Evaluation of performance fatigability through surface EMG in health and muscle disease: state of the art

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ABSTRACT

In literature, it is commonly reported that the progress of performance fatigability may be indirectly assessed through the changes in the features of the surface electromyogram (sEMG) signal. In particular, during isometric constant force contractions, changes in the sEMG signal are caused by several physiological factors, such as a decay in muscle fibers conduction velocity (CV), an increase of the degree of synchronization between the firing times of simultaneously active motor units (MUs), by the central nervous system, and a reduction of the recruitment threshold and a modulation of MUs firing rate. Amplitude and spectral parameters may be used to characterize the global contributions to performance fatigability, such as MU control properties and fiber membrane properties, or central and peripheral factors, respectively. In addition, being CV a physiological parameter, its estimation is of marked interest to the study of fatigue both in physiological and in presence of neuromuscular diseases.

Abbreviations: ApEn: Approximate Entropy; ARV: Average rectified value; BB: Biceps brachii; CD: Correlation dimension; CNS: Central nervous system; CV: Conduction velocity; DD: Double differential; DFA: Detrended fluctuation analysis; FD: Fractal dimension; HD-sEMG: High density surface EMG; IAP: Intracellular action potential; IED: Interelectrode distance; iMNF: Instantaneous mean frequency; iEMG: Intramuscular electromyography; MDF: Median frequency of the power spectrum; MNF: Mean frequency of the power spectrum; MSEn: Multiscale entropy; MU: Motor unit; MUAP: Motor unit action potential; MVC: Maximal voluntary contraction; RMS: Root mean squared value; RSE: Roughness scaling extraction; SampEn: Sample Entropy; SD: Single differential; VV: vastus lateralis and medialis

Intensively exercised muscles show a progressive decline in performance, a phenomenon physiologists term “neuromuscular fatigue” (Allen, Lamb, & Westerblad, 2008). The study of neuromuscular fatigue and the factors that limit, or regulate, performance during athletic events, ergonomic tasks and daily activities, intrigued scientists for centuries, but a clear explanation of the etiology of this condition remains elusive (Marino, Gard, & Drinkwater, 2011). Despite the large number of studies that have adopted the central-peripheral dichotomy (e.g., Bigland-Ritchie, Jones, Hosking, & Edwards, 1978; Gandevia, Allen, & McKenzie, 1995; Kent-Braun, 1999; Schillings, Hoebslout, Stegeman, & Zwarts, 2003), two major limitations with this approach have precluded the development of a consensus understanding on what causes fatigue (Kluger, Krupp, & Enoka, 2013). In fact, recent studies suggested that it is not possible to identify the etiology of fatigue by attempting to separate the decline in muscle force from sensations about fatigue, particularly during long-lasting contractions (Taylor & Gandevia, 2008). For instance, adjustments in the activation signal discharged by motoneurons during a voluntary contraction begin before a detectable reduction in muscle force, and are attributable to changes occurring within the muscle (Carpentier, Duchateau, & Hainaut, 2001; Farina et al., 2009). Moreover, most of the physiological processes involved in performing a voluntary action, such as the generation of the motor command or the cross-bridge cycle, can be challenged under appropriate experimental conditions and thereby contribute to the development of fatigue: a phenomenon that has become known as the task dependency of fatigue (Enoka & Stuart, 1992). It is also known that protocol specifications affect the findings and the underlying mechanisms of fatigue (Enoka, 1995). Different types of protocols

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are applied in healthy subjects to assess various aspects of fatigue, where submaximal protocols most likely challenge the central nervous system (CNS), while high-intensity exercises challenge the peripheral neuromuscular system (Taylor & Gandevia, 2008; Vollestad, 1997). Recently, Enoka and Duchateau (2016), suggested to refine the definition of fatigue and to adopt a unified taxonomy to guide its assessment and management. They proposed the conceptualization of fatigue as a disabling symptom or percept, characterized by feelings of tiredness and weakness, in which physical and cognitive function is limited by interactions between performance fatigability and perceived fatigability. Fatigue is defined in terms of fatigability, to allow the normalization of the level of fatigue reported by an individual relative to the demands of the task that produces it (Eldadah, 2010). Thus, when a person reports the level of fatigue during ongoing activity, the value at a specific time point will depend on the rates of change in its two attributes: performance and perceived fatigability.

1. Perceived fatigability
Perceived fatigability refers to the sensations that regulate the performer integrity; these sensations can be modulated by homeostasis fluctuations (e.g., core temperature, hydration status, substrate availability) and modifications in the psychological state (e.g., arousal, motivation, mood) that contribute to the perception of the effort required for the task (Figure 1). In contrast to performance fatigability, perceived fatigability can be assessed when a person is either at rest (Fieo, Mortensen, Rantanen, & Avlund, 2013; Glynn et al., 2015), or performing a physical task (Schnelle et al., 2012; Simonsick, Schrack, Glynn, & Ferrucci, 2014). High levels of perceived fatigability at rest may be attributed to deviation of one or more of the modulating factors (e.g., core temperature, hydration, motivation or pain) from normal baseline values. Conversely, perceived fatigability during ongoing activity comes from rates of change in the modulating factors used to regulate the performance pace and thereby control the development of fatigue. Duchateau and Enoka (2016) suggested that, although it seems that the influence of psychological factors on fatigue is mediated via perceived fatigability, it remains to be determined whether or not psychological factors can have a direct effect on fatigue without involving perceived fatigability. Moreover, perceived fatigability may be assessed by self-report scales under different constructs, such as physical or cognitive, or state versus trait.

2. Characterization of performance fatigability
Performance fatigability is an acute activity-induced reduction of force or power of a muscle, typically quantified as the decline in an objective measure of performance, such as the production of maximal voluntary force, the time to failure of a submaximal task, or the involuntary twitch response to electrical stimulation (Enoka & Duchateau, 2016). Performance and perceived fatigability are interdependent and they interact to modulate and determine the symptoms of fatigue.

