Simulation of a computational winding filament model with an exponential spring to represent titin

Robert LeMoyne, *Senior Member, IEEE*, Jeremy Petak, John Tester, and Kiisa Nishikawa

Abstract— **The goal of developing high fidelity simulation of muscle force is of considerable interest for the biomedical community. Traditionally Hill models have been incorporated. However, feasible scope of the Hill model is inherently limited, especially in light of the growing relevance of muscle history dependence. History dependence is considered to be significant for motor control and stability. Attempts have been made to augment the Hill model to emulate history dependence. The titin winding filament model best elucidates history dependence of muscle force including force enhancement. The recent version of the titin winding filament model accounts for the functionality of titin through a pulley linked with the contractile element and a linear spring to represent the elastic properties of titin. A new and more realistic amendment to the winding filament model is incorporation of an exponential spring to characterize the elastic properties of titin. A sensitivity study as a function of the titin exponential spring constant is presented. Overall the amalgamation of the titin exponential spring to the winding filament model improves the respective force enhancement characteristics with a relatively more optimal exponential spring constant that provides a maximal averaged coefficient of determination.**

Keywords: winding filament hypothesis, titin, muscle modeling, muscle history dependence, Hill model

I. INTRODUCTION

The ability to develop computational models of muscles is of interest to the scientific and engineering community [1,2]. The utility for high fidelity muscle models has multifaceted implications. Regarding orthopedic surgery, muscle modeling can augment surgical strategy and recovery forecast [1,3,4]. The efficacy of neuromuscular stimulation can be advanced by improved muscle modeling [2]. For the robotic industry, more efficient biomimetic locomotion can result from more genuinely realistic computational muscle models [5]. Prosthetic and orthotic devices can better assist patients through more biologically realistic muscle models [1,2,6].

Traditional strategies have incorporated the Hill muscle model [5]. History dependent muscle models are more efficient from a control/stability perspective relative to traditional Hill models [7]. In addition, current research has established the significance of history dependence. The winding filament hypothesis elucidates the intrinsic properties of muscle that are responsible for history dependence [8,9,10].

Petak et al. successfully implemented a version of the winding filament model. The approach incorporates traditional aspects, such as the contractile element, dashpot, and series spring. Novel mechanisms consist of the titin spring and pulley connecting the titin spring and contractile element. The current model accounts for titin through a linear spring. With parameter optimization a coefficient of determination of 0.93 was acquired for force enhancement for a specific isovelocity stretch condition [11,12]. However, a more realistic optimum should pertain to multiple isovelocity stretch conditions.

The objective of the current numerical modeling is to better account for the elastic properties of titin through an exponential spring. A sensitivity study to find the local optimum for the exponential spring constant is conducted. The optimum is relevant to six isovelocity conditions. The optimal exponential spring constant of 0.183 mm^{-1} with a dimensional constant of 1 N demonstrates a high coefficient of determination of 0.95 for a specific isovelocity condition and an averaged coefficient of determination of 0.89.

II. BACKGROUND

A. *Evolution of muscle modeling*

The timeline of significant discoveries and representations of muscle behavior is important to explain the current requirements for the state of the art. A.V. Hill published a broadly accepted strategy for numerically estimating muscle force production [5,13]. Approximately 20 years later, A.F. Huxley established the sliding filament hypothesis. The sliding filament model persists as the prevailing accepted theory [14,15]. The significance of titin was unknown until roughly 20 years after the sliding filament model, since titin was discovered in the 1970's [16,17]. Therefore the traditional muscle models did not respond to the discovery of titin [8]. Further attempts were made to evolve the Hill model. During the 1980's Zajac evolved the Hill model with attributes such as the pennation angle, approximating the spatial relation among muscle and tendon [2]. An extrapolation of the Zajac model is the internationally renowned OpenSim [18].

B. *History dependence of muscle force*

Another feature of muscle force production is history dependence, such as force enhancement and force depression. Force enhancement and force depression were originally considered to exert minimal influence on muscle force production. However, force enhancement and force

Manuscript received April 3, 2014.

*Research supported by NSF GRANTS IOS-1025806- and IIP-1237878.

R. LeMoyne, Ph.D., is a Post-Doctoral Scholar in the Department of Biological Sciences, Northern Arizona University, Flagstaff, AZ 86011-5640 USA (e-mail: robert.lemoyne@nau.edu, rlemoyne07@gmail.com).

