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Force transmission and interactions between synergistic muscles

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ABSTRACT

The classical view of muscles as independent motors has been challenged over the past decades. An alternative view has emerged in which muscles are not isolated but embedded in a three-dimensional connective tissue network that links them to adjacent muscles and other non-muscular structures in the body. Animal studies showing that the forces measured at the distal and proximal ends of a muscle are not equal have provided undisputable evidence that these connective tissue linkages are strong enough to serve as an extra pathway for muscular force transmission. In this historical review, we first introduce the terminology and anatomy related to these pathways of muscle force transmission and provide a definition for the term epimuscular force transmission. We then focus on important experimental evidence indicating mechanical interactions between synergistic muscles that may affect force transmission and/or influence the muscles' force generating capacity. We illustrate that there may exist different expressions of the highly relevant force-length properties depending on whether the force is measured at the proximal or distal tendon and depending on the dynamics of surrounding structures. Changes in length, activation level or disruption of the connective tissue of neighboring muscles, can affect how muscles interact and produce force on the skeleton. While most direct evidence is from animal experiments, studies on humans also suggest functional implications of the connective tissues surrounding muscles. These implications may explain how distant segments, which are not part of the same joint system, affect force generation at a given joint, and, in clinical conditions, explain observations from tendon transfer surgeries, where a muscle transferred to act as an antagonist continues to produce agonistic moments.

1. Introduction

The force generating capacity of muscles can be assessed at various levels of organization (from molecules and single myofibrils up to whole muscles) and under various experimental conditions (*in vitro*, *in situ*, *in vivo*). While there are no major limitations in measuring force and obtaining the basic contractile properties of isolated muscle preparations *in vitro*, obtaining them *in situ* or *in vivo*, with the intricacy of surrounding structures, is certainly more complex, and is typically based on several assumptions. Arguably, the most common assumption of muscle mechanics is that muscles act as independent motors. According to this classical view of muscles, the force generated by a muscle is directly transmitted to the skeleton via the myotendinous junction, with skeletal muscles being regarded as mechanically separate entities. From the classical view of muscles as individual motors, some basic predictions regarding their mechanical behaviour emerge (Fig. 1).

This view of muscles is largely based on classical anatomical studies of the muscular system in which muscles are dissected free from their surroundings. Traditional anatomical descriptions of skeletal muscles, like those in anatomical atlases, often neglect the structural continuity of the connective tissues enveloping muscles – it is obvious to anyone who has conducted muscle or fiber dissections that muscles are not isolated units but are embedded in a three-dimensional connective tissue network that attaches them to other muscles and other non-muscular structures in the body. Next time such a dissection is repeated, it is suggested to carefully acknowledge all the connective tissue structures that you may want to disrupt. Active muscle forces are generated through the interaction of intracellular contractile filaments and, therefore, need to be transmitted from the interior of muscle fibers through the cell membrane to structures attached to the skeleton. In this force transmission, the intramuscular connective tissue network – often divided into endomysium (connective tissue around muscle fibers),

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perimysium (around muscle fascicles), and epimysium (around the whole muscle) – is crucially involved. While precise inspection of actual skeletal muscle samples by light, transmission, or scanning electron microscopy suggests that such definitive subdivisions of the muscle connective tissues are simplistic and arbitrary, they serve didactic purposes and have been used to distinguish pathways of muscle force transmission – as we will introduce later in this review (Nishimura et al., 1994; Purslow, 2020; Purslow and Trotter, 1994).

We will focus this review on force transmission between a muscle and surrounding structures and, thus, the tough muscle coat called epimysium will receive special attention. For an understanding of force transmission pathways within the muscle belly (intramuscular), the reader is referred to previous reviews aimed at the muscle fiber and fascicle levels (Huijing, 1999; Monti et al., 1999; Patel and Lieber, 1997). We focus on force transmission between neighboring synergistic muscles because its occurrence challenges the common important assumption of muscles as independent motors. Additionally, investigations beyond the intramuscular domain are more recent than the analyses concerning intramuscular force transmission.

The view of muscles as independent motors has been questioned in numerous studies. Vanguard work on the 19th century (see Huijing, 2009) and several remarks in the past century indicated that the connective tissue structures surrounding muscles may affect their mechanical function (Denny-Brown, 1929; Devasahayam and Sandercock, 1992; Nichols, 1999). However, it took until the turn of the millennium for the start of experiments that systematically studied this issue. In 1999, Prof. Peter Huijing, who received the Muybridge award by the International Society of Biomechanics for his work on muscle force transmission, stated that, at the time, there was “no unequivocal evidence regarding the feasibility of extramuscular myofascial force transmission as yet”. Therefore, it is fair to say that while our understanding of the transmission of forces generated by the contractile filaments in the muscle fibers within skeletal muscles has been advanced considerably in the last 50 years, studies specifically aimed at investigating force transmission between a muscle and surrounding structures at the muscle organ level are probably only about 25 years old (Huijing, 2009).

In the late nineties, Prof. Huijing got inspired to systematically investigate force transmission via pathways other than the muscle’s origin and insertion by unexpected findings on the rat extensor digitorum longus (EDL) muscle (Huijing et al., 1998). EDL is a multi-tendon

muscle with a common aponeurosis and tendon proximally linked to four muscle heads, each with a separate aponeurosis and tendon distally (Maas et al., 2003b). Huijing et al. (1998) observed that when the distal tendons of EDL were cut one by one (removing force transmission via their myotendinous junction), the decrease in force was not proportional to the physiological cross-sectional area of the corresponding muscle heads, indicating force transmission between muscle heads via connective tissues at their interfaces. With this new perspective, the concept emerged that part of the force produced by a muscle can be transmitted to neighboring muscles and other surrounding structures through the continuous network of connective tissues. This opened a new field of investigation in muscle mechanics, aimed at assessing the mechanisms and physiological relevance of force transmission between muscles (Huijing, 2009), and since the first proof of such force transmission (Huijing and Baan, 2001; Maas et al., 2001), the number of papers on this topic has increased substantially.

