied subjects and the results showed that the algorithm was able to find electrode combinations matching the preset movement criteria for all subjects.

A multipad FES system embedded in a textile garment and an algorithm for automatically selecting subsets of electrodes were presented in [8], [9]. In this system stimulation was done with electrode arrays containing 30 electrodes applied at the upper and lower (volar) side of the forearm and electrodes applied at the thumb muscles. Isometric finger force and wrist torques were measured using a grasp assessment system based on load cells. Using the forces measured with the grasp assessment system, an algorithm automatically selected subsets of electrodes, leading to isolated finger movements. The system was tested in eight able-bodied subjects, and in all subjects activation regions for isolated

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[1]U. Hoffmann and T. Keller are with TECNALIA, Paseo Mikeletegi 1, 20009 San Sebastián, Spain

[2]M. Deinhofer is with Technikum Wien, Vienna, Austria

actuation of the middle and ring finger were found, while for other fingers some coupling was present.

A multipad FES system, targeted at achieving natural grasping movements in SCI patients, was presented in [4]. In this system stimulation was done with two 4×6 electrode arrays attached to the upper and lower side of the forearm. The system used asynchronous stimulation, i.e. instead of simultaneously activating all selected electrodes on an array, electrodes were activated one after the other with a delay of 2.5ms. A two-phase optimization method was employed to determine electrode subsets leading to movements with minimal deviation from a set of reference parameters. The optimization method first activated each of the electrodes on the two arrays in isolation and recorded the induced movements with goniometers. Then, using the recorded data, sets of eight electrodes leading to minimal errors when compared to the reference parameters were selected for each of the two arrays. The system was tested with six SCI patients and the results showed that the optimization method was consistently able to find stimulation patterns leading to movements with only small deviations from the reference movements.

Here, a multipad FES system targeted at positioning the wrist at a user-specified angle, stabilizing the wrist by coactivation of flexor and extensor muscles, and simultaneously opening or closing the fingers is presented. The system allows to specify the desired degree of wrist extension/flexion and finger flexion and can thus be adapted to different applications. Subsets of electrodes leading to the desired movements are determined automatically. Different to the previously discussed systems, a semi-automatic method is used for adapting the stimulation current for each of the electrodes on the array. Furthermore, an off-the-shelf dataglove is used for measuring movement parameters. An additional difference to most systems described in the literature is that the electrode arrays are covered with a uniform hydrogel layer (instead of isolated gel pieces on each electrode pad). This simplifies the donning and doffing of our system.

II. METHODS AND MATERIALS

A. Subjects

Experiments were performed with seven able-bodied subjects (4 F, 3 M, age 32 $\pm$ 5 years).

B. Stimulator and Electrodes

The INTFES [5], [6] stimulator and electrodes were used for performing the experiments. A small battery-powered single channel stimulator controllable via Bluetooth is used for stimulation. Two multiplexer boards distribute the stimulation pulses generated by the stimulator to up to 16 active pads on up to two 4×4 electrode arrays. The electrode arrays are made of a flexible substrate and the single electrode pads are made out of silver/silver-chloride. The surface area of individual electrodes is about 1cm^2 and the distance between electrodes is about 1cm[1] During preliminary tests separate small pieces of hydrogel were used for each of the pads. However, in later tests, as in [8], one large piece of high-impedance hydrogel (Axelgaard AG803) covering all electrode pads was used.

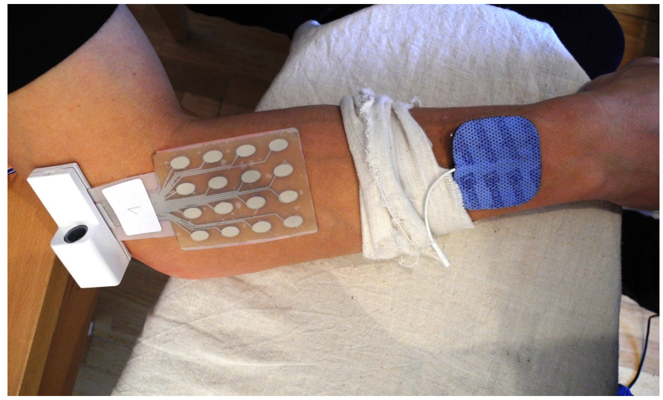

Fig. 1. Electrode array and anode attached to dorsal side of forearm.