J. Petak is a Graduate Student in the Department of Mechanical Engineering, Northern Arizona University, Flagstaff, AZ 86011-5600 USA (e-mail: jlp272@nau.edu).

J. Tester Ph.D. is a Professor in the Department of Mechanical Engineering, Northern Arizona University, Flagstaff, AZ 86011-5600 USA (e-mail: john.tester@nau.edu).

K. Nishikawa, Ph.D. is a Regents' Professor in the Department of Biological Sciences, Northern Arizona University, Flagstaff, AZ 86011-5640 USA (e-mail: kiisa.nishikawa@nau.edu).

depression are predicted to contribute up to 50% of isometric force [9]. History dependence may substantially influence the efficiency of motor control.

Recent endeavors to address muscle history dependent properties have been presented. Forcinito et al. developed a rheological approach for demonstrating force enhancement and force depression [19]. Conventional aspects of the muscle model are the contractile element along with the spring and dashpot configuration to account for variable muscle dynamics [19]. Ettema and Meijer achieved better force prediction through incorporating exponential decay features into a muscle model than the traditional Hill approach [20]. The exponential decay characteristics were representative of cross bridge cycle mechano-chemistry [20]. Ettema developed a modified Hill model that was augmented with muscle contractile history [7]. The contractile history model was contrasted to the standard Hill model using an antagonist dual muscle joint system. Impulse perturbation studies suggest superior stability and movement control characteristics, such as reduced peak movement amplitude, for the model incorporating contractile history relative to the Hill model [7]. Alternative models account for activation–frequency [21]. Another muscle modeling perspective addresses energetics of contraction [22]. These models that incorporate muscle history dependence offer inherently empirical methodologies. The winding filament model enables a more biomimetic strategy for addressing muscle history dependence [1,8,23].

C. *Winding filament model*

Dr. Kiisa Nishikawa suggested the winding filament model as a suitable biomimetic explanation accounting for muscle history dependence [8]. The essence of the novel muscle model focuses on the role of titin. Titin was discovered many decades after the acceptance of the Hill muscle model and sliding filament hypothesis. The release of Ca^{2+} causes the N2A region to bind to the actin filament. Potential energy is stored in the PEVK region of titin due to rotation of the actin thin filament. These aspects of the winding filament model are demonstrated in Figure 1. These features of titin enable the winding filament hypothesis to plausibly account for the muscle history dependence [1, 8,23].

D. *Winding filament computational model*

Significant progress has been made by Petak et al. regarding the computational version of the winding filament model [11,12]. Figure 2 illustrates the mechanical interpretation of the winding filament model. A contractile element functions in parallel to a viscous damper exerting force on a pulley. The pulley achieves a torque balance to titin exponential spring represented in equation (1). The pin center of the geared pulley is connected to a series spring. The pulley and titiin exponential spring constitute a noteworthy evolution from the conventional Hill model, since the pulley and exponential titin spring provides a mechanical representation of the potential energy properties of titin,

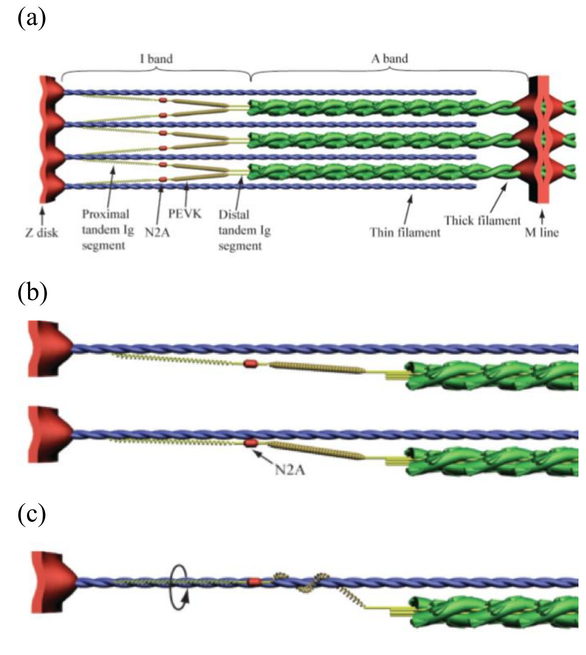

Figure 1. (a) Half-sarcomere schematic illustrating the arrangement of titin, thin filament, and thick filament. Key elements of titin include PEVK and N2A; (b) The N2A region of titin binds to the thin filament upon muscle activation; (c) Winding of titin on the thin filament stores potential energy the PEVK aspect of titin [1,8,23].