Recent experimental findings, therefore, have changed our understanding of how muscles work and have provided evidence against the assumption of muscles as independent motors. In this review, we will first introduce the terminology in use in the literature to refer to force transmission and highlight the anatomical pathways and structures that are likely involved in the interaction between synergistic muscles. We then describe important experimental evidence showing mechanical interactions between synergistic muscles and how these might influence the muscles’ force generating capacity. By covering the issue of force transmission between a muscle and its surroundings through the lenses of the force–length properties, we aim to highlight the limitations of assuming muscles as independent motors and to identify potential gaps that may have emerged in the recent history of this topic.

2. Terminology and anatomical pathways for force transmission

Force transmission via the sarcomeres in series, the intramuscular connective tissue network and the myotendinous junction to the tendon is arguably the main pathway through which forces produced by muscle fibers are transmitted to the skeleton. At the myotendinous junction, the muscle fibers embedded in connective tissue are linked in an interdigitated fashion to the collagen fibers eventually forming the tendon (Knudsen et al., 2015; Tidball, 1991). Prof. Huijing termed force transmission via the outer connective tissue layer “epimuscular myofascial force transmission”. Epimuscular refers to the involvement of the

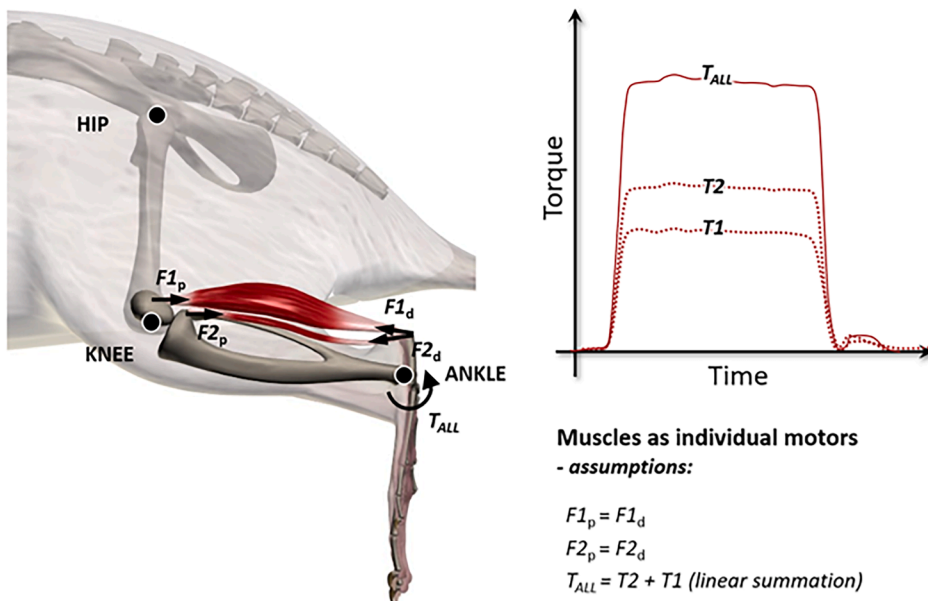


Fig. 1. On the left, a drawing of two synergistic ankle plantar flexors of the rat. While muscle 1 (bi-articular m. gastrocnemius) crosses both the ankle and the knee, muscle 2 (mono-articular m. soleus) crosses only the ankle joint. The model is based on a 3D graphical model of the rat hindlimb (Baan and Maas, 2022). According to the classical view of muscles as independent motors, changes in the position of the hip are not expected to influence the mechanics of either muscle 1 or 2, while changes in the knee position are thought to influence only muscle 1 – i.e. force/torque generated by a muscle is independent of the position of joints that are not crossed by the muscle. Additionally, according to this view, structures surrounding the muscle and the activation of neighbouring muscles do not influence force transmission between the proximal (subscript “p”) and distal (subscript “d”) muscle ends. On the right, the result of this assumption is pictured; i.e. force measured at either the proximal or distal ends of a muscle are identical and a linear summation of muscle torques is expected: the torque produced by the synergistic group (T_{ALL}) is thus equal to the sum of the torque produced by muscle 1 ($T1$) and muscle 2 ($T2$).

epimysium, and myofascial to the transmission of force from muscle fibers to the surrounding endomysial fascia. Others have indicated to prefer the term intermuscular to avoid presuming a mechanism (Herbert et al., 2008). This latter term, however, would not include force transmission from muscle to surrounding non-muscular structures. The use of the term lateral instead of myofascial has also been suggested based on the studies by Sibyl Street (Street, 1983; Street and Ramsey, 1965) as they showed that in addition to longitudinal transmission (between in series sarcomeres) force is transmitted laterally between muscle fibers and the interfiber matrix. Since our current review focuses on muscle at the organ level and, in anatomy, the term lateral has a very specific direction connotation (indicates location within the transverse axis in opposition to medial), we prefer the term epimuscular force transmission.

We define epimuscular force transmission as the transmission of forces from a muscle to the skeleton bypassing the muscle's own origin and/or insertion. Originally, two epimuscular pathways were described: (i) intermuscular, if force is transmitted between two neighboring muscles via the continuous connective tissue at their muscle belly interface, and (ii) extramuscular, if force is transmitted between the epimysium of a muscle and adjacent non-muscular structures (Fig. 2).

This distinction (intermuscular vs extramuscular) can be confusing as intermuscular interactions are not always directly mediated by connective tissue linkages between muscle bellies but can also involve non-muscular structures, such as the neurovascular tract. Additionally, force transmission between muscles may involve the epitenon. While the epimysium covering the muscle belly is continuous with the epitenon covering the tendon, the definition of epimuscular pathways has generally been limited to pathways between muscle bellies. We suggest, similarly to how Maas and Sandercock (2010) defined it, that forces transmitted out of the muscle via both the epimysium or the epitenon are considered under the umbrella of epimuscular force transmission (Fig. 2).