C. Positioning of Electrodes, Stimulation Parameters

The electrodes were placed according to recommendations found in [7]. For flexion of wrist and fingers the electrode array was placed on the lower side of the forearm, at about half of the length of the forearm, measured from the condyles of the elbow. For extension of wrist and fingers a second electrode array was placed on the upper side of the forearm at about one third of the length of the forearm, measured from the condyles of the elbow (cf. Fig. 1). For each electrode array a return electrode was placed near the wrist, one on the upper side of the forearm and one on the lower side of the forearm.

The stimulation frequency was set to 50Hz and as in [4] stimulation was asynchronous, i.e. there was a 1ms delay between consecutive activations of electrodes. Biphasic pulses with a pulsewidth of $300\mu s$ were used. To determine initial settings for the stimulation current, the current was manually increased in steps of 1mA until clearly visible finger flexion, finger extension, wrist flexion, and wrist extension movements were evoked by at least one of the electrodes on each of the arrays.

D. Dataglove

A virtual reality dataglove (DG5 VHand 2.0, DGTech Engineering Solutions, Bazzano, Italy) was used to measure wrist angle and flexion of the fingers. The glove measures wrist angle with a 3-axes accelerometer and finger flexion with five bend sensors, one at each finger. The glove was calibrated for each subject before starting the experiments.

E. Optimization Algorithm - Phase I

A two-phase algorithm was employed. In the first phase, the algorithm activated each of the 32 electrodes in isolation.

[1]On two out of the seven subjects participating in the experiments a slightly different version of electrodes was used. These electrodes had electrode pads with a surface area of about 2cm^2.

More specifically, each electrode was activated for 3s with the manually set initial stimulation current and the movement amplitudes were recorded. Breaks of 1s were used between activations of consecutive electrodes. A moving average filter was applied to the recorded data and an offset value measured without stimulation was subtracted from the data. Then, the maximum movement amplitude induced by the stimulation was determined from the filtered and offset corrected data. If for none of the measured joints (wrist and fingers 2-5) the induced movement was bigger than 10% of the range of motion, the stimulation current was automatically increased by 1mA. If after increasing the stimulation current again no sufficient movement was detected, the stimulation current was increased once more by 1mA but only after asking the user for agreement.

The results of phase I were the movement amplitudes of wrist and fingers induced by activating electrodes on the array in isolation and the stimulation current for each electrode, adapted to evoke clearly detectable movements.

F. Optimization Algorithm - Phase II

Using the results from phase I, in phase II of the optimization algorithm four different strategies (cf. Appendix) were used to build candidate activation arrays $\mathbf{A}_1, \ldots, \mathbf{A}_4$. Each activation array had size $2 \times 4 \times 4$ and contained ones for active electrodes, and zeros for inactive electrodes. Additionally, the stimulation current settings from phase I were used to build candidate stimulation current arrays $\mathbf{I}_1, \ldots, \mathbf{I}_3$ (cf. Appendix). The stimulation current arrays had size $2 \times 4 \times 4$ and contained the stimulation current for each electrode. To find the best activation and current settings, all twelve possible combinations of $\mathbf{A}$'s and $\mathbf{I}$'s were evaluated using measurements from the dataglove (cf. Algorithm I). The criterion function j used for evaluation was based on the wrist angle θ_w and the percentages $\theta_{f_2}, \ldots, \theta_{f_5}$ of finger flexion of the index, middle, ring and little finger measured during stimulation. The criterion function can be expressed as:

$$j(\boldsymbol{\theta}) = \|\mathbf{d}(\boldsymbol{\theta})\|, \tag{1}$$

where $\|\|$ denotes the Euclidean norm and $\mathbf{d}(\boldsymbol{\theta})$ measures the relative deviation of $\boldsymbol{\theta}$ from the user-specified target parameters $\boldsymbol{\phi}$:

$$\mathbf{d}(\boldsymbol{\theta}) = \begin{bmatrix} \frac{\theta_w - \phi_w}{\rho_w} \\ \frac{\theta_{f_2} - \phi_{f_2}}{\rho_f} \\ \frac{\theta_{f_3} - \phi_{f_3}}{\rho_f} \\ \frac{\theta_{f_4} - \phi_{f_4}}{\rho_f} \\ \frac{\theta_{f_5} - \phi_{f_5}}{\rho_f} \end{bmatrix}. \tag{2}$$

