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COMMENTARY

Muscle as a tunable material: implications for achieving muscle-like function in robotic prosthetic devices

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ABSTRACT

An ideal prosthesis should perform as well as or better than the missing limb it was designed to replace. Although this ideal is currently unattainable, recent advances in design have significantly improved the function of prosthetic devices. For the lower extremity, both passive prostheses (which provide no added power) and active prostheses (which add propulsive power) aim to emulate the dynamic function of the ankle joint, whose adaptive, time-varying resistance to applied forces is essential for walking and running. Passive prostheses fail to normalize energetics because they lack variable ankle impedance that is actively controlled within each gait cycle. By contrast, robotic prostheses can normalize energetics for some users under some conditions. However, the problem of adaptive and versatile control remains a significant issue. Current prosthesis-control algorithms fail to adapt to changes in gait required for walking on level ground at different speeds or on ramps and stairs. A new paradigm of 'muscle as a tunable material' versus 'muscle as a motor' offers insights into the adaptability and versatility of biological muscles, which may provide inspiration for prosthesis design and control. In this new paradigm, neural activation tunes muscle stiffness and damping, adapting the response to applied forces rather than instructing the timing and amplitude of muscle force. A mechanistic understanding of muscle function is incomplete and would benefit from collaboration between biologists and engineers. An improved understanding of the adaptability of muscle may yield better models as well as inspiration for developing prostheses that equal or surpass the functional capabilities of biological limbs across a wide range of conditions.

KEY WORDS: Muscle mechanics, Muscle models, Preflex, Titin

Introduction

Humans have evolved for high-performance locomotion (Alexander, 2003), deploying a wide variety of motor skills during walking and running (Torricelli et al., 2015). Commands from the brain, spinal reflexes and preflexes (see Glossary) generate adaptable patterns of limb kinetics and kinematics (Dickinson et al., 2000), which are actuated by an intricate matrix of biological materials, including muscles, tendons and bones. Yet, essential parts of the human body can be lost or missing as a result of traumatic injury, congenital defects and other causes. Approximately 1.8 million Americans live with an amputation, often involving the lower extremity (Ziegler-Graham et al., 2008). Most individuals with a lower limb amputation use some sort of prosthesis. Because of their light weight, low cost and durability, passive prostheses are used by most persons with an amputation. However, use of passive prostheses is linked to asymmetric, compensatory motor patterns that alter gait dynamics, often resulting in slower self-selected walking speeds and increased cost of transport (see Glossary; Waters et al., 1976). Increased stress on the unaffected limb (Sanderson and Martin, 1997; Snyder et al., 1995) may lead to a greater risk of joint pain and degradation (Gailey et al., 2008; Lemaire and Fisher, 1994) that can further reduce functional independence. Moreover, walking with a passive prosthesis is associated with increased fall risk. Approximately 50% of individuals using passive prostheses report falling at least once a year, with 10% of falls requiring medical attention (Miller et al., 2001). For above-knee amputations, health and mobility consequences are often worse (Geertzen et al., 2001; Helm et al., 1986; Kegel et al., 1978; Narang et al., 1984; Pohjolainen and Alaranta, 1991; Pohjolainen et al., 1990).

The ability of prostheses to emulate functions of the human leg has made substantial progress in recent decades (Collins et al., 2006), although significant challenges remain. A recent review (Chumacero et al., 2018) suggested that future improvements for powered ankle–foot prostheses (see Glossary) should include engineering advances, such as weight reduction and increased energy efficiency, as well as improved socket design (Keszler et al., 2019). Control of active robotic prostheses also poses significant challenges, including those related to gait-phase classification, prediction of user-intended motion and adaptability of function required for users to walk on a variety of terrains (Chumacero et al., 2018).

Muscles behave as tunable, non-linear, self-stabilizing springs (e.g. Rack and Westbury, 1974; Richardson et al., 2005), properties that contribute to the control of movement (Hogan, 1985), particularly in response to unexpected perturbations (Daley and Biewener, 2011; Daley et al., 2009; Nishikawa et al., 2013). The time-varying resistance of the ankle joint to applied forces is essential for walking and running (Lee et al., 2011; Rouse et al., 2014). We argue that at least some prosthesis control problems could be eliminated (e.g. identification of states or phases of gait) or solved (e.g. adaptation to varying terrain) by developing predictive models of muscle force and implementing these models or ideas inspired by them in algorithms for adaptive prosthesis control to achieve robust locomotion. Here, we begin by providing a brief overview of currently available lower extremity prostheses, along with an assessment of their features and limitations. Next, we discuss why current muscle models are of limited utility in designing control algorithms to provide adaptive control of robotic prostheses. Lastly, we describe a recent model of muscle mechanics, based on the idea that titin, the largest known protein and third most abundant protein in striated muscle sarcomeres (Lindstedt and Nishikawa, 2017), contributes to active muscle force production (Nishikawa, 2020). We discuss experimental evidence supporting titin's role as a tunable spring, whose stiffness and free length change with activation, and give an example of how a control

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Glossary

Active prosthesis
A prosthesis that uses battery-operated microprocessors to control motors that provide positive net work to emulate concentric muscle function.