Epimuscular interaction requires the presence of structures capable of transmitting forces (Fig. 3). At the interface between muscle bellies, layers of areolar and dense connective tissue as well as neurovascular structures are present (Langevin and Huijing, 2009; Taylor et al., 1994). In addition, skeletal muscles are linked to connective tissue layers surrounding synergistic muscle groups (e.g., compartmental fascia, interosseal membranes) (Huijing and Baan, 2001). The neurovascular tract is a structure that has received great attention in the studies on epimuscular force transmission. It is a collagen fiber-reinforced sheet of connective tissue in which nerves and blood and lymph vessels are embedded (Huijing et al., 2003). This tract is connected to the intramuscular connective tissue network (Maas et al., 2001) and to extramuscular elements such as bones, compartmental fascia and interosseous membranes (Huijing and Baan, 2001).

Both the direct connective tissue linkages (generally considered “loose”) and the neurovascular tract were shown to be strong enough to serve as a pathway for transmitting muscle forces (Maas et al., 2005,

2003a), but the latter structure appears to be stiffer. The amount of force transmitted via the different epimuscular and intramuscular pathways is dependent on their stiffness. However, the stiffness of epimuscular structures has not been reported frequently, which is indicative of the experimental difficulties for such an assessment. Comparisons of in series muscle stiffness (Olesen et al., 2014) with the estimates of net stiffness of intermuscular structures in the rat (Bernabei et al., 2016) indicates that the latter is 10–100 times lower than the in series stiffness (see also Maas, 2019).

Distinguishing the contribution of the different anatomical structures to muscle force transmission is a challenge as the connective tissue within the musculoskeletal system is intricately connected in a complex manner, and pathways for force transmission are defined by the muscle specific location and surroundings. It has been argued that the intramuscular connective tissue network is part of a broader system of connective tissue structures, often called the fascial system (Adstrum et al., 2017). The term fascia is used to refer to interconnected and interwoven connective tissue structure(s) that “surrounds, interweaves between, and interpenetrates all organs, muscles, bones and nerves” (Adstrum et al., 2017) and the term system as in “the fascial system”, carries the anatomical assumption that these structures are related in a synergistic manner towards a specific function.

The above-described anatomical structures can bear loads and transmit forces which are expected to affect the *in vivo* expression of muscle mechanical properties. When referring to pathways of force transmission, the term epimuscular force transmission is instrumental to describe the forces produced by the muscle fibers that are transmitted via connective tissue linkages to neighboring muscles or to non-muscular structures. However, as we will see in the subsequent sections of this review, the shear and tensile forces that are transmitted epimuscularly are not the single mechanism through which interactions between synergistic muscles can occur. Recently, the effects of compression on active muscle forces have received some attention. Muscles are contained within fascially enclosed compartments and are subject to increased pressure when they contract. Changes in the integrity of these fascial tissues and, hence, changes in pressure may affect force generation in a synergistic group.

3. Measurement of mechanical properties of skeletal muscles

Passive and active properties of single muscles can be measured *ex vivo* (Park et al., 2012) or *in situ* (MacIntosh et al., 2011) in animal models. *Ex vivo*, the muscle is dissected, removed from the body and placed in an oxygenated bath with Ringer solution. Thus, any effects of myofascial loads are eliminated. *In situ*, the muscle is dissected free from surrounding tissues but with the tendon of origin attached to the skeleton and the blood supply and innervation kept intact. Thus, all epimuscular structures, except the neurovascular tract, are removed. It was already reported in 1929 that in such a case, stimulation of the different muscles belonging to a specific nerve could result in intermuscular

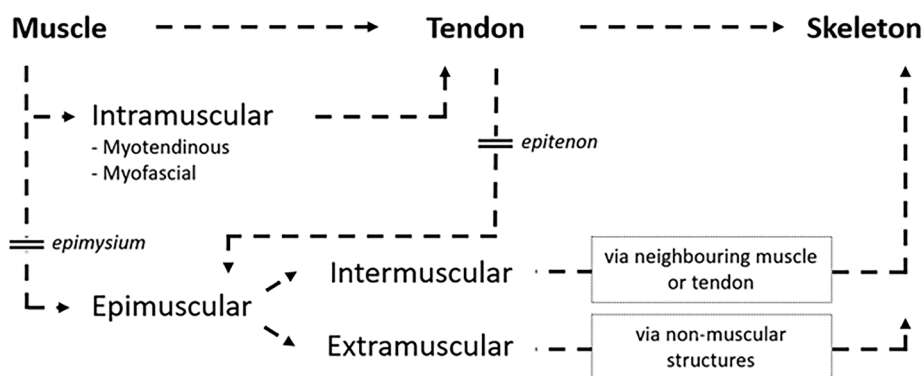


Fig. 2. The different pathways via which force generated within muscle fibers can be transmitted to the skeleton (Maas et al., 2003b). Besides the intramuscular pathways (myotendinous and myofascial), two epimuscular pathways are distinguished. (i) Intermuscular: force transmission between two neighboring muscles via the continuous connective tissue at their muscle–tendon interface. (ii) Extramuscular: force transmission between a muscle and adjacent non-muscular structures. The term epimuscular force transmission is used to indicate transmission through the epimysium via inter- or extramuscular pathways (Maas and Sandercock, 2010). Here, we included force transmission via the epitenon (Rijkkelijkhuizen et al., 2005) as part of the epimuscular pathway (see text for details).