The $\boldsymbol{\rho}$-parameters specified the range of motion and were set to 180 degrees for the wrist (ρ_w) and to 100% for the fingers (ρ_f).

G. Experiments

During the experiments subjects placed their forearm on a table such that wrist extension had to be done against gravity.

input : Activations $\mathbf{A}_1, \ldots, \mathbf{A}_4$ and currents $\mathbf{I}_1, \ldots, \mathbf{I}_3$
output: Best activation and current ($\mathbf{A}_{\text{best}}$, $\mathbf{I}_{\text{best}}$)

```
j_min ← ∞;
for i ← 1 to 4 do
    for k ← 1 to 3 do
        Stimulate(A_i, I_k);
        θ ← GetGloveData;
        if j(θ) < j_min then
            j_min ← j(θ);
            A_best ← A_i;
            I_best ← I_k;
        end
        Pause;
    end
end
```

Algorithm 1: Determination of best combination of activation maps and stimulation currents.

Subjects were instructed to keep their forearm muscles relaxed during testing. The experiment consisted of several parts, which were performed in the order specified in the following.

1) Application of electrodes, determination of initial stimulation currents, calibration of dataglove
2) One run of phase I of the optimization algorithm
3) Break of at least 3 minutes
4) Three consecutive runs of phase II of the optimization algorithm, with target parameters $\phi_w = 5°$, $\phi_{f_2}, \ldots, \phi_{f_5} = 15\%$ (hand closing)
5) Five repetitions of the best solution found in step 4
6) Three consecutive runs of phase II of the optimization algorithm, with target parameters $\phi_w = 5°$, $\phi_{f_2}, \ldots, \phi_{f_5} = 0\%$ (hand opening)
7) Five repetitions of the best solution found in step 6
8) Grasping a glass using the solutions found in steps 4 and 6

Only the results from 4), 6), and 8) are analyzed in the following.

III. RESULTS

For six out of the seven tested subjects positive results were obtained. For one of the subjects, the experiment was not completed because sufficient finger flexion could not be achieved while setting the initial stimulation parameters.

A. Grasping Test

At the end of the experiment subjects tried to grasp a glass and lift it off the table using FES. The stimulation parameters found by the optimization algorithm for hand opening were used at the start and end of the grasping movement, and the parameters for closing the hand and stabilizing the wrist were used to grasp the glass and lift it off the table. The grasping test was successful in six subjects, i.e. the subjects successfully lifted the glass off the table and released it again.

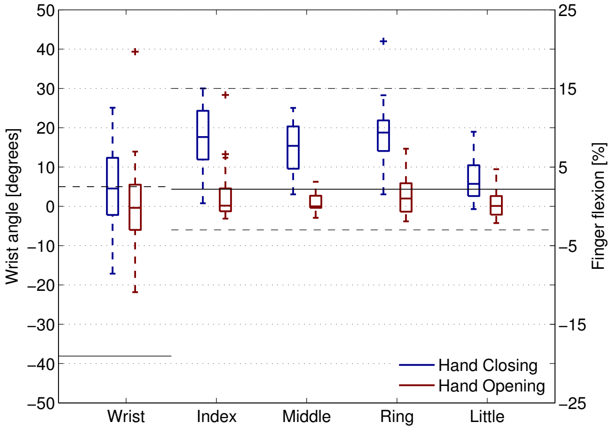

Fig. 2. Solution quality for hand closing and hand opening. Data from all subjects and runs is shown. Solid lines correspond to average starting positions, dashed lines correspond to target positions.