Although the taxonomy illustrated in Figure 1 lists many of the factors that can influence each attribute of fatigue (performance fatigability and perceived fatigability), the scheme acknowledges that most voluntary actions performed by humans involve significant interactions between the two domains. For example, several of the modulating factors that contribute to perceived fatigability, including the levels of blood glucose (Nybo, 2003), core temperature (Nybo, 1988), arousal (Klass et al., 2012), and mood (Steens, Heersema, Maurits, Renken, & Zijdewind,
can all modulate the capacity of the individual to generate the required amount of voluntary activation, which is a factor that influences performance fatigability. Similarly, afferent feedback generated during high-intensity exercise can influence the adjustments required to maintain homeostasis and thereby contribute to perceived fatigability (Kennedy, Fitzpatrick, Gandevia, & Taylor, 2015; Sidhu, Cresswell, & Carroll, 2013). The key feature of this scheme is that the level of fatigue experienced by an individual emerges from adjustments of factors that modulate each attribute of fatigability. With this construct, fatigue is defined as a disabling symptom in which physical and cognitive function is limited by interactions between performance fatigability and perceived fatigability. The level of fatigue experienced by an individual can be modulated by challenges to homeostasis, disturbances in the psychological state, reductions in contractile function, and limitations in the capacity to provide an adequate activation signal to the involved muscles (Enoka & Duchateau, 2016).

According to the definition proposed by Kluger et al. (2013), fatigue may be considered as a single entity which does not need to be modified by an accompanying adjective, such as central fatigue, mental fatigue, muscle fatigue, peripheral fatigue, physical fatigue, or supraspinal fatigue. Therefore, since the new definition considers fatigue as a symptom, its assessment requires the individual to interpret relevant psychological and physiological factors by providing responses to standardized questions (Avlund, 2013; Bennett et al., 2014; Halson, 2014; Schmidt et al., 2012; Yang & Wu, 2005). Consequently, conventional measures of fatigue, such as the time to complete a defined task, the reduction in maximal voluntary contraction (MVC) force or the decline in power production, may be regarded as indices of performance fatigability, but do not provide a measure of the symptom (Enoka & Duchateau, 2016).

3. Neuromuscular mechanisms

Many factors contribute to performance fatigability, which may be differentiated in central and peripheral (Figure 1). Central factors result from a combination, though not well understood yet, of intrinsic motoneuronal properties and decrease in voluntary activation of the muscle, which causes a decrease in the number of recruited motor units (MUs) and their discharge rate. Gandevia (2001) suggested that a reduction in the neural drive command from supraspinal sites that controls a muscle, results in a decline in the tension development (Fuglevand, 1996). Moreover, the discharge rate of MUs decreases to match the change in the mechanical state of the muscle during the fatiguing task (Bigland-Ritchie, Johansson, Lippold, Smith, & Woods, 1983a), a mechanism called the “muscle wisdom” (Barry & Enoka, 2007). The changes in the discharge rate have been suggested to be protective mechanisms to prevent muscle failure whenever the task was continued at the same intensity (Bigland-Ritchie & Woods, 1984).

In contrast, peripheral contributors include alterations that occur locally from excitation to muscle contraction, such as in neuromuscular action potential propagation, and decreases in the contractile strength of the muscle fibers, including the perturbation of calcium ions release from the sarcoplasmic reticulum, the accumulation of inorganic phosphate, and/or the transient large increase in adenosine diphosphate concentration (Boyas & Guevel, 2011). The peripheral factors concur in a hampered execution of the descending central commands (Allen et al., 2008). Some of these mechanisms are affected by blood flow, which is highly reduced during high contraction intensity (Crenshaw, Karlsson, Gerdel, & Friden, 1997; Sjogaard, Savard, & Juel, 1988), causing the muscle to operate in ischemic or sub-ischemic conditions (Dideriksen, Enoka, & Farina, 2011; Dideriksen, Farina, Baekgaard, & Enoka, 2010a).

4. Quantification of performance fatigability

At present there is no gold-standard to assess performance fatigability nor in healthy subjects, neither in chronic conditions; nonetheless, three categories of outcome measures used in literature may be identified: (1) strength-based outcomes, (2) neurophysiological outcomes and (3) indirect outcomes, as suggested in the systematic review of (Severijns et al., 2017).

In isometric conditions, strength decline is calculated as the ratio between the initial and the final strength during sustained or repetitive contractions, or the slope of the strength decline (e.g., Borji, Sahli, Zarrour, Zghal, & Rebai, 2013; Homma et al., 2015; Mehta & Agnew, 2012; Rantanen et al., 2000). Other authors reported a statistical comparison of the maximal strength, assessed before and after a specific task (e.g., (Delextrat, Piquet, Matthews, & Cohen, 2018; Severijns, Lemmens, Theolen, & Feys, 2016). Moreover, during isokinetic protocols, the ratio between the work done during the first contractions versus the last contractions (or the slope of torque decline) may be used (Clarkson et al., 1982; Hameau, Bensmail, Roche, & Zory, 2017).

Neurophysiological outcomes may help the researcher in exploring underlying mechanisms of fatigability. For instance, the twitch interpolation...
technique has been validated and is extensively employed in neuromuscular research to determine the changes in central and peripheral activation of the muscles under investigation, and used as an indication of loss of central drive (“central fatigue”) and “peripheral muscle fatigue” (Allen, Gandevia, & McKenzie, 1995; Gandevia, McNeil, Carroll, & Taylor, 2013; Kent-Braun & Le Blanc, 1996; Lepers, Maffulli, Rochette, Brugniaux, & Millet, 2002). Nonetheless, recently, the accuracy of the twitch interpolation technique has been questioned (Taylor, 2009), suggesting that it mainly reflects the amount of muscle activation in a qualitative way (Herzog, 2009).