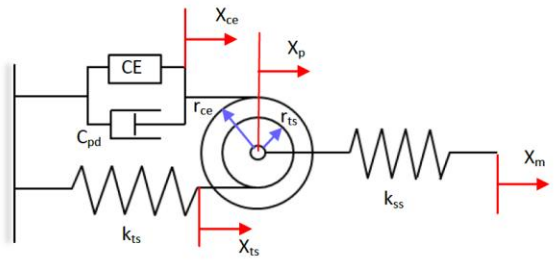

Figure 2. Mechanical organization of the winding filament model. CE representes the contractile element. C_{pd} is the damping coefficient for the viscous damper. K_{ss} and K_{ts} are the spring coefficients for the series element and titin element, respectively. For the geared pulley r_{ce} and r_{ts} are the radius for the contractile element and titin element, respectively. X_{ce} and X_{ts} are the linear displacement for the contractile element, and titin element, respectively. X_p and X_m are the linear displacment for the pin center of the geared pulley and the muscle linear displacement, respectively [1, 8,11,12,23].

$$F(x) = c(e^{kx} - 1) \tag{1}$$

$F: Force\ generated\ by\ titin\ spring\ (N)$
$k: Exponential\ spring\ constant\ (mm^{-1})$
c: dimensional constant (N)
$x: Displacement\ of\ spring\ (mm)$

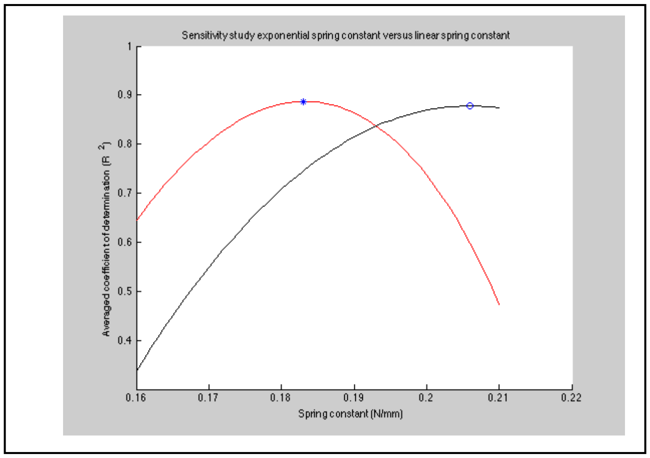

Figure 3. Titin spring constant sensitivity study (*:exponential spring optimal (light,red), o:linear spring optimal (dark, black)).

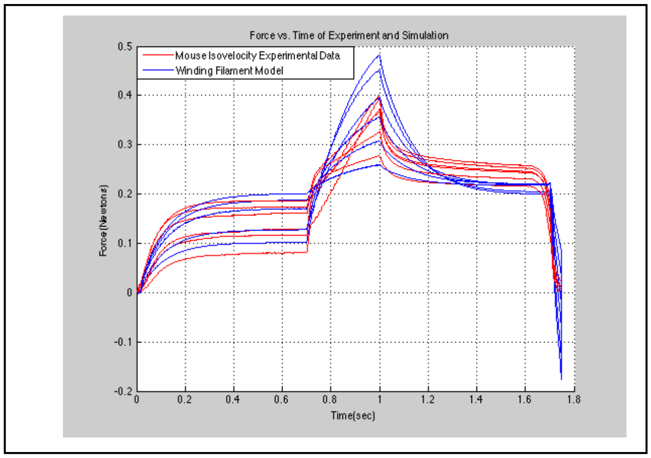

Figure 4. Experimental data and simulation of force response to isovelocity stretch profiles.

TABLE I. WINDING FILAMENT MODEL PARAMETERS FOR FORCE ENHANCEMENT

Velocity of stretch (Trial 1-6, mm/sec)					
27	24	20	14	10	5

in light of its N2A binding to the actin filament and rotation [1,8,11,12,23].

The objective of the mechanical simulation is to simulate the force velocity properties of the winding filament computational model with the newly incorporated exponential spring. The coefficient of determination is determined for six isovelocity stretch trials as specified in Table 1.