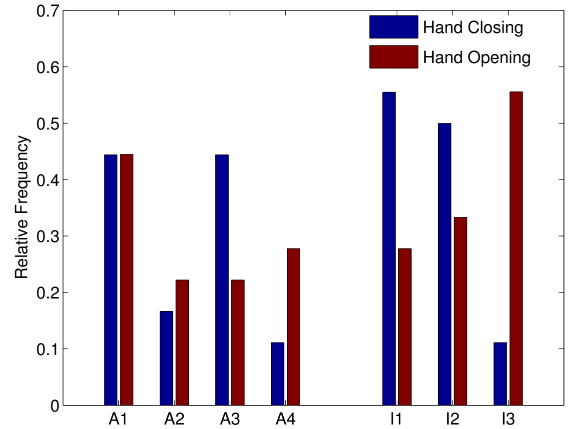

Fig. 3. Comparison of combinations of electrode subsets ($\mathbf{A}$'s) and stimulation currents ($\mathbf{I}$'s). Bars indicate the relative frequency with which the different combinations led to close-to-optimal movement parameters.

B. *Quality of Solutions*

Fig. 2 shows boxplots of the solution quality for hand opening and hand closing when taking into account all runs of phase II of the optimization algorithms for all six successful subjects. As can be seen, FES with stimulation parameters determined by the optimization algorithm moved wrist and fingers from the starting positions (solid lines) towards the target positions (dashed lines). For hand closing the median error at the wrist angle was about $1°$, and the median error at the index, middle, ring and little fingers was about 7%, 6%, 6%, and 12% respectively. For hand opening the median error at the wrist angle was about $5°$, and the median error at the index, middle, ring and little fingers was about 0%, 0%, 2%, and 0% respectively.

C. *Comparison of Heuristics*

To compare the heuristics for selecting subsets of electrodes and setting stimulation currents, the relative frequency of leading to close-to-optimal movement parameters was computed. This was done by counting for the six successful subjects and for three runs of the optimization algorithm how often the $\mathbf{A}_1, \ldots, \mathbf{A}_4$ and $\mathbf{I}_1, \ldots, \mathbf{I}_3$ parameters led to movements with $j(\boldsymbol{\theta}) \leq j_{\min} + \epsilon^2$ (cf. Alg. 1). The achieved score was then divided by the maximum possible score to obtain the relative frequency. As can be seen in Fig. 3 none of the heuristics for selecting electrode subsets had a relative frequency close to zero. For the stimulation currents relatively small currents were preferred for hand opening, while higher currents were preferred for hand closing. These results can be interpreted as a justification for the multiheuristic approach to optimization presented in this work.

D. *Separate Sheets of Gel vs. One Sheet of Gel*

During the development of the system, tests were first performed with small sheets of hydrogel, covering each of the electrodes on the array individually. Later, one large sheet of hydrogel was used, covering and connecting all electrodes simultaneously. This considerably simplified the donning and doffing of the array electrode. Furthermore, we found that using one large layer of gel made stimulation more comfortable. Obvious negative effects of using one layer of gel on the selectivity of stimulation could not be observed.

[2]Based on an analysis of data measured during calibration of the dataglove the tolerance ϵ was set to 0.007.

IV. CONCLUSIONS

In this work a new method for automatically determining parameters for multipad FES was presented. The method was tested on seven able-bodied subjects and for six of the seven tested subjects the presented optimization algorithm found stimulation parameters which allowed a simple grasping task to be performed with the help of FES. However, the results also show that optimizing stimulation parameters for hand opening and closing is a challenging task. Further research is necessary to reduce the variability of the results and to compare the presented algorithm with already existing approaches.

APPENDIX

A. *Heuristics for Activation Maps*

To build candidate activation maps, the joint excursion data recorded in phase I of the algorithm were used to rank the 32 electrodes according to six different criteria.