Concentric muscle function
Active force production during muscle shortening that produces positive work.

Cost of transport
A measure of the metabolic energy (joules) required to move a 1 kg organism a distance of 1 m.

Dorsiflexion
Ankle joint action that moves the toes closer to the knee (upwards).

Eccentric muscle function
Active force production during muscle lengthening that absorbs work.

Isometric muscle function
Muscle force production in the absence of changes in length.

Isotonic muscle function
Muscle force production during active shortening at constant load.

Length dependence of activation
Isometrically contracting muscles exhibit predictable delays between activation signals and changes in muscle force, typically activating much faster than they deactivate. However, length changes during activation or deactivation play an important role in modulating these delays. Stretch can substantially decrease the activation time, whereas shortening can increase it, and vice versa for deactivation.

Morphological computation
The idea that aspects of control are embedded in the structure and geometry of the body and its interactions with the environment, which simplifies supervisory control by the nervous system. The tunable stiffness of titin is an example in which activation tunes titin stiffness, modulating a muscle's response to deformation by applied forces, to achieve length-dependent activation dynamics.

Muscle impedance
The mechanical impedance of a muscle is a measure of how much it resists deformation when subjected to a force. Muscle impedance includes elastic forces for which resistance is proportional to strain and viscous forces for which resistance is proportional to strain rate.

Non-linear stiffness
Elastic materials have linear stiffness when they produce force in direct proportion to strain. Both titin and muscles have non-linear stiffness in which force increases exponentially with strain.

Passive prosthesis
An elastic or non-elastic prosthesis that operates without batteries or other external energy sources.

Plantarflexion
Ankle joint action that moves the toes away from the knee (downwards).

Powered ankle–foot prosthesis
An active, motorized prosthesis for persons with transtibial (below-knee) amputation.

Preflex
Instantaneous stabilizing response of muscles to changes in length that depends on viscoelastic muscle properties and requires no sensing or feedback from the nervous system.

Semi-active prosthesis
A prosthesis that uses battery-operated microprocessors to control clutch, damper and/or spring mechanisms to emulate isometric and eccentric muscle function.

Sonomicrometry
A technique using sound to measure distance or length. The technique determines the distance or length between piezoelectric crystals embedded in a medium by the time it takes to transmit and receive sound energy between the crystals compared with the known speed of sound through the medium.

State machine
This widely used control scheme is based on the premise that any process, such as walking, can be represented by a series of states. Sensing is used to identify changes in state, enabling the implementation of state-specific algorithms.

System identification
A field of engineering that infers mathematical models of dynamical systems from measured data.

Viscoelastic
Used to describe materials that resist deformation by producing forces in proportion to both strain (elastic forces) and strain rate (viscous forces).

algorithm based on tunable viscoelastic (see Glossary) properties of muscle can provide adaptive control of walking at variable speed and during stair ascent. Finally, we discuss the implications that a predictive understanding of muscle function based on tunable muscle impedance (see Glossary) may have for designing and controlling robotic prosthetic devices in general.

Overview of prosthetic devices

Historically, the purpose of prostheses was to cosmetically replace the lost or affected limb and to support the body weight (Price et al., 2019). As prosthetic designs advanced, more attention was directed toward restoring additional limb functions. Although most modern lower limb prostheses allow users to stand and engage in slow walking, more capabilities are necessary for users to engage in the varied activities of daily life. Expanding the functionality of prosthetic devices is achieved in two ways. Firstly, prostheses can be designed for specific activities, such as swimming (Colombo et al., 2011) or running (Webster et al., 2001). These devices must be exchanged when switching between activities. Alternatively, a single prosthesis that adapts to different conditions can be designed for versatility and convenience. In addition, two different approaches can be employed to achieve the multi-functional capabilities of human muscles. One is biomimicry, in which details of biological function are used to inspire design. The other is functional imitation, in which the intricacies of biological systems are circumvented by simpler engineering solutions that approximate the desired outcomes to an acceptable degree. Often, both approaches are used simultaneously as a consequence of trade-offs among cost, expertise and the current state of technological and scientific advancement.

Lower limb prostheses can be passive, semi-active or active (see Glossary). Passive prostheses typically lack an articulated joint and do not generate positive power. Semi-active prostheses usually include an articulating joint and use microprocessors to control clutch mechanisms or dampers based on the phase of the user's gait (e.g. swing-phase dorsiflexion; see Glossary). This allows for the timing of passive joint behavior to vary from step to step, but provides no propulsive power (Glanzer and Adamczyk, 2018; Shepherd and Rouse, 2017). Finally, active prostheses include an articulated joint and provide positive work to control the orientation of the foot and/or assist propulsion.

Because of considerations of weight, cost and durability, passive prostheses remain the most used devices for lower limb replacement. Passive prostheses can be either non-elastic or elastic. The most common modern example of a non-elastic prosthesis is the SACH Foot (solid-ankle cushioned-heel; Willow Wood, OH, USA), which has a non-articulated ankle, a keel at the ball of the foot to imitate forefoot 'rocker' action (Staros, 1957), and a cushioned heel that mimics the impact-absorbing function of the heel pad (Gefen et al., 2001). Although non-elastic prostheses allow users to stand and walk slowly, their rigidity makes other activities all but impossible.