III. MATERIALS AND METHODS

The winding filament hypothesis is modeled using Matlab. The winding filament model consists of five primary elements: a contractile element, viscous damping element, a pulley for torque balance, a series spring, and a titin exponential spring. By contrast the Hill model only consists of a dashpot, two springs, and a contractile element [5].

The proposed winding filament model was contrasted to the model of *in vitro* force response to isovelocity stretch conditions of the mouse soleus. The force response to isovelocity stretch relationship was acquired with the approval of Northern Arizona University's IACUC. The *in vitro* force response to isovelocity stretch experiment acquired data for the force enhancement aspect of muscle history dependence. The experiment involved an *in vitro* experiment of the mouse soleus with the mouse later being euthanized. The soleus muscle sample was placed in a Krebs solution and activated by a Grass stimulator. An Aurora Scientific force lever measured the force response of the soleus to active stretch at different velocities.

The model's ability to replicate the experimental force during active stretch was quantified by the coefficient of determination (R^2). Using parameters K_{ss} = 0.13 N/mm and C_{pd} = 0.003 N/(mm/sec), the optimal titin exponential spring constant was acquired as a function of the coefficient of determination for the multiple simulations and their associated force during active stretch.

The optimization profile for the titin exponential spring constant was based on the average of all six force response to isovelocity stretch scenarios. The bounds for the exponential spring constants were established, such that they did not induce numerical instability in the topology. The sensitivity study to acquire an optimal exponential spring constant for titin incorporated approximately 50 iterations between the bounds.

IV. RESULTS AND DISCUSSION

Figure 3 illustrates the sensitivity study for the titin exponential spring. The optimal spring constant for the exponential spring is 0.183 mm^{-1} with a dimensional constant of 1 N. The optimal spring constant for the linear spring is 0.206 N/mm. With the exponential spring incorporated into the winding filament model the simulated force velocity profile closely matches the experimental data as illustrated in Figure 4. An averaged coefficient of determination (R^2) of 0.89 was calculated.

The two profiles revealed in Figure 3 show quite different relationships between the spring coefficient and averaged coefficient of determination. Regarding the exponential spring, the profile drops off sharply at the minimum and maximum spring coefficient values. In contrast, the linear spring profile demonstrates a broader numeric stability about the maximum spring coefficient. Inferential statistics by means of a one-way ANOVA ($p < 0.05$) confirmed the statistical significance exponential spring profile compared to the linear spring profile.

The application of this muscle model based on the winding filament hypothesis that accurately accounts for history dependence, such as force enhancement, has significant implications. Parametric studies can be applied to evaluate the influence of non-optimal configurations for the titin exponential spring. Such studies may be highly relevant for the simulations to improve the understanding of the influence of aging on biomechanics. For example, Thelen applied a study using a Hill type muscle model. The research improved the comprehension of the effects of age-induced parametric variation on the musculature of the ankle-foot complex [24].

The research findings warrant further experimentation to evaluate the characteristics of titin in physiologically pertinent environments. An atomic force microscope could be applied to discover the actual exponential spring constant of titin. By attaching the tip of atomic force microscope to the titin *in vitro*, the force versus displacement profile of titin could be acquired.

V. CONCLUSION

The winding filament model shows promise for elucidating the history dependent properties of muscles. Correctly addressing history dependence has the potential to significantly impact the quality of motor control and stability for the computational simulation of muscle activity. A computational model that represents a mechanical interpretation of the winding filament model has been simulated using an exponential spring to represent titin. An optimal spring constant for titin was revealed by a sensitivity study. The results produced an improved coefficient of determination compared to experimental data for the mouse soleus for the force enhancement condition. Parametric studies can be applied for determining degenerative effects, such as aging. The findings underscore the scientific motivation for discovering the actual spring characteristics of titin in physiologically realistic conditions.

REFERENCES

[1] S. H. Yeo, “Computational Modeling of Neuromusculoskeletal Systems: from Filaments to Behavior,” Ph.D. dissertation, University of British Columbia, Vancouver, Canada, 2012.

[2] F. E. Zajac, “Muscle and tendon: properties, models, scaling, and application to biomechanics and motor control,” *Crit. Rev. Biomed. Eng.*, vol. 17, 359-411, 1989.