For the wrist joint, a set of wrist-extensor electrodes was built by selecting only those electrodes which led to a wrist angle greater than $\theta_{w_{\text{ext}}}$ degrees. Additionally, a set of wrist-flexor electrodes was built by selecting only those electrodes which led to a wrist angle smaller than $\theta_{w_{\text{flex}}}$ degrees[3]. This was done because one of the goals of the optimization algorithm was to stabilize the wrist joint by coactivation of extensor and flexor muscles. The wrist-extensor and wrist-flexor electrodes were then sorted according to a weighted

[3]For four subjects $\theta_{w_{\text{ext}}} = 10°$, $\theta_{w_{\text{flex}}} = -10°$ was used. For two subjects $\theta_{w_{\text{ext}}} = -30°$, $\theta_{w_{\text{flex}}} = -50°$ was used. For one subject $\theta_{w_{\text{ext}}} = 0°$, $\theta_{w_{\text{flex}}} = 0°$ was used.

criterion function j_w which put a large weight on the deviation of the wrist angle from the target angle, and relatively small weights on the deviations of the finger flexion. This can be expressed mathematically by premultiplying the relative deviation $\mathbf{d}$ (cf. Eq. 2) with a diagonal weighting matrix $\mathbf{W}_w$ with diagonal values $[1\ 0.5\ 0.5\ 0.5\ 0.5]$:

$$j_w(\boldsymbol{\theta}) = \|\mathbf{W}_w \mathbf{d}(\boldsymbol{\theta})\|. \tag{3}$$

The results of the operations described above were a sorted list $\mathcal{C}_{we}$ of wrist extensor electrodes, and a sorted list of wrist flexor electrodes $\mathcal{C}_{wf}$.

For the finger joints, the goal of the optimization algorithm was to select electrodes which led to a percentage of finger flexion close to the target percentage of flexion. As a first step towards this goal, the electrodes were sorted according to criterion functions $j_{f_2}, \dots, j_{f_5}$. As for the wrist joint the criterion functions for the fingers were built by premultiplying the deviation $\mathbf{d}$ with a diagonal weighting matrix. This can be expressed as

$$j_{f_i}(\boldsymbol{\theta}) = \|\mathbf{W}_{f_i} \mathbf{d}(\boldsymbol{\theta})\|, \tag{4}$$

where the i-th value of the weighting matrices $\mathbf{W}_{f_i}$ is set to 1, and all other values on the diagonal are set to 0.5. The results of the operations applied for the finger joints were four sorted lists $\mathcal{C}_{f_2}, \dots, \mathcal{C}_{f_5}$.

After sorting the electrodes as described above three different heuristics were used to build candidate sets of electrodes.

a) Heuristic I: ($\mathbf{A}_1$) The candidate set of electrodes built by heuristic I consisted of the best cell of each of the lists $\mathcal{C}_{we}, \mathcal{C}_{wf}, \mathcal{C}_{f_2}, \dots, \mathcal{C}_{f_5}$. The maximum number of electrodes selected with heuristic I thus was six.

b) Heuristic II: ($\mathbf{A}_2$) The candidate set of electrodes built by heuristic II consisted of the two best electrodes of each of the lists $\mathcal{C}_{we}, \mathcal{C}_{wf}, \mathcal{C}_{f_2}, \dots, \mathcal{C}_{f_5}$. The maximum number of electrodes selected with heuristic II thus was twelve.

c) Heuristic III: ($\mathbf{A}_3$, $\mathbf{A}_4$) The idea underlying heuristic III was to predict the effect of combining electrodes as the sum of the effects of single electrodes. The prediction was then used to select electrode sets with minimal predicted deviation from the target movement parameters. To make this approach feasible, first a subset of maximally 12 unique electrodes was selected from the sorted lists $\mathcal{C}_{we}, \mathcal{C}_{wf}, \mathcal{C}_{f_2}, \dots, \mathcal{C}_{f_5}$. Then all possible combinations of electrodes from this subset were ranked with a criterion function j_p. Denoting by $i_1, \dots, i_N$ the indices of electrodes constituting a specific combination, and by $\boldsymbol{\theta}^{i_1}, \dots, \boldsymbol{\theta}^{i_N}$, the movement parameters from phase I for these electrodes, the criterion function can be expressed as follows:

$$j_p(\boldsymbol{\theta}_{i_1}, \dots, \boldsymbol{\theta}_{i_N}) = \|\mathbf{d}_p(\boldsymbol{\theta}_{i_1}, \dots, \boldsymbol{\theta}_{i_N})\|. \tag{5}$$