Indirect measures comprise different types of outcomes, such as the time until a maximal voluntary force declined to 50% of the initial MVC (e.g., Peters & Fuglevand, 1999) or the number of repetitions performed until inability to maintain a target force (Dodd et al., 2011; Grisdale, Jacobs, & Cafarelli, 1990). In people with impaired ambulation, performance fatigability may be assessed as the deceleration index after a walking task (Phan-Ba et al., 2012), or as the distance walked (Leone et al., 2016; Mcdonald et al., 2013; Mercuri et al., 2016). Finally, indexes of fatigability may be extracted from gait kinematics (e.g., Boudarham et al., 2013; Engelhard, Dandu, Patek, Lach, & Goldman, 2016; Sehle, Vieten, Mundermann, & Dettmers, 2014) and electromyography (Vollestad, 1997).

5. Electromyography
Changes in the electromyogram were first used to investigate fatigue in the 1950s (Cifrek, Medved, Tonkovic, & Ostojic, 2009), and are now one of the most widely used indirect indices of performance fatigability in humans (Vollestad, 1997). There are two types of electromyography (EMG): intramuscular EMG (iEMG) and surface EMG (sEMG); with sEMG being the most commonly used, due to the fact of being non-invasive, with signals recorded from the skin surface (Merletti & Farina, 2016). In the present review we focus on sEMG descriptors of neuromuscular fatigue.

6. Surface EMG
The signal from the sEMG is the instantaneous algebraic summation of the electrical contributions made by the recruited MUs, in response to the activation provided by motor neurons (Farina, Merletti, & Enoka, 2004, 2014). In contrast to iEMG, the information extracted from the sEMG is considered a global measure of MU activity of the selected muscle. Moreover, amplitude and power spectrum of the sEMG signal are dependent on the timing of the MUAPs and the membrane properties of the muscle fibers, suggesting that the sEMG is reflective of both central and peripheral properties of the neuromuscular system (Farina et al., 2004). sEMG has been used in a number of different applications, such as in estimating muscle force, exploiting the almost linear relationship between signal amplitude and force (Bigland-Ritchie, Donovan, & Roussos, 1981; Inman, Ralston, Saunders, Feinstein, & Wright, 1952; Lippold, 1952), to investigate muscle activity during gait analysis (Sutherland, 1966), and to evaluate fatigability of skeletal muscles (Merletti, Knaflitz, & De Luca, 1990). More recently, the development of multi-channel electrode arrays (Merletti, Farina, & Gazzoni, 2003) expanded the number of applications of sEMG to other fields, such as neurorehabilitation (Liu, Ren, Xu, Kang, & Zhang, 2020), obstetrics (Cescon et al., 2014; Zacesta, Rezeberga, Paudiis, Drusany-Staric, & Cescon, 2018), occupational medicine (Rathleff et al., 2016), ergonomics (Januario et al., 2016) and assessment of interventions (reviewed in Drost, Stegeman, van Engelen, & Zwarts, 2006; Frigo & Crenna, 2009). Finally, the combination of techniques of spatial filtering (De Luca, Adam, Wotiz, Gilmore, & Nawab, 2006), spatial sampling (Gazzoni, Farina, & Merletti, 2004) and source separation (Holobar & Zazula, 2007) has provided a robust solution to fully decompose the sEMG signal into the discharge times of single MUs, with an accuracy comparable to iEMG decomposition (Del Vecchio et al., 2020). One of the pioneer studies that used sEMG techniques to track changes in the EMG signal during a fatiguing task was conducted by Piper (1912), who observed a progressive “slowing” of the signal during isometric voluntary sustained contractions. This phenomenon consisted in a shift of the spectral components of the signal towards lower frequencies (Piper rhythm). Besides such a frequency shift, (Cobb & Forbes, 1923) found a consistent increase in the amplitude of the sEMG signal. The traditional approach to acquire sEMG signals, which is still very often used in physiological and clinical studies, is based on a pair of electrodes placed on the skin (bipolar detection) in the region above the muscle. The signal detected however, is strongly dependent on the location, the interelectrode distance (IED), the size of the electrode pair, and the position along the muscle fiber, which can result in very different amplitude and spectral characteristics (Barbero, Rainoldi, & Merletti, 2012; Farina, Cescon, & Merletti, 2002a; Farina & Merletti, 2001; Merletti & Muceli, 2019; Mesin, Merletti, & Rainoldi, 2009b; Nishihara et al., 2010). The main advantage of bipolar sEMG is its high suitability for assessing global muscle activation in dynamic actions, such as sports, but inferences
regarding MU behavior (such as recruitment properties and rate coding) are limited. A relatively more recent approach consists in the use of multiple electrodes aligned in one- or two-dimensional arrays (known as high-density sEMG, HD-sEMG).

At least three detection modalities (also called electrode montages, or spatial filters) that can be applied when using linear electrode arrays: monopolar, single differential (SD) and double differential (Merletti & Farina, 2016). The monopolar provides the voltage of each electrode of the array with respect to a reference; the SD provides the output of the set of differential amplifiers and is obtained by taking the difference between adjacent channels; the DD provides the difference between adjacent SD channels. Each of these modalities gives three different signals with different properties. Monopolar montage senses all of the information in the signal but is the most prone to common disturbances affecting all channels, such as the end-of-fiber effect. The SD montage reduces the common components, and facilitates the identification of the innervation zone.

The DD montage further attenuates non-propagating signals and is therefore preferred in estimating muscle fiber CV (Cescon, Rebecchi, & Merletti, 2008; Farina et al., 2001b), whose measurement is influenced by the presence of non-propagating signals. Moreover, the three detection modalities have different volumes of detection and therefore detect a different number of MUs: the monopolar montage can detect “far” sources while the SD and DD modalities are more selective and detect “close” sources (Merletti & Muceli, 2019).

The multi-channel approach grants access to a set of physiologically relevant variables on the global muscle level or on the level of single MUs, providing new methods for the study of performance fatigability. For instance, multi-channel sEMG allows (1) a more precise estimation of muscle fiber CV, (2) the assessment of regional changes in the sEMG signal due to fatigue and (3) the analysis of single MUs, with the chance to obtain information about MU control and fiber membrane changes (Gazzoni, Botter, & Vieira, 2017; Merletti et al., 2003).