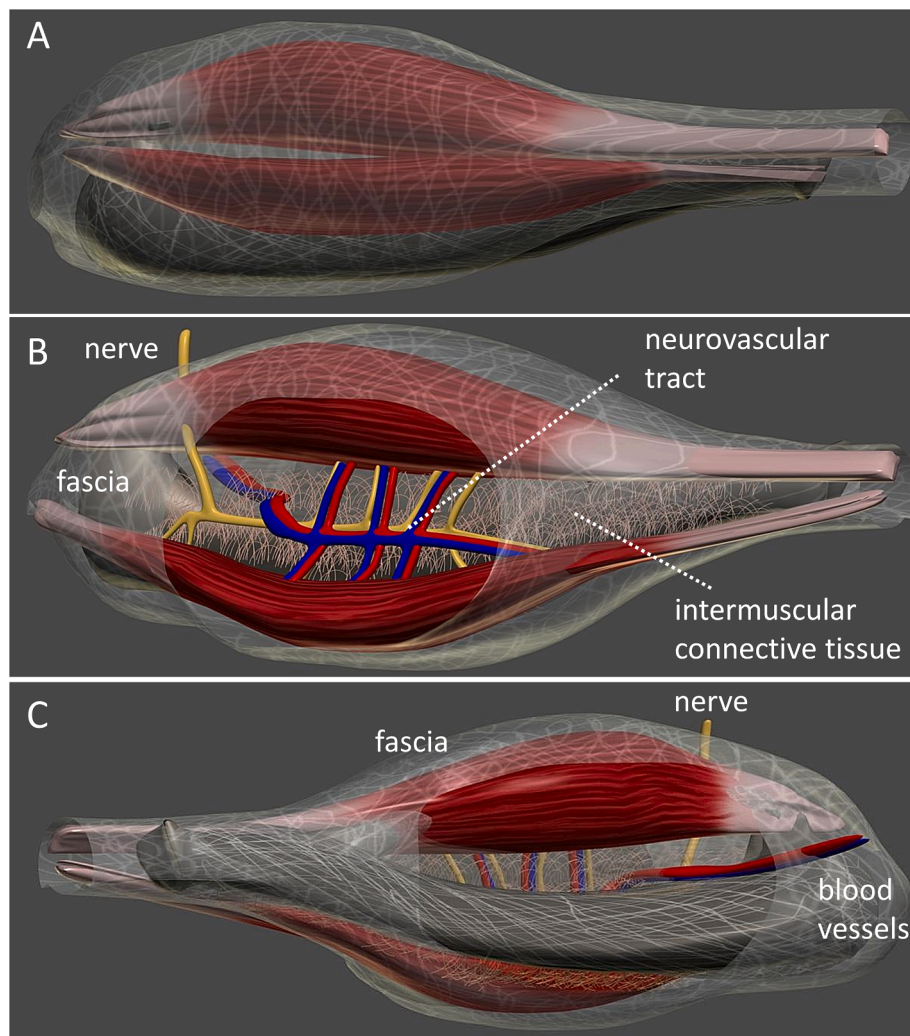


Fig. 3. Drawings of structures involved in epimuscular force transmission. A: Drawing of a theoretical compartment with two muscles and one bone embedded within fascial layers. B: Same compartment as in A, but in an enlarged view with a window into the fascia to visualize intermuscular connective tissues and the neurovascular tract. C: Opposite view as in B, illustrating the connections between muscles and bone.

interactions (Denny-Brown, 1929). Also, in later experiments, mechanical interference via the intact neurovascular tract was observed (Devasahayam and Sandercock, 1992).

Prior to the introduction of epimuscular force transmission, connecting only one end of a muscle to a force transducer was considered sufficient when measuring the mechanical properties of skeletal muscles in animal models. Studying the effects of epimuscular force transmission on muscle mechanical properties requires that muscles and connective tissue structures in which they are embedded are kept intact. The first measurements aimed at studying this new mechanism were performed on the muscles within the anterior crural compartment of the rat, which consists of the extensor digitorum longus, extensor hallucis longus and tibialis anterior muscles (Huijing and Baan, 2001; Maas et al., 2001). Subsequently, similar experiments have been performed for other muscles in the hindlimb, such as the triceps surae (Bernabei et al., 2015; Rijkkelijkhuizen et al., 2005; Tijs et al., 2016a), and muscles in the forelimb (Maas and Huijing, 2009). The proximal and distal tendons of muscles, and the tendons of neighboring muscles are typically cut from the skeleton in these experiments and connected to different force transducers. This involves disrupting connective tissues at the tendons, but the epimuscular pathways at the muscle bellies are kept intact. Measuring forces of both tendon ends of a muscle allows for obtaining the most direct proof of epimuscular force transmission, which is a difference in the forces exerted at the origin (proximal) and insertion

(distal) of a muscle. An approach to assess which structures serve as an epimuscular pathway is to repeat the above-described measurements following dissection of these structures (Tijs et al., 2016b).

Another common observation indicating force transmission between muscles is that lengthening one muscle affects forces exerted at the tendons of neighboring muscles kept at a constant muscle-tendon unit length. Through the manipulation of the length and relative position of a muscle within a compartment, the influence of epimuscular force transmission on muscle mechanics has been investigated. More recently, effects of muscle relative position on behavior of muscle spindles and tendon organs have been used to assess effects of epimuscular forces (Maas and Noort, 2023; Maas et al., 2022; Smilde et al., 2016). Additionally, the effect of activating neighboring muscles on the maximal force capacity of muscles in the rabbit quadriceps group was recently tested in a systematic way through the individual stimulation of femoral nerve branches in a combined and isolated manner (Han et al., 2019).

To study epimuscular interactions *in vivo* and enhance our understanding of its physiological significance, a new experimental paradigm was introduced by Maas and Sandercock (2008). This involved the assessment of mechanical interactions between muscles in an intact limb through the manipulation of a joint. In a two-joint system with one muscle crossing only one joint and another muscle that is bi-articular, the effects of lengthening one muscle on forces exerted by the neighboring muscle could be assessed by manipulating the joint that is crossed

by the bi-articular muscle only. This paradigm has been applied in experiments investigating intermuscular interactions in rat (Tijs et al., 2015a, 2016b), but more importantly, paved the way for many experiments in humans.

A typical laboratory setting in human studies involves studying joint systems with mono- and bi-articular muscles. By changing the joint angle crossed by the bi-articular muscle only and recording torque output at the joint, the associated muscle fascicle lengths, muscle shear modulus, and/or movements at the interface of the muscles have been used to make indirect inferences about force transmission. In clinical settings, evaluations of relative tissue movements following surgical interventions and intraoperative assessments of muscle or sarcomere length and muscle force have allowed examination of the role of epimuscular force transmission.