The predicted relative deviation $\mathbf{d}_p$ was computed as follows:

$$\mathbf{d}_p = \sum_{i \in i_1, \dots, i_N} \begin{bmatrix} \frac{\theta^i_w - \phi_w}{\rho_w} \\ \frac{|\theta^i_{f_2} - \phi_{f_2}|}{\rho_f} \\ \frac{|\theta^i_{f_3} - \phi_{f_3}|}{\rho_f} \\ \frac{|\theta^i_{f_4} - \phi_{f_4}|}{\rho_f} \\ \frac{|\theta^i_{f_5} - \phi_{f_5}|}{\rho_f} \end{bmatrix}. \tag{6}$$

After sorting all possible cell combinations according to j_p, the two best ranked combinations of electrodes were returned by heuristic III.

B. Heuristic for Stimulation Currents

The result of phase I of the algorithm, namely stimulation currents for each electrode was used to build stimulation current arrays $\mathbf{I}_1, \mathbf{I}_2, \mathbf{I}_3$. This was done by subtracting 1mA, 2mA, and 3mA from the currents for all pads. The motivation for this was, that the joint activation of electrodes usually led to stronger muscle contractions than the isolated activation of electrodes.

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REFERENCES

[1] J. Powell, A.D. Pandyan, M. Granat, M. Cameron, and D.J. Stott, Electrical Stimulation of Wrist Extensors in Poststroke Hemiplegia, Stroke, vol. 30, pp. 1384-1389, 1999.
[2] S. Mangold, T. Keller, A. Curt, and V. Dietz, Transcutaneous functional electrical stimulation for grasping in subjects with cervical spinal cord injury, Spinal Cord, vol. 34, pp. 1-13, 2005.
[3] S.B. O'Dwyer, D.T O'Keeffe, S. Coote, and G.M. Lyons, An electrode configuration technique using an electrode matrix arrangement for FES-based upper arm rehabilitation systems, Medical Engineering and Physics, vol. 28, pp. 166-176, 2006.
[4] D.B. Popović, and M.B. Popović, Automatic determination of the optimal shape of a surface electrode: Selective stimulation, Journal of Neuroscience Methods, vol. 178, pp. 174-181, 2009.
[5] R. Velik, N.M. Malesevic, L. Popović, U. Hoffmann, and T. Keller, INTFES: A multi-pad electrode system for selective transcutaneous electrical muscle stimulation, in Proc. 16th Annual International Functional Electrical Stimulation Society Conference, Sao Paulo, 2011.
[6] N.M. Malesevic, L.Z. Popović Maneski, V. Ilic, N. Jorgovanovic, G. Bijelic, T. Keller, and D.B. Popović, INTFES: A Multi-Pad Electrode based Functional Electrical Stimulation System for Restoration of Movement, Journal of NeuroEngineering and Rehabilitation, submitted for publication.
[7] Electrode Placement and Functional Movement, PALS Clinical Support, http://www.palsclinicalsupport.com/
[8] T. Keller, M. Lawrence, M. Lang, and A. Kuhn, Textile Neuroprosthesis Garment for Functional Electrical Stimulation, in Proc. International Workshop on Functional Electrical Stimulation, Krems, Austria, 2007.
[9] T. Keller, B. Hackl, M. Lawrence, and A. Kuhn, Identification and control of hand grasp using multi-channel transcutaneous electrical stimulation, in Proc. 11th Annual Conference of the International FES Society (IFESS), Zao, Japan, 2006.
[10] D.B. Popović, M.B. Popović, T. Sinkjær, A. Stefanovic, and L. Schwirtlich, Therapy of paretic arm in hemiplegic subjects augmented with a neural prosthesis: A cross-over study, Can. J. Physiol. Pharmacolm vol. 82, pp. 749756, 2004.