A PHYSIOLOGICALLY BASED NON-LINEAR MUSCLE ACTIVATION MODEL OF VARIABLE STIMULATION FREQUENCY RESPONSE
Gonzalo H. Otazu*, Takashi Watanabe, Ryoko Futami and Nozomu Hoshimiya
Graduate School of Engineering, Tohoku University
Aramaki aza aoba 05, Aoba-ku, Sendai 980-8579, Japan
E-mail*: gonzalo@hoshimiya.ecei.tohoku.ac.jp

ABSTRACT
Muscle fiber response to a train of variable-frequency pulses is complex and dependent on stimulation history. This response includes the post-tetanic potentiation and catch-like effect. These phenomena have shown the potential to reduce the number of pulses necessary to achieve a certain force level. For better understanding of these phenomena, we built an activation model with emphasis on the calcium liberation from and re-sequestration into the sarcoplasmic reticulum, including Calcium Induced Calcium Release (CICR). The model had double stable equilibrium points in the calcium concentration. Changes from low to high equilibrium point could be produced by high frequency trains of pulses and would be accountable for the post tetanic potentiation. The performed computer simulations showed a change in the resting calcium concentration after a short train of high frequency pulses. Subsequent low frequency train of pulses produced increased force compared to the previous generated forces with the same low frequency stimulation. The simulated catch-like effect was mutually exclusive with the Post-Tetanic Potentiation.

Keywords: FES, muscle model, catch-like effect, post-tetanic potentiation, calcium

INTRODUCTION
The use of electrical signals to restore the function of paralyzed muscles is called Functional Electrical Stimulation (FES). The muscle force is controlled by changing the number of active motor units by pulse amplitude modulation or pulse width modulation, using constant-frequency stimulation. After a high frequency train of pulses, successive pulses elicit an increment in the force that last several minutes called Post Tetanic Potentiation (PTP)[1]. The inclusion of briefly spaced pulses in the middle of a lower frequency train of pulses produces a long lasting increment in force called catch-like effect [3]. The true catch effect occurring in molluscan smooth muscle does not require continuous stimulation [9].

When the muscle has already been potentiated, the catch-like effect loses its ability to create long-lasting forces [4]. These effects could be used to reduce the number of applied pulses necessary to produce certain level of force reducing the impairment of action potential propagation associated with higher frequencies of stimulation [10]. Most muscle models used in FES did not include these effects. Only Chou and Hannaford model [5] included the catch-like effect. In their model, the catch-like effect appeared because there were two stable equilibrium points for the calcium-activation relationship. The double equilibrium point model was based on nonlinear binding and unbinding rates of troponin–calcium. However, there was no clear physiological base for these relationships. In addition, the model did not include potentiation. Our research purpose is to build a myofibril model that includes the potentiation effect and the catch-like effect under isometric conditions. The basic hypothesis of our model is that potentiation and catch-like effect are both produced by the elevation in the intracellular calcium ion concentration ([Ca$^{2+}$]) after a high frequency train of pulses [11]. We demonstrate the appearance of a double equilibrium point in the resting calcium concentration because of the interaction between the liberation of calcium ion from the sarcoplasmic reticulum (SR) and the reuptake by a calcium pump.

MODEL STRUCTURE
The action potential is transmitted through the muscle fiber membrane. The muscle fiber membrane penetrates into the muscle fiber. This structure is called transversal (T) tubule. The T-tubule contacts the SR (see Fig.1). The SR is the reservoir where the Ca$^{2+}$ is stored. When the T-tubule depolarizes, the voltage activated channels of the SR open and the calcium

![Diagram of muscle activation model](image-url)
concentration ([Ca$^{2+}$]) increases inside the myofibril. The Ca$^{2+}$ is returned inside the SR by a calcium pump. When the thin filament protein troponin binds to Ca$^{2+}$, actin and myosin can interact to produce sarcomere contraction. The liberation of Ca$^{2+}$ is under direct neural control, but the existence of calcium activated channels has been postulated [12]. These channels are opened and closed according to the [Ca$^{2+}$] near the surface of SR. The Ca$^{2+}$ diffuses from the liberation points in the surface of the SR to the middle of the fiber, where the troponin is located. We considered that there are two concentrations of Ca$^{2+}$ [8]. [Ca$^{2+}$]$_{PROX}$ is near the SR surface, where the liberation channels and the pump are located. [Ca$^{2+}$]$_{DIST}$ is the concentration in the myofibrilar space. Ca$^{2+}$ also binds parvalbumin that acts as a buffer [13].