The relation between the sEMG signal and changes occurring in a muscle during a fatiguing task is very complex and affected by many factors. Therefore, in order to reduce the influence of some of these factors, the first type of contraction that was studied using sEMG techniques, was isometric or static contractions (Lloyd, 1971). However, although the recording of the signals is easier with respect to dynamic contractions, even in isometric constant force contractions, many factors affect the sEMG features (Table 1), ranging from anatomical to the detection system, to the estimation algorithm used (Farina et al., 2002a; Farina, Madeleine, Graven-Nielsen, Merletti, & Arendt-Nielsen, 2002c; Farina & Merletti, 2000, 2001; Farina, Merletti, Nazzaro, & Caruso, 2001a), complicating the interpretation of the acquired signals. In contrast to isometric contractions, the interpretation of the sEMG signal changes during fatiguing dynamic contractions, is complicated by a number of other factors, such as the changes in joint angle, that causes a shift in the underlying muscle fibers with respect to the recording electrodes, and the non-stationary nature of the signal, which causes the fact that classical spectral parameters may not be appropriate for extracting information (Farina, 2006; Merletti & Farina, 2016).

For instance, the two main factors that impacts on the sEMG signal in isometric conditions, are the decrease in muscle fiber CV and the variations of shape and increase of the spatial support and time duration of the transmembrane action potential, also

| BIOPHYSICAL | Anatomical | Spatial distribution of motor unit fibers | PERIPHERAL | Fiber membrane properties | Average muscle fiber conduction velocity |
|-------------|------------|-----------------------------------------|------------|---------------------------|----------------------------------------|
|             |            | Fibers’ length                          |            | Distribution of motor unit conduction velocities |
|             |            | Spread of the innervation zone and tendon regions among motor units |            | Distribution of muscle fibers conduction velocities within the motor units |
|             |            | Presence of more than one pinnation angle |            | Shape of the intracellular action potential |
| Detection system | Skin-electrode contact | (impedance, noise) |            | Number of the recruited motor units |
|             |            | Spatial filter for signal detection |            | Distribution of motor unit discharge rates |
|             |            | Interelectrode distance |            | Statistics and coefficient of variation for discharge rate |
| Geometrical | Electrode size and shape | Electrodes location |            | Motor unit synchronization |
|             |            | Inclination of detection system relative to muscle fibers orientation |            | |
|             |            | Muscle fiber shortening |            | |
|             |            | Muscle shift relative to the detection system |            | |
| Physical    | Conductivities of the tissues |                  |            | |

Table 1. Factors that influence the surface EMG signal.
called intracellular action potential (IAP) (Andreassen & Arendt-Nielsen, 1987; Arendt-Nielsen, Mills, & Forster, 1989; Dimitrov, Arabadzhiev, Hogrel, & Dimitrova, 2008; Dimitrova & Dimitrov, 2003). The decrease in muscle fiber CV impacts on the sEMG power spectrum causing a compression towards lower frequencies (Brody, Pollock, Roy, De Luca, & Celli, 1991; Kupa, Roy, Kandarian, & De Luca, 1995).

A fundamental characteristic of sEMG signals that are recorded during isometric constant force contractions is that the signal can be assumed to be stationary, thus allowing frequency-based techniques, such as Fourier transform or discrete fast Fourier transforms to be used to determine changes in the sEMG signal due to performance fatigability. However, even in such a controlled condition, non-stationarities may manifest, often related to the appearance of fatigue or changes in temperature (Bonato, Roy, Knaffitz, & De Luca, 2001).

In the last 40 years a large number of parameters extracted from the sEMG signal to indirectly assess performance fatigability was developed. It is not the intention of this paper to describe them all, but rather to review and further discuss the classical (amplitude and spectral parameters), non-linear parameters and the estimation of muscle fiber CV. Some recent works in literature give an exhaustive overview and critical analysis of methods for EMG fatigue evaluation using bipolar electrodes (Cifrek et al., 2009; Gonzalez-Izal, Malanda, Gorostiaga, & Izquierdo, 2012; Merletti & Farina, 2016; Rampichini, Vieira, Castiglioni, & Merati, 2020; Rogers & MacIaac, 2013) or with a multi-channel approach (Gazzoni et al., 2017).

### 6.1. Amplitude-based parameters

The averaged rectified value (ARV) and the root mean squared value (RMS, which is the square root of the area under the power spectrum) are the main parameters used to investigate the amplitude of the sEMG signal:

\[
\text{ARV} = \frac{1}{n} \sum_{n} |x_n|
\]

\[
\text{RMS} = \sqrt{\frac{1}{n} \sum_{n} x_n^2}
\]

where \(x_n\) are the values of the sEMG signal, and \(n\) is the number of samples.

Initially, the amplitude of the signal was related to central factors only (recruitment and discharge rates of the active MUs (Moritani, Muro, & Nagata, 1986; Solomonow et al., 1990)). In fact, during maximal isometric contractions amplitude falls progressively, in parallel with the decrease in force (Bigland-Ritchie et al., 1983a; Bigland-Ritchie, Johansson, Lippold, & Woods, 1983b; Bigland-Ritchie & Lippold, 1979), whereas during submaximal contractions it is rather to review and further discuss the classical (amplitude and spectral parameters), non-linear parameters and the estimation of muscle fiber CV. The averaged rectified value (ARV) and the root mean squared value (RMS, which is the square root of the area under the power spectrum) are the main parameters used to investigate the amplitude of the sEMG signal due to performance fatigability. However, even in such a controlled condition, non-stationarities may manifest, often related to the appearance of fatigue or changes in temperature (Bonato, Roy, Knaffitz, & De Luca, 2001).

