On the Dynamics and Mechanisms Responsible for Non-linear Force Summations in Mammalian Muscle

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Abstract— The underlying mechanisms responsible for non-linear summation and timing effects observed in mammalian skeletal muscle activated by N-let pulse trains are investigated. N-lets are sets of \( N \) high frequency pulses with highly variable inter-pulse intervals that have been shown to improve fatigue resistance, reduce fibre type transformation and maximise the force-time integral per pulse of skeletal muscles activated by Functional Neuromuscular Stimulation (FNS). Investigations are performed in simulation using a recently developed physiologically based mathematical model of mammalian skeletal muscle. This model enables investigations of the internal system dynamics of skeletal muscle to be conducted under both isometric and non-isometric conditions. The results obtained compare well with recent experimental input-output data for skeletal muscle. An analysis of the underlying system dynamics suggests that a subtle interplay between the rate of muscular contraction and non-linearities within the \( \text{Ca}^{2+} \) release and re-accumulation dynamics may be responsible for the non-linear summation effects observed. It is also found that the disappearance of the doublet effect observed when muscle is transformed from fast to slow fibre type may be due to changes in the \( \text{Ca}^{2+} \) dynamics of muscle. These mechanisms may be an important consideration in the design of N-let control strategies for FNS.

Index terms— Muscle, N-lets, neuromuscular stimulation, modelling.

I. INTRODUCTION

It has long been known that the muscular force generated in response to two closely spaced electrical stimulation pulses of the motor nerve is substantially and non-linearly increased above that for a single twitch [3]. It has also been demonstrated experimentally that the tension output of muscle activated by low frequency stimulation pulses may be significantly increased by adding a single pulse with a small interpulse interval (IPI), to form a ‘doublet’ [1] [2]. Doublet, and larger N-let (sets of \( N \) high frequency pulses with variable inter-pulse intervals), pulse trains have recently been shown during Functional Neuromuscular Stimulation (FNS) to improve fatigue resistance [12], maximise muscle’s isometric force generated over time [12]-[14] [19] and prevent losses in muscle power by reducing fibre type transformation [11]. These desirable properties have lead to doublets and N-lets being used in cardiomyoplasties, skeletal muscle ventricles and the restoration of both function and skeletal motion to the paralysed [5] [8] [15] [17].

Yet, while doublets have been studied extensively in mammalian skeletal muscle [12] [14]-[18] the underlying mechanism responsible for the non-linear summation effects observed remains unclear.

A number of mechanisms have previously been suggested as driving these non-linear summations. They include, amongst others, additional recruitment, eccentric contraction effects, the force-length relation and higher muscle stiffness [16] [18]. However, all of these mechanisms have recently been shown to play no significant role in the generation of non-linear force summations [4] [6] [7] [12]. In contrast, the modification of intracellular excitation-contraction processes, and in particular intensified release of \( \text{Ca}^{2+} \) from the sarcoplasmic reticulum (SR), is a highly likely driving mechanism. Non-linear summations in the SR \( \text{Ca}^{2+} \) release dynamics, which may cause non-linear force summations, have clearly been identified during doublet activation of barnacle muscle [7]. Unfortunately, similar results do not exist for mammalian skeletal muscle, due to difficulties in performing the necessary experiments on mammalian muscle fibres. However, it has recently been demonstrated in simulation that non-linearities in the SR \( \text{Ca}^{2+} \) release and re-accumulation dynamics can indeed account for a wide variety of non-linear summation effects in mammalian skeletal muscle [4].

Kwende et al. [13] recently showed that doublet and N-let non-linear force summations are abolished in mammalian skeletal muscles converted from predominantly fast fibre type to predominantly slow fibre type by chronic stimulation at 10Hz for six weeks. This result is made more puzzling by the fact that the reason for such a dramatic change in muscle’s contraction properties is unknown.

The goal of this paper is to identify whether changes in the \( \text{Ca}^{2+} \) release and re-accumulation dynamics of these transformed muscle fibres can account for the elimination of doublet non-linear force summations observed.

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II. MATHEMATICAL MODEL

All simulations were performed using a recently developed physiologically based mathematical model of human skeletal muscle [4]. This model has electrical stimulation pulses as inputs and the force developed as an output. In contrast to typical FNS muscle models, the contractile machinery incorporates sub-models for the physiological systems responsible for neural, neuromuscular, calcium release, calcium re-accumulation and muscle contraction dynamics. As a result significant insight is provided into the complex internal dynamics responsible for force generation in skeletal muscle.