The dynamics of [Ca$^{2+}$]$_{PROX}$ is given by

$$\frac{d[Ca^{2+}]_{PROX}}{dt} = \gamma_{VOLT} + \gamma_{Ca} + \gamma_{PUMP}$$

In addition, the change in [Ca$^{2+}$]$_{DIST}$ is:

$$\frac{d[Ca^{2+}]_{DIST}}{dt} = \frac{[Ca^{2+}]_{PROX} - [Ca^{2+}]_{DIST}}{\tau_{PROX}}$$

$-$[CaTN]'$-$[CaPARV]' where $\gamma_{VOLT}$, $\gamma_{Ca}$ and $\gamma_{PUMP}$ are the time derivative of [Ca$^{2+}$]$_{PROX}$ produced by Voltage Activated channels, Calcium Activated channels and pump respectively. [CaTN]' and [CaPARV]' are the derivative of calcium concentration bound to troponin and parvalbumin respectively. $\tau_{PROX}$ and $\tau_{DIST}$ are the diffusion time constants.

The $\gamma_{VOLT}$ is modeled as a half sinusoidal pulse with 4 ms half period and $k_{VOLT}$ amplitude when a pulse arrives [15]. Additionally there is also a small leakage Ca$^{2+}$ efflux (leak) that flows even in the absence of a stimulation pulse.

The calcium-activated channel has two Ca$^{2+}$ binding sites, one activating and one inactivating. To open the channel, the activating site must be bound to 2 calcium ions and the inactivating site must not be bound [8].

Activating sites dynamics

$$\frac{da}{dt} = \alpha_a (1-a)([Ca^{2+}]_{prox})^2 - \beta_a a$$ (3)

Inactivating site dynamics

$$\frac{di}{dt} = \alpha_i (1-i)([Ca^{2+}]_{prox} - \beta_i i$$ (4)

The liberated calcium outflow will be:

$$\gamma_{VOLT} = r_{Ca}(1-i)a$$ (5)

where $a$ is the probability of activation of the channel, $i$ is the probability of calcium inactivation of the channel. $\alpha_a$ and $\alpha_i$ are the activating and inactivating site binding constant. $\beta_a$ and $\beta_i$ are the activating and inactivating site unbinding constant. $r_{Ca}$ is the maximum time derivative of [Ca$^{2+}$]$_{PROX}$ that can be produced by calcium activated channels.

The calcium pump is modeled using a simple Michaelis-Menten type of equation [6].

$$\gamma_{PUMP} = \frac{r_{PUMP}[Ca^{2+}]_{PROX}}{K_{PUMP} + [Ca^{2+}]_{PROX}^3}$$ (6)

Both troponin and parvalbumin bind calcium. Their dynamic equations are given by for parvalbumin [2]:

$$\frac{d[Ca^{2+}]}{dt} = \alpha_{PARV}[Ca^{2+}]_{DIST}([PARV] - [Ca^{2+}]) - \beta_{PARV}[Ca^{2+}]$$ (7)

And for troponin:

$$\frac{d[Ca^{2+}]}{dt} = \alpha_{TROP}[Ca^{2+}]_{DIST}([TN] - [Ca^{2+}]) - \beta_{TROP}[Ca^{2+}]$$ (8)

[TN] and [PARV] are the total troponin and parvalbumin concentration. [CaTN] and [CaPARV] are the concentrations of calcium that are bound to troponin and parvalbumin. $\alpha_{TROP}$ and $\alpha_{PARV}$ are the troponin and parvalbumin binding constant. $\beta_{TROP}$ and $\beta_{PARV}$ are the troponin and parvalbumin unbinding constant.