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### 6.2. Spectral parameters

Two characteristic frequencies have been used to quantify the changes in the spectral content, based on the Fourier transform: the mean (or centroid, MNF) and the median frequency of the power spectrum (MDF). The MDF is the 50th percentile of the power spectrum, i.e., the value splitting it in two parts of equal energy (Gonzalez-Izal et al., 2012):

\[
\int_{f_1}^{f_{\text{median}}} PS(f) \cdot df = \int_{f_{\text{median}}}^{f_2} PS(f) \cdot df
\]

where \(PS(f)\) is the power spectrum calculated using the Fourier transform, and \(f_1\) and \(f_2\) determine the lowest and highest frequency of the bandwidth, respectively, typically ranging from 20 to 400 Hz. MNF is however calculated as follows:

\[
MNF = \frac{\int_{f_1}^{f_2} f \cdot PS(f) \cdot df}{\int_{f_1}^{f_2} PS(f) \cdot df}
\]
where PS(f) is the sEMG power spectrum calculated using Fourier transform, and f1 and f2 determine the bandwidth of the surface electromyography (f1 = lowest frequency and f2 = highest frequency of the bandwidth).

MDF and MNF are related to changes in muscle fiber CV and subsequent changes in the IAP duration (Bigland-Ritchie et al., 1981). It was shown during static contractions that MNF shifts towards lower frequencies during increasing fatigue (Lindström, Kadeferos, & Petersen, 1977; Merletti et al., 1990; Merletti & Lo Conte, 1997; Viitasalo & Komi, 1977), due to the diminished CV as a consequence of local metabolic changes in the working muscle, mainly H+ and K+ distribution across the sarcolemma (Dimitrova & Dimitrov, 2003; Masuda, Miyano, & Sadoyama, 1983). However, the modifications of the MUAP shape, MU firing rate and synchronization may also contribute to MNF changes (Bigland-Ritchie & Woods, 1984; Brody et al., 1991; Gabriel & Kamen, 2009). MDF is less sensible to noise (Hof, 1991) and more sensitive to simulated variations in the sEMG spectrum (Bonato et al., 2001) than MNF, in particular during dynamic contractions. The probability of discerning the relative contribution of physiological, anatomical and source of detection affecting spectral descriptors, as regards amplitude descriptors, requires careful reflection.

The behavior of the spectral variables during dynamic contractions was shown to be variable: Tesch et al. (1990) found decrements of MNF, whereas others observed no change during fatiguing walking exercises (Ament, Bonga, Hof, & Verkerke, 1996; Arendt-Nielsen & Sinkjaer, 1991), for various reasons, collectively termed dynamic factors. Merletti and Farina (2016) indicated that those factors include recruitment and de-recruitment of active MUs near to the electrodes, the time-varying spatial filter which changes as the muscle change its shape (Mesin, Joubert, Hanekom, Merletti, & Farina, 2006), and the movement of the innervation zone relative to the surface electrodes. Moreover, also the skin and intramuscular temperature may have an effect on spectral variable during dynamic tasks (Coletta, Mallette, Gabriel, Tyler, & Cheung, 2018; Petrofsky & Lind, 1980), though it does not act as a primary factor (Masuda, Masuda, Sadoyama, Inaki, & Katsuta, 1999). Collectively, these findings suggest that, when certain methodological measures are taken, traditional spectral descriptors may be well adapted for studying fatigue under both isometric and dynamic conditions.

Besides parameters derived from the Fourier transform, the use of time-frequency techniques has been proposed, such as the instantaneous mean frequency (iMNF) (Bonato et al., 2001) and wavelet spectral parameters (González-Izal et al., 2010). However, even though the first studies suggested that iMNF was affected by the same physiological factors as the classical spectral parameters, Farina et al. (2014) showed that during simulated ramp contractions, no association between the estimates of iMNF and recruitment and de-recruitment of MUs was found, suggesting the iMNF was insensitive to changes in MU population during a fatiguing task.

### 6.3. Non-linear parameters

Over the last quarter of century, great interest has been given in literature, particularly in the fields of physics, mathematics and chaos theory, to non-linear dynamics. Unlike linear systems, which are simple, proportionate and can be viewed as the sum of their parts (Goldberger, 1996, 2006), non-linear systems are characterized by a lack of proportionality, with small adjustments having dramatic, unpredictable consequences, thus restricting their ability to predict their long-term behavior (Peng, Costa, & Goldberger, 2009). Non-linear systems are regarded as complex, chaotic and unpredictable; characteristics which are of great interest to scientists.

Previous works suggested that also the sEMG waveform could be better modeled as an output of a non-linear dynamic system, rather than as a stochastic output of a linear white-noise driven system (Abarbanel, Brown, & Kadakke, 1989; Nieminen & Takala, 1996). As a non-linear signal, sEMG displays chaotic behavior, i.e., its time series (1) evolves over the time, (2) depends on the initial state, and (3) is fractal in the terms of dimensionality (Nieminen & Takala, 1996). Non-linear analysis offers a powerful approach for the investigation of physiological time series because it provides a measure of the signal complexity, and may be able to detect additional EMG changes during a fatiguing task. Moreover, it has been found that non-linear parameters, such as entropy, percent of determinism based on recurrence quantification analysis, and dimensionality based on fractal analysis are highly sensitive for hidden rhythms on sEMG in subjects under fatigue and condition of increased MU synchronization (Del Santo, Gelli, Mazzocchio, & Rossi, 2007; Farina, Fattorini, Felici, & Filligoi, 2002b; Filligoi & Felici, 1999; Gitter & Czerniecki, 1995).