Within the intact human body, direct measurement of muscle forces is impossible. Rarely, muscle forces have been assessed invasively using either S-shaped (Schuind et al., 1992), buckle-type (Gregor et al., 1987; Komi et al., 1987) or optic fiber tendon force transducers (Komi et al., 1996). Such studies have described the human *in vivo* force-length relationships at muscle-tendon level in isometric conditions (Arndt et al., 1998), during dynamic movements (Finni et al., 2001, 2000) or in both (Finni et al., 2001). A recently introduced non-invasive shear wave method to assess tendon forces during human movement (Martin et al., 2018) shows promise for many applications. However, the above-mentioned studies were not designed to investigate epimuscular force transmission. Also, assessing forces from a common tendon shared by multiple muscles (e.g., Achilles tendon) can provide only limited information about epimuscular force transmission.

Typically, muscle forces are estimated from externally measured forces or torques. In such a case, calculating muscle forces requires information about moment arms and estimation of relative force between synergistic muscles using physiological cross-sectional area (Albracht et al., 2008; Ward et al., 2008), electromyography (Bigland and Lippold, 1954; Lloyd and Besier, 2003; Simonetti et al., 2022) or shear wave elastography (Hug et al., 2015; Lima et al., 2018). Typically, these estimations are made ignoring any potential interactions between muscles. In clinical studies, muscle forces have been measured intraoperatively and influences of tendon transfer (Lieber et al., 2005), tenotomy (de Bruin et al., 2011) or soft tissue dissection on force transmission have been evaluated (Smeulders and Kreulen, 2007).

Because of difficulties in assessing forces *in vivo*, human studies have also used indirect ways to make interpretations of force transmission, such as relative tissue movements and muscle lengths typically assessed using imaging methods such as B-mode ultrasonography (Bojsen-Møller et al., 2010), shear wave ultrasonography (Yoshitake et al., 2018) or MRI (Huijing et al., 2011). Changes in fascicle length or deformations of structures that are not directly manipulated have been used to evaluate effects of epimuscular forces. Also, observations of relative tissue displacements, i.e. tissue shear, have been used to make interpretations of force transmission between muscles (Asakawa et al., 2002; Finni et al., 2017). These should be distinguished from studies that can actually investigate forces since they do not allow interpretation of the mechanical consequences.

4. Intermuscular interactions and changes in force - length relationships

When the length of a muscle-tendon unit changes, its potential to produce force is altered. Therefore, mechanical interactions with surrounding structures that can change the length of a muscle are important for its force output. Besides the active force generating capacity of muscles, which is elicited upon activation, muscles can respond to passive deformation with increasing resistance. The changes in passive force when a muscle is lengthened (i.e., the passive force-length property) or the observed strains when external forces are applied have been of particular interest in the field of epimuscular force transmission. For

the reasons mentioned in the section above, most experiments in this field are in animal models, using an experimental setup similar to that introduced by Huijing and colleagues.

In the past 25 years, evidence for epimuscular force transmission in muscles has been reported repetitively in both passive and active state. If an external force is exerted on the muscle belly or tendon of a muscle, its force-length properties can be affected. The effect will depend on the type (e.g. shear, compression) and magnitude of the loads applied and on whether the net load is pulling the muscle in the proximal or distal direction (Bernabei et al., 2015; Siebert et al., 2014; Tijs et al., 2016a). Additionally, changes in the length of muscle fibers and/or sarcomeres may occur as a result of these external forces, leading to changes in their force generating potential (Tijs et al., 2015b).

Interactions between adjacent muscles may also be brought about by a shared tendon, acting as a common elasticity, or by changes in intermuscular pressure as a result of the three-dimensional deformation of muscles within their anatomical compartment during contraction. Some of these effects have been explained by very simple physical models (for illustrations see Maas 2019), while other results require further studies to elucidate the mechanisms (de Brito Fontana et al., 2019). In the following two sections, we will describe experimental evidence obtained from animal studies and experiments on human subjects that have expanded our understanding on force transmission and interactions between synergistic muscles. Even though force transmission has been reported for synergistic as well as antagonistic muscles in both the forelimb and hindlimb of rodents (Huijing, 2007; Maas and Huijing, 2009), we will limit the description to force transmission between synergists, according to the scope of this review.

4.1. Experimental evidence from animal models

In animal models, forces and torques can be measured in the passive and active state for individual muscles under a variety of experimental conditions. Such experiments have shown that the force-length relationship measured at the distal tendon (i.e. insertion) can be different than that of the proximal tendon (i.e. origin) (Fig. 4A & B). Force-length characteristics may vary also as a function of muscle relative position (Fig. 4C & D). This means that muscle parameters often assessed for musculoskeletal modeling, such as slack length, muscle stiffness, and force at optimal length, cannot be described by a single value (Bernabei et al., 2015).

The greater the relative displacement, the greater the strain and, hence, stress on the epimuscular connections, resulting in increased external loads and more pronounced changes in the force-length relationship. Indirect evidence suggests that the stress-strain relationship of epimuscular linkages is nonlinear (Maas, 2019). Interestingly, the contribution of passive forces to epimuscular force transmission seems to be smaller compared to the epimuscular forces that can be generated with activation. Changes in force of a mono-articular muscle in response to lengthening of a bi-articular muscle were approximately 10 % of optimal force in case all muscles were excited maximally, but less than 1 % in case muscles were kept in the passive state (Bernabei et al., 2015; Tijs et al., 2016a).

Conditions in which the material properties of the connective tissues serving as epimuscular pathway are altered may be accompanied by changes in epimuscular force transmission and, hence, affect the force-length relationship. In a mouse model of Ehlers-Danlos syndrome (i.e. tenascin-X knockout, TNX KO), in line with the expected more compliant connective tissue structures, a significant reduction in intermuscular interactions was observed (Huijing et al., 2010). In contrast, in a mouse model for Duchenne Muscular Dystrophy (mdx mouse), in which the *trans*-sarcolemmal protein complexes linking the cytoskeleton to the extracellular matrix are affected, enhanced intermuscular interactions have been found (Meijer, 2007). Besides stiffer epimuscular pathways, increased passive forces and higher passive stiffness also indicated an increased stiffness of the in-series structures within the