Elastic energy storage and return (ESAR) feet improve on shock-absorbing functions compared with inelastic devices, while also allowing for elastic behavior similar to that provided by the calf muscles and Achilles tendon. Commonly made from carbon fiber spring elements, ESAR feet absorb and store energy during early to mid-stance and return some energy later in stance to assist propulsion. Although ESAR feet have greater functionality compared with non-elastic prostheses (Casillas et al., 1995; Schneider et al., 1993; Thomas et al., 2000; Torburn et al., 1990), they are incapable of providing the positive power necessary for emulating able-bodied push-off (Geil, 2001; Versluys et al., 2009). Furthermore, ESAR devices are unable to modulate the timing of energy return, releasing energy earlier than optimal (Grabowski and D'Andrea, 2013).

With the addition of actuators that can modulate the timing of energy storage and return or damping, semi-active prostheses are able to emulate isometric and eccentric muscle function (see Glossary). This innovation is accomplished through the inclusion of microprocessors that control damper and clutch mechanisms (Collins and Kuo, 2010). The first semi-active lower limb device was the C-Leg prosthetic knee (Ottobock, Duderstadt, Germany) for transfemoral amputations. The C-Leg uses a linear hydraulic system to control stance- and swing-phase resistance based on input from onboard angle sensors and strain gauges. Through learning algorithms, the C-Leg adapts to the user's gait in real-time, potentially improving safety (Blumentritt et al., 2009) and the ability to change speed and traverse different terrains (Hafner et al., 2007).

Despite improvements provided by semi-active prostheses, users' gaits continue to be asymmetric and metabolically costly compared with those of able-bodied individuals (Grimmer and Seyfarth, 2014). This is because of the inability of semi-active prostheses to emulate concentric muscle function (see Glossary) by providing push-off or toe-lift power. Powered robotic devices may be required to enable a user's full engagement in activities of daily life, yet significant challenges prevent their widespread use. Active prostheses aim to emulate biological function by providing positive work. Additionally, some active prostheses vary joint impedance to emulate the non-linear stiffness (see Glossary) of biological joints (Holgate, 2017). Active prostheses also use sensors to modulate the timing of powered assistance and to predict the user's intention (Au et al., 2007, 2008).

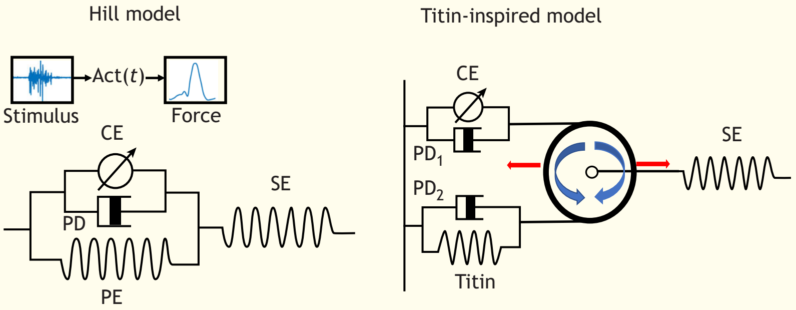
Series elastic actuators (SEAs) are most commonly used for power production in active prostheses. A SEA consists of an actuator and spring in series, tethered between an anchor point and load at the effector limb. Similar to a muscle within a muscle–tendon unit, the actuator in a SEA actively changes the length of the spring, thus changing joint stiffness. When timing is properly controlled, SEAs can reduce motor speed (Grimmer et al., 2014) and power demands (Holgate, 2017) via the elastic properties of the spring. The BiOM T2 (BionX, Boston, MA, USA) – the first commercially available robotic ankle–foot prosthesis capable of powered push-off – combines a SEA with a parallel spring, further reducing the torque output required from the motor (Au et al., 2007, 2008). The BiOM T2 prosthesis assists powered plantarflexion (see Glossary) in stance and dorsiflexion in swing. This improves metabolic costs, preferred walking speed and ankle biomechanics in people with a transtibial amputation (Herr and Grabowski, 2012), making gait more similar to that of able-bodied individuals.

Numerous studies have shown that powered ankle–foot prostheses can normalize gait in people with unilateral transtibial amputation (Agrawal et al., 2013; Aldridge et al., 2012; D'Andrea et al., 2014; Russell Esposito et al., 2014; Gates et al., 2013; Grabowski and D'Andrea, 2013; Sinitski et al., 2012). However, many users fail to show any benefits (Gardinier et al., 2018), and walking over varying terrain remains a challenge for these devices (Aldridge et al., 2012; Russell Esposito et al., 2016; Montgomery and Grabowski, 2018; Pickle et al., 2016) because it is difficult to detect when or how much assistance the motor should provide under different conditions (Farrell and Herr, 2011; Kannape and Herr, 2016; Tkach and Hargrove, 2013). In prosthesis control, state-machine approaches typically depend on sensing and pattern-recognition algorithms to identify different phases of gait (e.g. stance versus swing phases of level walking; Au et al., 2007) and terrain (e.g. level walking versus stair ascent; Wilken et al., 2011). However, the ability to implement an appropriate control strategy is limited, as most control approaches optimize assistance for a few predetermined gaits and therefore lack adaptation to varying conditions. A common assumption is that some combination of manual actuation (e.g. Alimusaj et al., 2009), mechanical sensing or other volitional signals [e.g. neural signals measured using electromyography (EMG)] is required to implement transitions from one control strategy to another to provide adaptation in varying environments (Tkach and Hargrove, 2013).