#### 6.3.1. Entropy

Entropy, as expressed in the second law of thermodynamics, is a measure of disorder or randomness which, in an isolated system, tends to a maximum (Schneider & Kay, 1994; Seely & Macklem, 2004). As far as dynamic systems are concerned, entropy can be defined as the rate of information output (Eckmann & Ruelle, 1985; Richman & Moorman, 2000; Seely & Macklem, 2004) and can be used to
measure the apparent randomness and regularity of a system, i.e., the complexity (Pincus, 1991; Seely & Macklem, 2004). A number of parameters were developed to estimate the entropy of the sEMG signal, e.g., Pincus (1991) developed the Approximate Entropy (ApEn), as a model-independent quantification of the regularity of sequences and time-series data, motivated by applications to relatively short, noisy data sets. Richman and Moorman (2000) developed a new parameter, called Sample Entropy (SampEn), which was shown to be more consistent and performant than ApEn. Thereafter, Costa, Goldberger, and Peng (2002) introduced the multi-scale entropy (MSEn) method, which was intended to better detect the presence of complexity in the time series. Cashaback, Cluff, and Potvin (2013) applied the MSEn to the sEMG signal to evaluate short-term complexity at different contraction intensities, although the complexity level at MVC was only slightly different compared to 70% MVC, probably due to the fact that the complexity of the signal was mostly influenced by the firing rate rather than MU recruitment.

Entropy methods have been applied to sEMG signal to detect fatigability changes. For instance, Hernandez and Camic (2019) recently found that SampEn values decreased differently during maximal concentric, eccentric and isometric knee extensions. Similar results were found by other authors during submaximal and maximal contractions until task failure (Cashaback et al., 2013; Navaneethakrishna, Karthick, & Ramakrishnan, 2015). The authors of these studies hypothesized that the reduction of complexity was related to central (MUs synchronization) and/or peripheral factors (decrease in muscle fiber CV).

### 6.3.2. Fractal analysis

The fractal's theory refers to the discovery of Benoit Mandelbrot (1982): 'an object or a signal which can be split into parts, each of which is a reduced-size copy of the whole, might be defined as fractal and this property is called self-similarity'. Mandelbrot coined the term "fractal" few years earlier, from the Latin fractus, the past participle of the verb frangere, "to break," (1977).

Fractals have subsequently come to be defined by a set of four characteristic properties: self-similarity, scaling, the fractal dimension (FD) and statistical properties (Di leva, 2016; Eke, Herman, Kocsis, & Kozak, 2002): 1) The self-similarity fractals exhibit, may be either geometrical or statistical. Geometrically self-similar objects are those with smaller, exact replicas of the entire object (Eke et al., 2002; Mandelbrot, 1982). Statistically self-similar objects are “kind of like” the whole; the pieces’ statistical properties are proportionate to the statistical properties of the whole (Bassingthwaigte & Raymond, 1994). 2) Owing to the self-similarity, features in one resolution are correlated with features in other resolutions. Scaling refers to how the measured values depend on the resolution used to make the measurement (Di leva, 2016); thus, the length measured at finer resolutions would be longer, because it includes finer features. The FD offers a quantitative measurement of self-similarity and scaling, explaining how many new pieces, similar to the entire object, are revealed when the resolution is finer (Di leva, 2016). The statistical properties of fractals include the fact that there might not be a mean or variance in fractal processes. For the mean, as more data are analyzed, rather than converging to a single value, the mean tends to increase to an ever-larger value or decreases to an ever-smaller value (Liebovitch, 1998). For the variance, self-similarity means that small irregularities are replicated on a larger scale as larger irregularities, and as more data are examined, those larger irregularities increase the variance, which then becomes infinite (Di leva, 2016).

Many complex anatomical structures display fractal-like geometry, and unlike the geometric fractals developed by mathematicians, which may be defined as exact fractals, these structures are statistical fractals (Eke et al., 2002). The sEMG signal itself, which originates from a strong non-linear combination of similar templates (i.e., action potentials of different MUs) that undergo spectral and magnitude compression, has self-similarity properties, and therefore fractal analysis seems appropriate (Anmuth, Goldberg, & Mayer, 1994). As outlined above, the description of a fractal structure occurs through the determination of the FD, which is a measure of self-similarity and geometrical complexity of the signal. FD gives a quantitative indication of the chaotic behavior of a signal, and is also related to the degree of interference of the signal, which is inversely related to the ‘smoothness’ of the signal (Mesin, Cescon, Gazzoni, Merletti, & Rainoldi, 2009a). At least eight different methods for estimating FD of sEMG waveforms have been applied in literature, including the box-counting method (Barnsley & Hurd, 1989), the Hurst exponent (Hurst, 1951), a method based on power spectral density (Kaplan, 1999; Raghav & Mishra, 2008; Spasic, 2007), the methods proposed by (Higuchi, 1988), (Sevcik, 2010), (Petrosian, 1995) and (Katz, 1988) and two variants of the latter (Castiglioni, 2010). These methods were compared and reviewed by (Coelho & Lima, 2014), who evidenced that the normalized version of the Katz’s estimation method, followed by the Hurst
exponent, significantly outperform the others in terms of generating more discriminatory features. However, the Katz’s method provides FD estimates that may depend on the length of the time series (Castiglioni, 2010) and in another study, the Higuchi algorithm was preferred over the Katz’s, since it provided a more accurate and consistent estimation of FD for physiological signals (Esteller, Vachtsevanos, Echauz, & Litt, 2001). Thus, an accurate selection of FD algorithm is required for specific applications.

The Katz’s method has been revised by Anmuth et al. (1994) to be applied to sEMG signal during isometric contractions. Given a signal lasting 3 seconds, FD was estimated for the middle 1 s as:

$$FD = \frac{\log N}{\log N + \log \left(\frac{d}{L}\right)}$$

where $N$ is the number of samples in the signal, $d$ is the planar extent of the waveform (computed as the distance between the first point of the sequence and the point of the series that provides the farthest distance), and $L$ the total length of the signal (sum of distances between successive points) (Rampichini et al., 2016).

In addition, Wang et al. (2019) introduced a new algorithm named ‘roughness scaling extraction’ (RSE) to evaluate FD based on a single morphological image. It was found that RSE algorithm was much more accurate than the traditional algorithms.