The equilibrium state is found without applied stimulation ($\gamma_{VOLT}=leak$) making all time derivatives equal to zero. From eq. 2 we can say that in the equilibrium state, diffusion stops and [Ca$^{2+}$]$_{PROX}$ and [Ca$^{2+}$]$_{DIST}$ become equal. [Ca$^{2+}$] is given as the roots of the third order polynomial

$$(r_{Ca}(1-i) - r_{PUMP} + \text{leak})([Ca^{2+}]_{PROX})^3 + K_{PUMP}(\text{leak} + r_{Ca}(1-i)([Ca^{2+}]_{PROX})^2 + \frac{\beta_a}{\alpha_a}(\text{leak} - r_{PUMP})[Ca^{2+}]_{PROX} + \frac{\beta_i}{K_{PUMP}}\text{leak} = 0$$
Depending on the value of the slow varying inactivation \( i \), we can have three equilibrium points. However, only two of the three equilibrium points are stable as \( i \) changes slowly. One can go from the low equilibrium point to the higher equilibrium point by a high frequency train of pulses or by a doublet pulse. The system does not remain forever in the high equilibrium state, because of the higher calcium concentration, \( i \) increases until a point where there is again only one single equilibrium.

**SIMULATION RESULTS**

The contraction dynamics (isometric condition) was modeled using a second order system with a threshold function at the input. The input was \([\text{CaTN}]\). The input should reach a threshold to initiate contraction, so even when \([\text{Ca}^{2+}]\) is elevated, the force falls down to zero.

We tested the model for potentiation, catch-like and missing pulse [3] effect. We showed that potentiation was produced by an elevation in the resting calcium concentration (see Fig.2). Potentiation lasted around 15 seconds, before the calcium returned to its previous value.

Catch-like effect appeared when the muscle was stimulated for long time and the resting \([\text{Ca}^{2+}]\) has already fallen (see Fig. 3 A and B1) to the low equilibrium point (Over potentiated). The addition of a single extra pulse caused a long lasting increase in force. Because there was one single equilibrium point, the absence of a single pulse caused a return to a lower level of force (missing pulse effect).

If the muscle was already potentiated, the resting \([\text{Ca}^{2+}]\) was in the high equilibrium state (see Fig. 3B2) and the effectiveness of an extra pulse disappeared (see Fig.3A). Because of the stability of the high equilibrium state, the missing-pulse effect did not produce a return to a low level of force.

The long lasting increase in force produced by an extra pulse appeared only in narrow range of frequencies, between 10.5 and 17 Hz. For lower frequencies, the muscle didn’t reach the high force level. For higher frequencies, the system went to the higher level without the help of the additional pulse.

**DISCUSSION**

The model could reproduce potentiation and catch-like effect as reported in slow muscle [4] using the elevation produced in calcium concentration after high-frequency stimulation. The high level in \([\text{Ca}^{2+}]\) is higher compared with Lee’s value of 0.25µM [11]. However, \([\text{Ca}^{2+}]\) resting level has also been measured to reach 0.5µM, following stimulation [14]. The resting level was also under 0.6µM, the threshold for muscle contraction [7].

The multiple equilibrium point characteristic is independent of diffusion and calcium binding to protein processes (see eq. 9). These other parameters affect the stimulation frequency and duration necessary to potentiate the muscle.

The model showed that the catch-like effect didn’t occur when the muscle was already potentiated. Potentiation could occur when the system had two stable equilibrium points (bistable) and \([\text{Ca}^{2+}]\) was in the low equilibrium point. The catch-like effect appeared when the system had one single equilibrium point (monostable).

We have to study the frequency range to produce force increase and missing pulse effect in more detail, changing parameters values. The model has to be examined in experiments with human subjects.

![Fig. 2 Simulation of Post Tetanic Potentiation (PTP). After 2 seconds of 9.3 Hz stimulation, the calcium concentration returned to its initial resting value (0.059µM). After a potentiating stimulation at 50 Hz, 2 s the calcium concentration remained elevated (0.56µM). The next 9.3 Hz train generated 68% more force than the previous 9.3 Hz train of pulses.](image)
CONCLUSION

A myofibrilar model that shows multiple equilibrium points in the calcium concentration has been developed using the interaction between calcium activated channels and calcium pump in the SR. The model could serve to explain some of the characteristics from potentiation and catch-like effect in skeletal muscle.

ACKNOWLEDGMENT

This research was supported in part by a grant from the Ministry of Education, Science, Sports and Culture of Japan under a grant-in-aid for Scientific Research, and the Proposal-Based New Industry Creative Type Technology R&D Promotion Program from the NEDO of Japan.

REFERENCES

7. Ebashi S. and Endo M., Calcium ion and muscle contraction, Progress in Biophysics and Molecular Biology, 18, 123-83 (1968)