In contrast to motors used to actuate prostheses, which are bidirectional and symmetric, muscles are highly versatile and adaptable asymmetrical 'machines' that can function like brakes or springs when actively stretched, like struts when isometric, or like motors or shock absorbers when actively shortening, depending on the phasing of activation and strain (Dickinson et al., 2000). Muscles have tunable, non-linear, self-stabilizing properties (e.g. Rack and Westbury, 1974; Richardson et al., 2005) that contribute to the control of movement (Hessel et al., 2017; Hogan, 1985; Seiberl et al., 2013, 2015), particularly in response to unexpected perturbations (Daley and Biewener, 2011; Daley et al., 2009; Nishikawa et al., 2013). When muscles are stretched by an applied load, muscle stiffness increases to resist overstretch. Likewise, during unloading, muscles become more compliant. Muscle equilibrium length and stiffness change in response to activation (Monroy et al., 2007) and these properties adjust instantaneously in response to changes in load (i.e. preflexes) without input from the nervous system (Nichols and Houk, 1976; Nishikawa et al., 2007; Libby et al., 2020). Yet, most robotic prostheses are designed based on the kinetics and kinematics of biological muscle–joint function,

Box 1. Comparison of Hill and titin-inspired muscle models

Both models share a damped contractile element (CE) that represents cross-bridges and functions like a damped linear motor. Hill-type models typically consist of at least four modules. The activation dynamics module Act(t) is a transfer function, typically consisting of first to third order sets of differential equations with 4–8 parameters, that translates an input stimulus into active muscle force. The other modules include a non-linear passive tension curve representing changes in force associated with the length of a passive elastic element (PE); and active force–length and force–velocity relationships associated with the overlap of thick and thin filaments and parallel damping (PD) of the CE, respectively. The muscle force (F_m) is equal to $P_0\times\mathrm{Act}(t)\times F_\mathrm{a}(l)\times F_\mathrm{a}(v)+F_\mathrm{p}$, where P_0 is the maximum isometric force, t is time, $F_\mathrm{a}(l)$ represents the active force–length relationship, $F_\mathrm{a}(v)$ represents the active force–velocity relationship and F_p represents the passive force–length relationship for a given combination of muscle length and velocity (for additional details, see Wakeling et al., 2021). In the titin-inspired model, muscle is a composite material composed of springs and dampers. Activation modulates the viscoelastic properties and thereby changes the response of a muscle to deformation. Activation of the CE rotates a movable pulley (with mass M and radius R) in the counter-clockwise direction (blue arrows), and the pulley rotates back in the clockwise direction during deactivation. Pulley rotation simulates time-dependent activation–deactivation dynamics. The pulley, which represents actin filaments in muscle sarcomeres (Nishikawa et al., 2012), translates along the long axis of the muscle when stretched or shortened by external or internal forces (red arrows). The length dependence of activation results from superposition of pulley rotation and translation. SE, series elastic element; PE, parallel elastic element. The muscle force F_m is obtained by superposition of pulley rotational and translational acceleration. For equations of motion, see Tahir et al. (2018).



rather than on tunable impedance or response to perturbations (Shorter and Rouse, 2018). The problem with imitating joint kinetics and kinematics in assistive devices is that these properties change with gait, cadence and terrain, whereas an approach that emulates tunable muscle impedance could provide a control strategy that adapts to changing conditions.

Muscles as motors

The traditional view of muscles as motors originates from the sliding filament (Huxley and Hanson, 1954; Huxley and Niedergerke, 1954) and swinging cross-bridge theories (Huxley, 1973, 1957; Rayment et al., 1993). These theories formed the basis for Hill-type muscle models (Box 1; Zajac, 1989), widely used in human biomechanics (Seth et al., 2011) and prosthesis controller design (Geyer and Herr, 2010). Hill-type models describe muscle force production in terms of transfer functions that transform an activation input into a muscle force, and then multiply that force by scaling factors related to the isometric force–length relationship (Gordon et al., 1966) and the isotonic (see Glossary) force–velocity relationship (Hill, 1938) measured in *ex vivo* muscles using standard techniques (Caiozzo, 2002). Thus, muscles are viewed as motors that produce force depending on activation, strain and velocity (Punith et al., 2018).