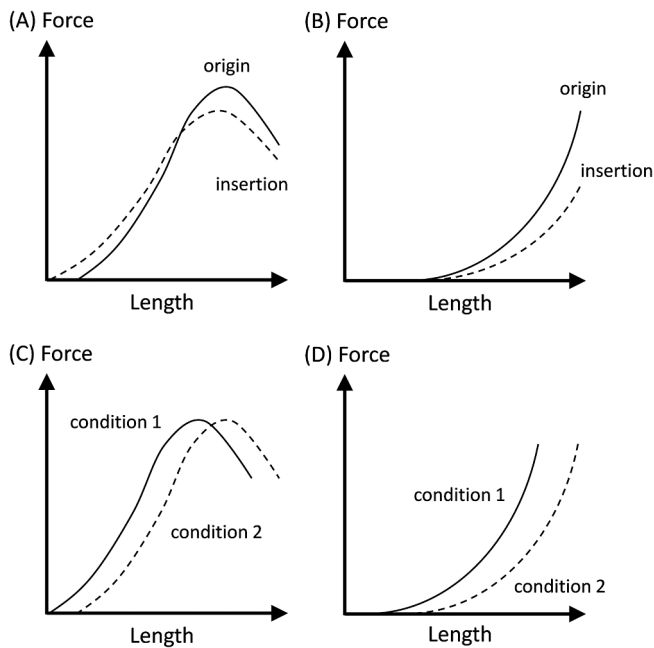


Fig. 4. Schematic representations of consequences of epimuscular force transmission on force-length characteristics. (A) Active and (B) passive forces exerted at the origin and insertion of a muscle. The difference between the curves illustrates the force that is transmitted via epimuscular pathways. (C) Active and (D) passive force-length curves measured at the insertion of the same muscle for two conditions. The illustrated difference can result from different positions of the muscle relative to surrounding structures, but also before and after disrupting epimuscular structures. Note that the scale of the y-axis of active (A & C) and passive (B & D) forces differs. The idealized data is based on the findings by Bernabei et al. (2015), Huijing and Baan (2003) and Maas et al. (2001).

muscle-tendon unit. To what extent these changes in epimuscular force transmission affect muscle (dys)functioning or disease progression, is currently unknown.

In contrast, other studies analyzing the effect of epimuscular transmission in pathological conditions did not find significant changes. Specifically, the extent of interaction between muscles in the forelimb, as assessed by lengthening one muscle while measuring changes in force at the tendon of a neighboring muscle, was unchanged following an experimentally induced photothrombotic stroke in the rat (Paudyal et al., 2021). Additionally, comparisons between intermuscular interactions of triceps surae muscles in a spastic rat model and those in a control group revealed no differences (Olesen et al., 2014). The force-length characteristics, however, were different in the spastic rats in a similar way as expected from muscle properties of human patients.

Epimuscular force transmission has also been analyzed after surgical interventions as they often result in the formation of scar tissue near the site of tissue disruption. Tendon transfers (i.e. transferring the tendon of insertion of a muscle to another location on the skeleton) are performed to improve motor function in individuals with disabilities and the consequences of epimuscular transmission on the mechanical outcomes cannot be ignored (Riewald and Delp, 1997). In rats, transferring a forearm wrist flexor to the extensor side was shown to increase the stiffness of epimuscular pathways and, hence, enhanced the extent of intermuscular interactions (Maas et al., 2013; Maas and Huijing, 2012a). Similar to the results from experiments in human patients (Riewald and Delp, 1997), this resulted in a different mechanical effect of the transferred muscle than predicted based on the new moment arm at the joint (Maas and Huijing, 2012b), which could be considered a disadvantage of epimuscular connections.

Besides the mechanical interactions that can emerge through scar tissue formation, it is known that muscles can transfer load to

surrounding muscles after tenotomy or a rupture of muscle and/or tendon (Maas and Finni, 2018; Maas and Sandercock, 2008; Watrous and Olmsted, 1938). As force transmission between origin and insertion is disrupted after tenotomy, any distal mechanical effect measured through the activation of the tenotomized muscle should be ascribed to the transmission of forces via epimuscular pathways to surrounding intact muscles. In the cat, Maas and Sandercock (2008) showed that soleus contraction resulted in significant plantar flexion torques even after transecting its distal tendon. In fact, about 50 % of the original torque was retained after soleus tenotomy, suggesting that, for this condition that may mimic a peripheral tendon injury, a substantial part of the force is transferred to the joint through epimuscular pathways. Epimuscular force transmission may in this case have a beneficial effect, namely that of a safety barrier for traumatic events in a muscle or tendon by allowing forces to be partly distributed to adjacent structures. This might prevent the myotendinous route of force transmission from further trauma and facilitate the recovery process (Maas and Finni, 2018).

In several locations within the body, muscles connect to common tendons before their insertion to the skeleton. For example, muscles of the quadriceps muscle group merge distally into the patella tendon and triceps surae muscles merge distally into the Achilles tendon in some animals. As such, changes in muscle-tendon unit length of one muscle can affect the muscle belly length of the neighboring muscles and, hence, their force production. This may result in the individual force generating capacity of muscles not adding up linearly to the force generated when muscles are activated simultaneously. This effect of a common series elasticity on the nonlinear summation of muscle force is schematically explained in Fig. 5. Note that the effect of a common elasticity on the magnitude of nonlinear summation depends on which region of the force-length relationship the muscles operate. If muscles work on the descending limb, the force capacity when stimulated simultaneously (D in Fig. 5) is expected to be higher than the sum of muscle forces obtained through individual stimulation (C and B in Fig. 5). If muscles work on the ascending limb (not shown in Fig. 5), an opposite effect can be expected, with force in D being smaller than the sum of the forces produced in C and B. Previous studies that showed nonlinear summation to not depend on the region of the force-length relationship suggest that common series elasticity is not the sole mechanism for nonlinear summation.

Only a few studies have investigated nonlinear moment summation between muscles, with experiments including ankle moments exerted by cat triceps surae muscles (Perreault et al., 2002; Sandercock and Maas, 2009), experiments in the rat hindlimb (Jarc et al., 2013; Tijs et al., 2014) and in the rabbit quadriceps muscles (de Brito Fontana et al., 2019, 2018). Tijs et al. (2014) showed that the magnitude of the ankle torque exerted by the soleus and gastrocnemius muscles and the direction of their vectors in the transverse, frontal and sagittal planes did not sum linearly. Their results were similar to the ones observed by Perreault et al. (2002) with a difference between individual sum and the simultaneous stimulation of 3–9 % of torque production in favor of the condition in which muscles were stimulated in isolation.