Nevertheless, another popular estimator of the FD is the box-counting method on the EMG signal interference pattern (Gitter & Czerniecki, 1995). The exact calculation of FD through the box-counting method is given in detail in the General methods. FD values close to 1 reflect smoothed signals whereas values approaching 2 are typical of signals with high space-filling propensity (Beretta-Piccoli et al., 2015). The box-counting algorithm has been used to evaluate sEMG signals during isometric contractions in healthy subjects (Beretta-Piccoli et al., 2017; Mesin et al., 2009a; Troiano et al., 2008), elderly (Boccia et al., 2016) and persons with multiple sclerosis (Beretta-Piccoli et al., 2020).

FD was initially used to characterize levels of muscle activation during isometric and isokinetic contractions (Anmuth et al., 1994; Gupta, Suryanarayanan, & Reddy, 1997; Talebinejad, Chan, Miri, & Dansereau, 2009) and patterns of MU recruitment (Gitter & Czerniecki, 1995; Xu & Xiao, 1997). Arjunan and Kumar (2010) investigated the complexity of muscle activation using the FD during wrist and finger flexions. Later, FD was proposed as an index to monitor changes in sEMG signal during a fatiguing task (Beretta-Piccoli et al., 2015; Boccia et al., 2016; Mesin et al., 2009a). Indeed, we clearly showed a significant negative normalized slope of FD, during fatiguing isometric contractions in different muscles (vastus lateralis and medialis and BB) and at different intensities (Beretta-Piccoli et al., 2020; Beretta-Piccoli et al., 2015; Beretta-Piccoli et al., 2017; Boccia et al., 2016; Meduri et al., 2016), suggesting a reduction in signal complexity (Figure 2).

Moreover, a decrease in FD was also associated to ageing and disease (Arjunan & Kumar, 2013; Boccia et al., 2016; Goldberger et al., 2002). These findings suggest a possible benefit of the fractal analysis of the sEMG signal as a complementary tool for the evaluation of fatigability during a performance test. However, although the use of non-linear analysis of the sEMG signal is desirable, as more sensitive than spectral analysis for the assessment of performance fatigability (Farina et al., 2002a), it is difficult to relate these parameters to physiological changes in muscle properties resulting from fatigue (Merletti & Farina, 2016). Mesin et al. (2009a) compared FD to other linear and non-linear muscle fatigue indices’ computed from both synthetic and experimental sEMG signals: they found that FD was the parameter least affected by CV changes, weakly affected by fat layer thickness and mostly related to the level of MU synchronization, which suggested its possible use as index of central components of fatigue. Szu-Yu, Chih, Hsin, Wu, and Po-Shan (2015) using the Katz’s calculation of FD, did not report any changes during isotonic repeated submaximal contractions (pedaling). Lastly, Mesin, Dardanello, Rainoldi, and Boccia (2016) investigated the effect on FD of both the percentages of MU synchronization (from 0–20%) and different firing rates (5–40 Hz), respectively. The authors demonstrated the presence of an inverse relationship between FD and MU synchronization and a positive relationship with the MU firing rate. Such results have brought new light to the understanding of FD changes induced by fatigue, rendering FD no longer regarded as an exclusive index of MU synchronization only. Other authors have used different fractal parameters, such as detrended fluctuation analysis (DFA) and multifractality. DFA, developed by Peng et al. (1994), relates to the color of noise and detects long-range correlations in time-series, thus providing an indication of temporal fractal scaling. Further details of the DFA calculation are given by Stanley et al. (1999). An extended version of the DFA method was applied to identify the components of the multifractal dynamics, since complex systems may generate not only monofractal time series, but also multifractals. Wang, Ren, Li, and Wang (2007) and Talebinejad, Chan, and Miri (2010) applied the multifractal DFA to investigate performance fatigability during static, as well as cyclic and random contractions, respectively.
Finally, among others non-linear methods, the evaluation of the correlation dimension (CD) (Grassberger, Schreiber, & Schaffrath, 1991) has been used to classify the sEMG dynamics, both at rest and during light and fatiguing muscle contractions. CD is a measure of the amount of correlation contained in a signal connected to the FD (Rampichini et al., 2020). During a fatiguing task a reduction in the dimensionality of the system, as assessed by CD was demonstrated: this has been ascribed to MU synchronization and reduction in the propagation velocity of the IAP and firing rate, which may reduce the neuromuscular system adaptability (Nieminen & Takala, 1996).

However, a precise connection between the physiologic adaptation to fatigue in muscle activity and the changes in CD of sEMG signals is still lacking.

7. Multi-channel electrodes

With respect to the classical bipolar approach, the use of methods based on more than two channels arranged serially (linear arrays) allows the detection of sEMG signals along the longitudinal or transverse axis of a muscle (Merletti et al., 2003; Wood, Jarratt, Barker, & Brown, 2001). Additionally, bi-dimensional electrode arrays (grids of electrodes) may be used to determine the distribution of EMG amplitude and spectral descriptors across the entire skin area covering the target muscle (Falla & Farina, 2007; Gallina, Merletti, & Gazzoni, 2013a; Vieira, Botter, Minetto, & Hodson-Tole, 2015). In addition, multi-channel sEMG allows a more precise and reliable estimation of muscle fiber CV (reviewed in Beretta-Piccoli, Cescon, Barbero, & D’Antona, 2019) and the assessment of regional changes in the sEMG signal due to fatigue in skeletal muscle (reviewed in Gazzoni et al., 2017).