[3] S. L. Delp, J. P. Loan, M. G. Hoy, F. E. Zajac, E. L. Topp, and J. M. Rosen, “An interactive graphics-based model of the lower extremity to study orthopaedic surgical procedures,” *IEEE Trans. Biomed. Eng.*, vol. 37, 757–767, 1990.

[4] www.lifemodeler.com

[5] G. A. Bekey, *Autonomous Robots: From Biological Inspiration to Implementation and Control*. Cambridge, MA: The MIT Press, 2005.

[6] H. Geyer and H. Herr, “A muscle-reflex model that encodes principles of legged mechanics produces human walking dynamics and muscle activities,” *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 18, 263–273, 2010.

[7] G. J. Ettema, "Effects of contraction history on control and stability in explosive actions," *J. Electromyogr. Kinesiol.,* vol. 12, 455-461, 2002.

[8] K. C. Nishikawa, J. A. Monroy, T. E. Uyeno, S. H. Yeo, D. K. Pai, and S. L. Lindstedt, “Is titin a 'winding filament'? A new twist on muscle contraction,” *Proc. R. Soc. B.*, vol. 279, 981-990, 2012.

[9] W. Herzog, “History dependence of skeletal muscle force production: implications for movement control,” *Hum. Mov. Sci.*, vol. 23, 591-604, 2004.

[10] K. C. Nishikawa, J. A. Monroy, K. L. Powers, L. A. Gilmore, T. A. Uyeno, and S. L. Lindstedt. "A Molecular Basis for Intrinsic Muscle Properties: Implications for Motor Control," In *Progress in Motor Control*, New York: Springer, 2013, 111-125.

[11] J. Petak, N. Heckathorn, R. LeMoyne, J. Dyer, S. H. Yeo, D. Pai, J. Tester, and K. Nishikawa, “Winding filament muscle model for musculo-skeltal simulations,” Proceedings of the 37th Annual Meeting of the American Society of Biomechanics, pp.1-2, Omaha, NE, 2013.

[12] J. Petak, N. Heckathorne, R. LeMoyne, J. Dyer, S. H. Yeo, D. Pai, J. Tester, and K. Nishikawa, “A new muscle model for neuro-musculo-skeletal simulations,” Proceedings of Dynamic Walking Conference, pp. 1, Pittsburgh, PA, 2013.

[13] A. V. Hill, “Constants of Muscle The Heat of Shortening and the Dynamic,” *Proc. R. Soc. Lond. B.*, vol. 126, 136-195, 1938.

[14] R. R. Seeley, T. D. Stephens, and P. Tate, *Anatomy and Physiology*. New York: McGraw-Hill, 2003.

[15] E. R. Kandel, J. H. Schwartz, and T. M. Jessell, *Principles of Neural Science*. New York: McGraw-Hill, 2000.

[16] K. Maruyama, “Connectin, an elastic protein from myofibrils,” *J. Biochem.*, vol. 80, 405–407, 1976.

[17] K. Wang, J. McClure, and A. Tu, “Titin: major myofibrillar components of striated muscle,” *Proc. Natl Acad. Sci. USA*, vol. 76, 3698–3702, 1979.

[18] opensim.stanford.edu

[19] M. Forcinito, M. Epstein, W. Herzog, “Can a rheological muscle model predict force depression/enhancement?,” *J. Biomech.*, vol. 31, 1093-1099, 1998.

[20] G. J. Ettema, and K. Meijer, “Muscle contraction history: modified Hill versus an exponential decay model,” *Biol. Cybern.*, vol. 83, 491-500, 2000.

[21] D. Song, G. Raphael, N. Lan, and G. E. Loeb, “Computationally efficient models of neuromuscular recruitment and mechanics,” *J. Neural. Eng.* vol. 5, 175-184, 2008.

[22] G. A. Tsianos, C. Rustin, and G. E. Loeb, “Mammalian muscle model for predicting force and energetics during physiological behaviors,” *IEEE Trans. Neural. Syst. Rehabil. Eng.*, vol. 20, 117-133, 2012.

[23] J. Tester, S. H. Yeo, D. Pai, and K. Nishikawa, “A new muscle model with implications for actuation and control,” Proceedings of Dynamic Walking Conference, pp. 1-3, Pensacola Beach, FL, 2012.

[24] D. G. Thelen, “Adjustment of muscle mechanics model parameters to simulate dynamic contractions in older adults,” *J. Biomech. Eng.,* vol. 125, 70-77, 2003.