With the advent of new technologies, such as sonomicrometry (see Glossary) and ultrasound, it is now possible to measure the strain and force of individual muscles during *in vivo* locomotion. Using these techniques, recent studies have found that Hill-type muscle models predict *in vivo* forces with low accuracy during human (mean R^2=0.54; Dick and Wakeling, 2017) and animal (R^2=0.26–0.51; Lee et al., 2013) locomotion. It is reasonable to ask why, given decades of research, traditional muscle models do a poor job of predicting *in vivo* muscle force. There are likely to be many reasons, but two are particularly important. The first is the large difference between the static and quasi-static conditions under which *ex vivo* muscle function is typically measured, versus the dynamic conditions under which muscles function *in vivo* (Nishikawa et al., 2018). The isometric force–length and isotonic force–velocity relationships fail to predict muscle force under dynamic changes of length or load (McGowan et al., 2013).

The second reason is that muscle force production is a complex process requiring estimation of at least five or six parameters for accurate model predictions. Recent models have up to eight estimated parameters (Wakeling et al., 2021). Some features that complicate predictions of *in vivo* muscle forces include the length dependence of muscle activation (see Glossary; Shue and Crago, 1998). Time delays between neural activation and force production measured in isometrically contracting muscle can be substantially altered when muscle length changes during activation. Complex interactions between length, activation and force make it difficult to identify which, among a multitude of possible models, best fit the observed data – even for well-established methodologies such as system identification (see Glossary). *In lieu* of a black-box system identification approach, biological inspiration can help us understand the theoretical basis for the versatility and adaptability of muscle function, which may provide inspiration for designing human-engineered devices.

Muscles as tunable materials

A new approach to understanding muscle mechanics focuses on the idea that titin is a critical element that has been overlooked in cross-bridge theories and Hill-type muscle models (Nishikawa et al., 2012). Recent research suggests that the giant titin protein (Fig. 1) is a tunable spring (Dutta et al., 2018; Nishikawa, 2020), whose stiffness and free length depend on muscle activation. Titin is the largest known protein and the third most abundant protein in striated muscles (Lindstedt and Nishikawa, 2017). A single titin molecule with a

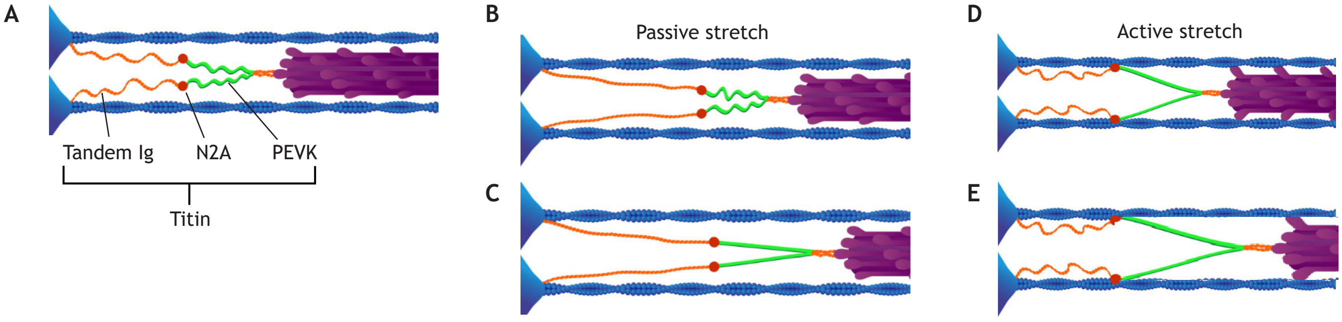


Fig. 1. Titin is a tunable spring in muscle sarcomeres. (A) Layout of titin in muscle sarcomeres. Each titin molecule is bound to the thin filament (blue) and to the thick filament (purple). The N2A segment (red) is located between the proximal tandem Ig segments (orange) and the PEVK segment (green). (B) As a sarcomere is stretched passively, the proximal tandem Ig segments unfold at low force. (C) After the proximal tandem Ig segments reach their contour length, further passive stretching extends the stiffer PEVK segment. (D) Upon activation, N2A titin binds to actin. (E) Only the stiffer PEVK segment extends when an active muscle is stretched, because of binding of N2A to thin filaments. Adapted from Nishikawa (2016).

diameter of 4 nm and a length of 1200 nm spans from one end of a half-sarcomere to the other. Titin molecules are bound to both thick and thin filaments (Fig. 1A). Between these anchor points, titin molecules consist of several segments that function as viscoelastic springs (Linke et al., 1998). The tandem Ig domains straighten during extension and produce relatively low force, whereas the PEVK domain extends at higher force (Fig. 1B,C). The N2A segment of titin, located between the compliant Ig domains and the stiffer PEVK domain, binds to actin in the presence of calcium during active stretch (Fig. 1D; Dutta et al., 2018), increasing titin stiffness and decreasing free length, so that only the stiffer PEVK region extends (Fig. 1E). This mechanism accounts for many important muscle properties that contribute to the versatility and adaptability of muscle function (Nishikawa et al., 2018), including the length dependence of muscle force and activation.