This model has previously been shown to capture a host of general muscle properties, including a variety of non-linear force summation and stiffness variation effects observed experimentally when activating skeletal muscle with by N-let or constant frequency pulse trains. While the model has a Hill-type macrostructure its contractile element, which is outlined in Fig. 1, is novel. The calcium release and re-accumulation dynamics of the sarcoplasmic reticulum (SR) form a vital part of this model, and their electrical equivalent circuit is illustrated in Fig. 2. A complete description of the model’s structure, equations, derivation and validation may be found elsewhere [4].

III. SIMULATIONS

A model of fast human muscle fibre-type, with the equations and parameters presented previously [4], was implemented using commercially available modelling software and simulated. The parameters governing the rate of Ca$^{2+}$ release and re-accumulation by the SR were then changed to accurately model those of slower muscle fibre types, as described in [10]. The contraction dynamics parameters were also changed to those of a slower muscle fibre type [9]. Such a change was made to increase the twitch contraction time for the slow muscle fibre model to three times that of the fast muscle model. This factor was chosen as it is precisely the factor by which the twitch contraction time of fast muscle increased in experiment when chronically stimulated at 10Hz for six weeks [13].

The force response of the model to a series of doublet electrical stimulation pulse pairs applied to the motor nerve with various interpulse intervals (IPIs) was obtained. The force-time integral per pulse (FTIpP) was calculated from the muscle model’s response to each doublet. The FTIpP for a pulse train of N pulses is defined as [12]-[14]:

$$FTIpP = \frac{\text{Force–time integral for } N \text{ pulses}}{N \times \text{(Twitch force–time integral)}}$$  (1)

The greater the FTIpP is than unity the greater the non-linearity in the force generated over a period of time for a given number of stimulation pulses.

IV. RESULTS

The variation in the FTIpP index as a function of doublet IPI experimentally identified for fast rabbit muscle by Kwende et al. [13] is shown in Fig. 3(a). Also shown is the FTIpP variation predicted by the fast muscle model. From Fig. 3(a) one may see both the substantial non-linear force summation that takes place in fast skeletal muscles at small IPIs and the agreement of the fast muscle model’s simulation predictions with the experimental observations.

In Fig. 3(b) the FTIpP variation, as a function of doublet IPI, found in simulation using the same model, but with parameters describing slow fibre type is shown. The experimental FTIpP variation found in the investigation of Kwende et al. [13] for chronically stimulated rabbit muscle is also shown.
It was shown in Fig. 3 that the model used predicts the elimination of doublet non-linear force summations when the parameters for SR Ca\(^{2+}\) and muscle contraction dynamics are changed from fast muscle to slow muscle values. The transformation from a more-than-linear summation to a less-than-linear summation, at small doublet IPIs, which has been observed in experiment [13] is also accurately predicted. In other simulations conducted during this brief study it was found that changing either the SR Ca\(^{2+}\) or muscle contraction dynamics in isolation is not capable of predicting the experimentally observed effects.

These mechanisms may be an important consideration in the design of N-let control strategies for use in applications such as cardiac assistance and the initiation of skeletal motion.

The results presented strongly suggest that it is changes in both Ca\(^{2+}\) release and re-accumulation dynamics and the fibre contraction dynamics which are responsible for the experimentally observed disappearance of non-linear summation effects in muscle transformed from fast to slow fibre type by chronic electrical stimulation. While these results are obtained in simulations using a model of human muscle the author looks forward to a future investigation of Ca\(^{2+}\) dynamics during doublet activation of mammalian skeletal muscle as a means of experimentally testing the conclusions drawn here.

**REFERENCES**


Stephen J. Dorgan was born in Dublin, Ireland, in 1971 and entered University College, Dublin (U.C.D.) in 1989. He received the B.E. degree in electronic engineering with first class honours from the National University of Ireland in 1993. In 1997 he was awarded the Ph.D. in electronic engineering from the same University.

Between 1991 and 1993 he spent time in industry, both in Europe and the USA, working on artificial intelligence and robotic control projects. While a Ph.D. student he was a U.C.D. Presidential Research Scholar, a Lord Edward Fitzgerald Scholar, an Irish-American Partnership Scholar and a U.C.D. Open Postgraduate Scholar. In 1997 he won the IEE Younger Members Written Paper Premium. Since July 1997 he has been a European Union Marie Curie Fellow in the Institute of Automatic Control Engineering at the Technical University of Munich, Germany. His research interests include non-linear dynamics, control theory and modelling physiological systems.

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