De Brito Fontana et al. (2018) also found lower knee joint torques during simultaneous maximal activation of the rabbit quadriceps compared to the sum of torques for the individual stimulation. The observed nonlinearity was consistent across joint angles and was much greater (~20 %) than what had been described for the triceps surae. The difference between studies suggest that these interactions may depend on the agonistic muscle group tested but experiments also were different with regard to the levels of activation tested (maximum [de Brito Fontana et al., 2018] vs ~20 % of maximum [Tijs et al. 2014]). The common series elasticity and epimuscular transmission in both the quadriceps and triceps surae may partly explain the lower force production during simultaneous activation. However, as explained above, the effect of a common elasticity depends on the region of the force-length relationship in which muscles operate. The above-mentioned

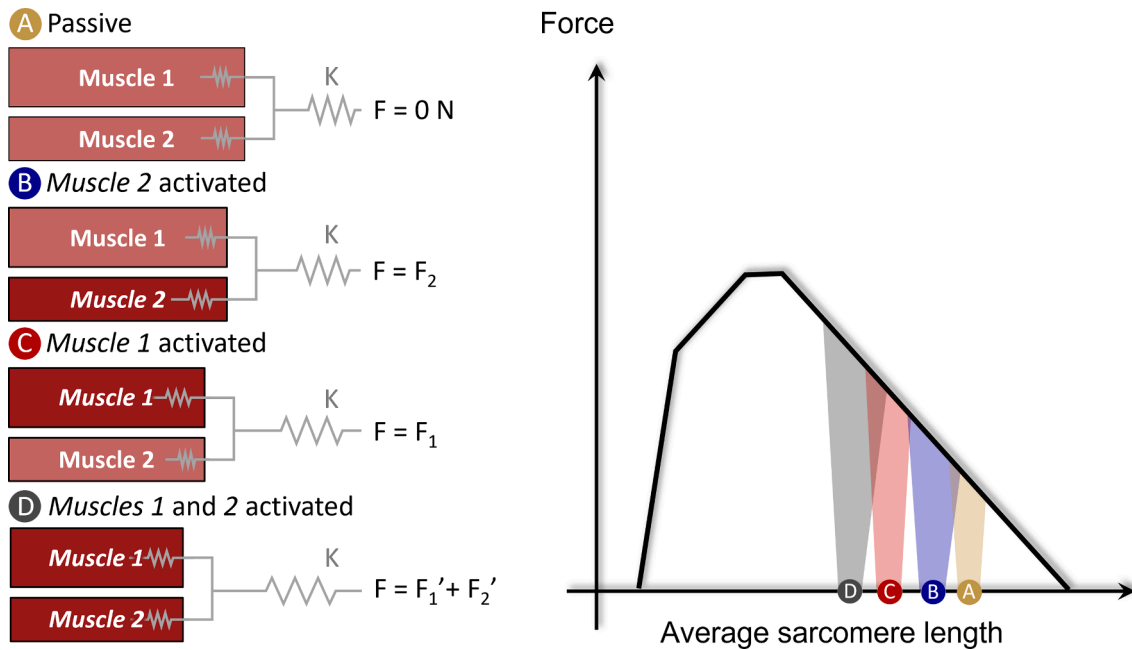


Fig. 5. Interactions between muscles can affect their force generating capacity. Here, we introduce the hypothesis that this effect is mediated by common series elasticity. On the left, a simplified model of the effect of common elasticity on force production (F) for different conditions of activation (A, B, C and D). Muscles 1 and 2 represent two muscles with different force generating capacities (muscle 1 is stronger than 2) that share a common elasticity, K : any elastic component that is stretched by the contraction of fibers in either muscle 1 or 2. F is the force measured at the distal insertion. On the right, hypothetical average sarcomere lengths of muscles activated for each condition. F_1 is different than F_1' , and F_2 is different than F_2' because average sarcomere length becomes shorter as F increases ($A < B < C < D$). Also, the sum of the force generating capacity in B and C ($F_1 + F_2$) is different than the force generating capacity in D ($F_1' + F_2'$) due to nonlinear summation of muscle forces. If muscle 1 and muscle 2 work on the descending limb of the force-length relationship (as exemplified on the right) the force generated when the muscles are activated simultaneously (D) can be expected to be greater than the sum of the forces produced when they are activated individually (as in C and B): note that, in D, average sarcomeres are shorter and working closer to optimal length when compared to C and B.

studies (de Brito Fontana et al., 2019, 2018; Tijs et al., 2014) found that the magnitude of nonlinear summation did not change across angles, despite the fact that the angular range evaluated included both the ascending and descending limbs of the torque-angle relationship.

In a follow up study (de Brito Fontana et al., 2019), alternative mechanisms for the nonlinear torque summation were tested. Intermuscular connections between the rabbit quadriceps muscles were removed with blunt dissection and tendon forces were measured simultaneously with joint torques. The results showed that nonlinear summation persisted after dissection (Fig. 6). Additionally, regardless of joint angle and intermuscular connections, the differences in torque during simultaneous activation and the sum of torques produced during individual activation of the quadriceps muscles were also observed for the directly measured force values, ruling out changes in moment arm as the reason behind the nonlinear summation.

Previous studies have shown that the capacity of a muscle to produce force can change when the muscle is compressed transversely. Siebert et al. (2014) demonstrated that increasing the transverse pressure exerted on the rat gastrocnemius muscle by a plunger (from 1.3 Ncm^{-2} to 5.3 Ncm^{-2}) resulted in an almost linear decrease in muscle force (from 4.8 % to 12.8 %) (Siebert et al., 2016, 2014). In order to explore the possible role of intermuscular pressure for nonlinear torque summation in the rabbit quadriceps, de Brito Fontana et al. (2019) systematically changed the intermuscular pressure by performing experiments at different levels of muscle activation. Contrary to their hypothesis, they observed that the absolute magnitude of nonlinear summation was independent of the force, and thus presumably the intermuscular pressure.