Several observations support the existence of an elastic element with tunable stiffness in muscle. An early hint was that when myofibrils were stretched beyond overlap of the thick and thin filaments so that no cross-bridges could form, their stiffness was greater when calcium-activated than when stretched passively (Leonard and Herzog, 2010). Furthermore, stiffness increases in the early stages of activation after calcium release but before cross-bridge attachment (Bagni et al., 2002, 2004; Cornachione and Rassier, 2012; Nocella et al., 2014). This early increase in stiffness is larger in muscles that express stiffer titin isoforms (Cornachione et al., 2016). After deactivation of an actively stretched muscle, more tension is present than when the muscle is stretched passively (Herzog and Leonard, 2002; Joumaa et al., 2007). This extra tension is abolished by mild digestion with trypsin, which selectively breaks down titin, but remains after troponin C extraction, which prevents cross-bridge formation. In addition, the extra force produced by muscles after active stretch (Minozzo and de Lira, 2013) increases with the stiffness of their titin isoform (Shalabi et al., 2017). Whereas early research suggested that cross-bridges were responsible for most of the energy stored in muscles during active stretch, a more recent analysis suggests that titin alone can account for 66% of this energy, which remains unexplained by other mechanisms including cross-bridges (Linari et al., 2003).

Tunable titin stiffness provides length dependence of activation dynamics (see Box 1), by morphological computation (see Glossary) of muscle force. The computed force results from combining the effects of activation (neural input) and strain (deformation by applied forces) in the action of a single mechanical element. When we consider titin as a tunable viscoelastic element, muscle can be thought of as a composite material that actuates movement by developing force in response to the combined effects of activation – which tunes the muscle's viscoelastic properties – and deformation by applied loads (Nguyen and Venkadesan, 2020 preprint). A muscle's *in vivo* strain trajectory is therefore a record of its response to applied forces. The view of muscle as a tunable material leads inevitably to an alternative view of movement control from the traditional view of muscles as motors. The central nervous system, whose neurons activate muscles by secreting acetylcholine at the neuromuscular junction, can anticipate future loading regimes based on experience and learning. However, the nervous system cannot predict deformations of muscle that will occur during the next step or at any future time. *In vivo* studies of locomotion in humans and animals reveal significant step-to-step variability in the timing of activation, muscle length and force production, and this variability increases with perturbations (Daley and Biewener, 2011). Step-to-step variability exists because the timing and amplitude of forces produced by an activated muscle emerge from the interaction between tunable muscle properties and deformation by applied loads, the exact nature of which varies with every step and cannot be predicted in advance.

Case study of a 'muscle as a tunable material' algorithm for prosthesis control

In previous work, we developed a muscle model that emulates the function of titin in muscle sarcomeres, used the model to develop a control algorithm for the BiOM T2 powered foot–ankle prosthesis (Fig. 2A), and tested its adaptability in a two-subject case study of level walking at different speeds and stair ascent (Tahir et al., 2018). In the titin-inspired algorithm, ankle moments produced by virtual dorsiflexor and plantarflexor muscles (Fig. 2B) are calculated based on muscle length and activation, which changes 'titin' length via a rotating pulley mechanism (see Box 1). In the muscle model, cross-bridges rotate a pulley representing actin, which changes the free length of a 'titin' spring in proportion to muscle activation. Length changes of the virtual anterior and posterior muscles were calculated from real-time ankle angle sensor inputs using virtual shank geometry (Fig. 2B). A simple activation scheme was used in which the anterior virtual muscle was activated during early swing, late swing and early stance, and the virtual posterior muscle was activated during powered plantarflexion at a constant percentage of maximum force selected by each user during an initial fitting session (Tahir et al., 2018). The net ankle moment predicted by the model was used to determine the current applied to the motor.