8. Muscle fiber conduction velocity

Muscle fiber CV is not only a mathematical descriptor, but also a significant physiological variable directly related to fiber membrane properties, fiber diameter and fiber contractile properties (Andreassen & Arendt-Nielsen, 1987). Muscle fiber CV is associated to the size principle (Henneman, Somjen, & Carpenter, 1965) has been positively correlated with

![Figure 2. Time course of fractal dimension (FD), muscle fiber conduction velocity (CV), mean frequency of the power spectrum (MNF) and average rectified value (ARV) for a representative person with multiple sclerosis (from Beretta-Piccoli et al., 2020). BB, biceps brachii; VV, vastus lateralis and medialis.](image-url)
the percentage of myosin heavy chain type I fibers (Farina, Ferguson, Macaluso, & Vito, 2007) and can be used to assess MU recruitment during static and dynamic exercise (Merletti et al., 2010; Nicolò, Bazzucchi, Felici, Patrizio, & Sacchetti, 2015; Piitulainen, Botter, Merletti, & Avela, 2013; Pozzo, Alkner, Norrbrand, Farina, & Tesch, 2006). Muscle fiber CV has also been proposed as a non-invasive tool to infer MU recruitment and de-recruitment during incremental cycling exercises (Lenti, De Vito, Sbriccoli, Scotto di Palumbo, & Sacchetti, 2010; Sbriccoli et al., 2009). Moreover, since during dynamic contractions the number of active MUs changes significantly, the analysis of CV is preferred over spectral analysis to extract information on MU recruitment (Farina, 2006).

The CV of the action potentials in human muscles has been measured successfully by the use of needle electrodes in the late 50s: Buchthal, Guld, and Rosenfalck (1955) used 3 to 6 coaxial needle electrodes, while Stålberg (1966) used a multi-contact needle electrode. Later, Nishizono, Saito, and Miyashita (1979) conducted the first estimation of muscle fiber CV using up to 8 sEMG electrodes placed on the BB. In their study Nishizono et al. (1979) suggested that “if muscle CV could be measured accurately using sEMG, it could be applied effectively, for instance, to the detection of muscle disorders and to the estimation of muscle fiber composition”. As described earlier, changes in CV during fatiguing contractions, have profound impact on the shape of the MUAP waveform and therefore, on the amplitude and spectral variables extracted from the sEMG signal. In particular, during isometric constant force contractions, changes in the EMG signal due to fatigue are mainly caused by three physiological factors: (1) a decay in muscle fibers CV (Buchthal et al., 1955; Stalberg, 1966), mainly related to a decrease of the intracellular pH (Bouissou, Estrade, Goubel, Guezennec, & Serrurier, 1989; Brody et al., 1991; Komi & Tesch, 1979); (2) an increase of the level of MUs synchronization by the CNS (Merletti et al., 1990) and (3) a reduction of the recruitment threshold of MUs (Adam & De Luca, 2003).

Therefore, the estimation of CV slope (i.e., rate of change), might be useful to characterize the components of muscle fatigue (mainly peripheral during an isometric task) (Merletti & Farina, 2016) and this variable may be considered as one of the most robust EMG fatigue indices (Figure 2; Deding, Roos af Hjelmsäter, Elfving, Harms-Ringdahl, & Németh, 2000; Kollmitzer, Ebenbichler, & Kopf, 1999; Linssen et al., 1993; Rainoldi, Bullock-Saxton, Cavarretta, & Hogan, 2001).

Muscle fiber CV is generally estimated from sEMG signals collected with multi-channel electrodes positioned parallel to the muscle fibers. However, most fibers within in-depth pinnate muscles, do not lay in planes parallel to the skin, and as a result, electrodes and muscle fibers are not located in parallel planes. In such muscles, CV estimates are biased towards values far over the physiological range (Merletti & Farina, 2016). Moreover, a pair of electrodes placed above an unspecific muscle region may provide very misleading information. Recent publications suggested that in pinnate muscles such as the medial gastrocnemius, and the tibialis anterior, it is possible to reliably assess physiological estimates of CV, using HD-EMG, from their distal region (Gallina, Ritzel, Merletti, & Vieira, 2013b; Houtman, Stegeman, Van Dijk, & Zwarts, 2003), where fibers run parallel to the skin surface.

Multi-channel sEMG allows a more precise estimation of muscle fiber CV (on the global muscle level) and the estimation of CV of individual motor units (MUs). The two approaches diverge mainly on the complexity of the estimation method. The estimation of muscle fiber CV is usually performed through a multichannel algorithm, based on the matching between signals filtered in the temporal and spatial domains, on the selected channels. When applied to the global signal, the estimated CV is an average value originating from the actual CV of all MU action potentials (MUAPs) detected in the considered time window. On the contrary, the estimation of CV of individual MUs is generally performed using MUAPs templates obtained via spike-triggered averaging based on the firing instants identified by decomposition of multi-channel sEMG recordings (Keenan et al., 2006). Estimation of the CV from a MUAP template is relatively simple, but it is considerably more complex for an interferential signal, which is the sum of the contributions of different asynchronously appearing MUs (Farina & Merletti, 2000). However, at the present time, as reported by Gazzoni et al. (2017) the number of MUs extracted by different decomposition methods (few tens) may not provide CV histograms sufficiently representative of the MUs within the electrodes’ detection volume.

Changes in CV during fatiguing contractions, have profound impact on the shape of the MU action potential waveform and therefore, on the amplitude and spectral variables extracted from the sEMG signal. The estimation of CV slope (i.e., rate of change), might be useful to characterize the peripheral components of fatigability during an isometric task (Merletti & Farina, 2016) and this variable may be considered as one of the most robust EMG fatigability indices (Deding et al., 2000; Kollmitzer et al., 1999; Linssen et al., 1993; Rainoldi et al., 2001).

9. Conclusion
The sEMG undergoes several changes during an isometric fatiguing muscle contraction. Amplitude and
spectral parameters, as well as muscle fiber CV and FD of the sEMG signal may be used as indirect fatigability indices to monitor these changes in health and in neuromuscular diseases. In particular, available studies demonstrate that sEMG is suitable for use when investigating CV, which is mostly sensible to peripheral aspects affecting performance fatigability, whereas the use of FD, as index of central factors affecting performance fatigability, may be considered above a certain level of force, regardless of muscle contraction intensity. The use of the fractal dimension of the sEMG signal to infer central aspects of performance fatigability should be promoted in particular, in those muscles were motor unit decomposition techniques are limited by anatomical constraints.

Disclosure statement

No potential conflict of interest was reported by the authors.

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