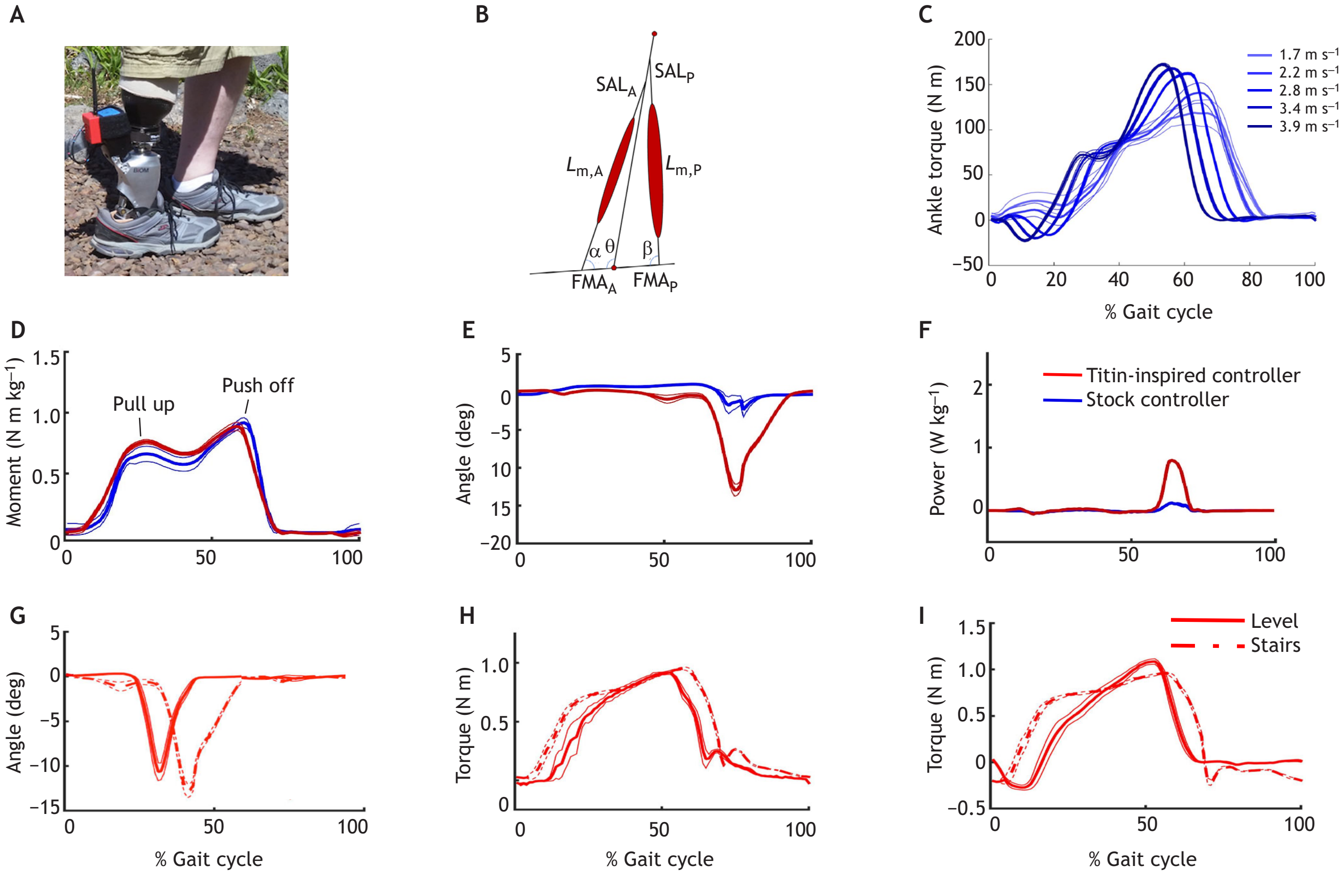


Fig. 2. Titin-inspired control algorithm. (A) BiOM T2 prosthesis. (B) Geometry of the virtual shank, showing anterior and posterior muscles with lengths $L_{m,A}$ and $L_{m,P}$. FMA_A and FMA_P are foot moment arms, and SAL_A and SAL_P are shank attachment lengths of the respective muscles. Muscle attachment angles are α for the anterior muscle and β for the posterior muscle. θ is the ankle joint angle. (C) The titin-inspired algorithm adapts to increasing walking speed. The amplitude and phase of peak dorsiflexion and plantarflexion torques increase with speed. (D) Average ankle moment was similar for titin-inspired (red) and stock controllers (blue) during stair ascent. (E) Average plantarflexion angle was greater and (F) average ankle power was ∼5 times higher for the titin-inspired controller (red) compared to the stock controller (blue). (G) During stair ascent (dashed lines), plantarflexion is larger and occurs later in the gait cycle than during level walking (solid lines). This change in ankle angle produces different virtual muscle lengths, which change the moments produced by anterior (not shown) and posterior (H) muscle models. The torque command sent to the motor represents the net ankle moment (I). Fine lines indicate 1 s.e.m. D–I adapted from Tahir et al. (2018).

When non-amputees walk at variable speeds, the timing and amplitude of both dorsiflexion and plantarflexion angles and moments at the ankle adapt to provide the additional muscle power required for faster walking (Liu et al., 2008). Specifically, peak dorsiflexion and plantarflexion angles and moments increase in magnitude and occur earlier in the gait cycle as walking speed increases. Several previous studies found that prosthesis controllers based on neuromuscular models of ankle function also showed speed adaptation (Markowitz et al., 2011; Eilenberg et al., 2010). Using the titin-inspired muscle model (Box 1), Tahir et al. (2018) found that the control algorithm enabled adaptation of ankle dorsiflexion and plantarflexion torques during walking at variable speed. The titin-inspired model achieves speed adaptation by virtue of its response to changes in virtual muscle lengths, calculated from the prosthetic ankle angle sensor, without requiring changes in activation or model parameters (Fig. 2C).

Ascending stairs differs biomechanically from walking on a level surface. From heel-strike to heel-strike, level walking includes one pair of ankle moments: a dorsiflexion moment which lifts the toes to prevent tripping, and a plantarflexion moment that produces a ground reaction force for forward propulsion (Au et al., 2008). Ascending stairs involves an additional pair of dorsiflexion and plantarflexion moments. The first pair of moments pulls the center of mass up from the previous stair, whereas the second pair pushes the center of mass up to the next stair (Fig. 2D; Wilken et al., 2011; Aldridge et al., 2012). During stair ascent, the titin-inspired algorithm produced plantarflexion angles (Fig. 2E) and peak power (Fig. 2F) that were ∼5 times larger on average than those produced by the stock controller, and similar to those of able-bodied individuals. The BiOM T2 prosthesis uses a state machine (see Glossary) in the stock controller that identifies the toe-off phase of walking using onboard sensors for timing of user selected plantarflexion assistance. In contrast, the titin-inspired controller adapts to different terrains specifically by reacting instantly to perturbations in length, whether predictably associated with different types of terrain or completely unexpected.

The titin-inspired controller provides adaptive ankle torque assistance during level walking and stair ascent (Fig. 2E,F) based only on changes in virtual muscle length calculated from the prosthetic ankle angle sensor (Fig. 2G–I). Although it is generally assumed that different operational modes are required for ambulation in different terrains (Tkach and Hargrove, 2013), the titin-inspired controller demonstrates the feasibility of adaptive torque control across different walking speeds and terrains using a set of equations and parameters derived from principles of muscle mechanics (Tahir et al., 2018).

Although useful as proof of concept for the adaptive forward control of titin-inspired models, Tahir et al.'s (2018) case study has several limitations. It does not provide a sensitivity analysis of model parameters, nor does it directly compare prediction accuracy with that of Hill models. Future studies should comprehensively describe the mathematical behavior of titin-based models, systematically compare the accuracy of force predictions to other models, and especially develop approaches for estimating the model parameters experimentally.

Conclusions

Development of robotic prosthetic devices has come a long way towards restoring the functional capabilities of people with an amputation. Nevertheless, many significant challenges remain to improve the capacity of these devices to functionally replace lost and missing limbs. Clearly, improving the adaptability and versatility of robotic prostheses is essential for restoring functionality to persons with an amputation. Understanding the mechanical basis for the inherent adaptability of muscle may inspire new directions toward achieving this goal.

Historically, there have been numerous barriers to achieving muscle-like adaptation in prosthetic devices, including the limited utility of current muscle models for predicting *in vivo* muscle force. Recent advances in our understanding of muscle function present an opportunity to overcome these barriers. Although traditional theories of muscles as motors, and models based on them, have focused on static and quasi-static properties, the evolving view of muscles as tunable materials leads to new insights into the dynamic relationship between force and activation. In particular, forces produced by muscles are an activation-dependent response to deformation by applied forces, the exact nature of which cannot be anticipated by the central nervous system. Therefore, muscle activation must be permissive rather than instructive of the timing and amplitude of force production.

The *in vivo* strain trajectory of a muscle is a record of its deformation by applied loads, and provides as much or more information about resulting muscle force as the activation input. Recent work by Tahir et al. (2018) demonstrates that a muscle model based on tunable elastic properties of titin can achieve adaptive control. Using constant activation and virtual muscle length inputs from the prosthetic ankle angle sensor, no changes in model parameters were required to achieve adaptive control of prosthetic ankle torque with walking speed and when ascending stairs. One caveat is that the design of prostheses requires the integration of controllers and motors. For example, it might be energetically unfavorable to program a high-torque motor to provide muscle-like, variable compliance. To emulate muscle-like actuation may therefore require the design of new actuators that can store and return energy in a muscle-inspired fashion to reduce the demand for power.

The new paradigm of muscle as a tunable material has significant implications for biologically inspired prosthesis design and control. For example, the concept that the strain of muscle fascicles is more closely related to muscle force than activation suggests that *in vivo* ultrasound imaging of muscle fascicle strain could be more effective than surface EMG or other neural signals (Kannape and Herr, 2014, 2016) in the development of prostheses capable of muscle-like actuation and adaptive control of movement under varying conditions. In fact, *in vivo* ultrasound imaging is increasingly used for control of wearable devices (Rabe et al., 2020). Additionally, the development of improved methods for amputation will likely increase the practicality of real-time ultrasound imaging data from residual limbs (Herr et al., 2021) for adaptive control of prosthetic devices, at least for some users. Hand prostheses are particularly amenable to this approach, as many forearm muscles remain intact. Additionally, there is an important opportunity for biologists and engineers to collaboratively develop adaptive control algorithms that use simple joint models (e.g. Fig. 2B) based on ultrasound studies in able-bodied people.

As materials, energy sources and computing power continue to improve, it is evident that achieving adaptive control under varying conditions will remain a major area for improvement of prosthesis function. Inspiration for achieving adaptive control may come from new insights into the adaptability and versatility of muscles. Some ideas that might prove useful include: (1) the asymmetric function of muscles not only as motors but also as struts, shock absorbers, brakes or springs during isometric, concentric and eccentric contraction; (2) the use of morphological computation based on springs and dampers to achieve embedded control of movement; and (3) the increasing evidence that muscle fascicle strain provides as much information or more than EMG about muscle force production under dynamic conditions. Although understanding of the mechanistic basis for the adaptability and versatility of *in vivo* muscle function is far from complete, these ideas about tunable viscoelastic properties and permissive versus instructive control have potential value for developing predictive models of *in vivo* muscle function and for designing prostheses that function as well as or better than biological limbs.

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Competing interests
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