Studies that removed or released the fascial layers that enclose a muscle or groups of muscles within a compartment also have observed changes in force production. In the rat anterior crural compartment, a full lateral compartmental fasciotomy significantly decreased active

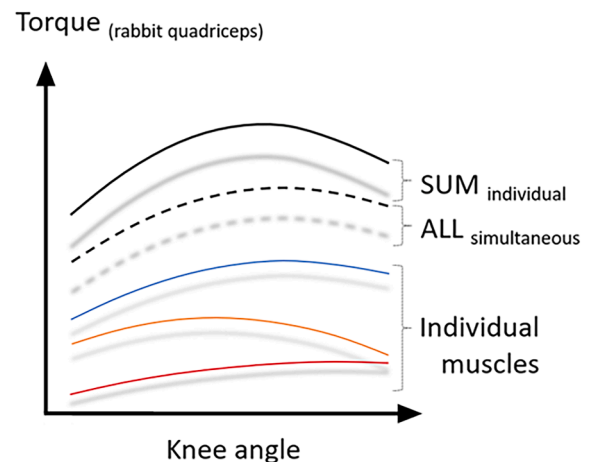


Fig. 6. Schematic representations of the nonlinear summation of torque in the rabbit quadriceps muscle for maximal contractions. Curves are based on the mean ($n = 10$) isometric torque normalized to peak torque (ALL) (adapted from de Brito Fontana et al., 2018) across 7 different joint angles. An increase in knee joint angle represents an increase in quadriceps muscle length. Note that the SUM of the individual torques is approximately 20 % higher than when ALL muscles are stimulated simultaneously. The shaded curves in the figure represent the effect of removing intermuscular connections (as observed by de Brito Fontana et al., 2019). While lower torques are found (curves shifted downwards), the shape and relative difference between SUM and ALL remains.

force and shifted the optimal fascicle length (Huijing and Baan, 2001a, b). Similar results were found for dogs (Garfin et al., 1981) with an accompanying reduction in intramuscular pressure. In the wing muscle in wild turkeys, the downward shift in the length-tension curve showed

that removal of fascia reduced maximum force output to approximately 2/3 of that in the intact condition (Ruttiman et al., 2018) confirming that the reduction in force at each angle could not be explained by a shift in the force–length relationship.

The mechanisms underlying the observations described in this section have not been fully clarified yet. However, these findings reinforce the limitations of the assumption that removal of a muscle from its surrounding does not affect its force generating capacity in a significant manner.

4.2. Experimental evidence from humans

Assessment of muscle length and/or forces in humans during surgical operations have offered possibility to examine the effect of soft tissue dissection (Freehafer et al., 1979; Smeulders and Kreulen, 2007) or cutting of tendon (tenotomy) on force–length properties (de Bruin et al., 2011; Kreulen et al., 2003). The results confirmed what had been shown in animal models: dissecting a muscle free from its surrounding connective tissue connections decreases its passive tension and can change the optimum length of active force production. Regarding tenotomy, de Bruin et al (2011) demonstrated in cerebral palsy patients that after the distal tendon of flexor carpi ulnaris is cut and not spanning over the wrist joint, it still contributes to the wrist flexion torque. In such a case, the only feasible explanation is that the force is transmitted via epimuscular pathways.

Another avenue of clinical research allowing evaluation of the role of epimuscular force transmission in humans is tendon transfer studies. In such an operation, impaired agonist muscles are supported by inserting a tendon from a donor muscle with the idea that it could then function as the agonist muscle. Smeulders and Kreulen (2007) transferred the tendon of flexor carpi ulnaris to extensor carpi radialis brevis and observed increased passive stiffness from force–length curves while the optimum region of the active force–length curve had moved to a shorter muscle length. The authors concluded that changes may be partially attributed to changes in intra-, inter- or extramuscular connective tissues. Studies where rectus femoris was transferred to function as knee flexor, showed the operation to be ineffective in transferring the function of the muscle; even after the distal tendon was attached to the posterior side of the knee, rectus femoris still acted as a knee extensor (Asakawa et al., 2002; Riewald and Delp, 1997). In such surgeries, the remaining intermuscular connections and post-operative scarring can influence the pathways of force transmission limiting the intended new function reflecting a disadvantage of epimuscular force transmission.

Non-invasive human experiments have typically utilized ultrasound imaging to observe muscle fascicle lengths or relative movement between synergistic muscles in order to make indirect inferences about epimuscular force transmission. In a situation where the ankle joint angle is kept unchanged and the knee is flexed in a passive condition, researchers have reported that the soleus muscle fascicles elongate slightly (~2 mm) but significantly while the gastrocnemius shortens (Tian et al., 2012). Additionally, the changes in soleus muscle fascicle length can depend on the site of measurement, being different in proximal (~1 mm shortening) and distal soleus (~2 mm lengthening) (Finni et al., 2017). This non-uniformity along the length of the soleus observed by Finni et al. (2017) may be related to differences in intermuscular connections in proximal and distal regions of the calf (Bojsen-Møller et al., 2004). With an MRI approach, inhomogeneities of fiber strain in medial gastrocnemius muscle upon change in muscle–tendon length in passive (Pamuk et al., 2016) or active (Karakuzu et al., 2017) muscle conditions have also been taken as evidence of epimuscular myofascial force transmission. However, validity of the reported inhomogeneities remain uncertain. Since *in vivo* assessments of individual muscle forces in humans pose technical and ethical challenges, direct inferences to force transmission cannot be made. However, the absence of direct observations does not necessarily mean that epimuscular force transmission could not occur and the observed changes in fascicle length are

expected to influence the force generating capacity of the muscle.

How much force do epimuscular pathways transmit in humans? The magnitude of intermuscular force transmission on passive force–length properties was estimated by Tian et al. (2012) with the assumption that gastrocnemius and soleus muscles act independently. They concluded that in passive conditions the magnitude of intermuscular force transmission is very small: 1–6 % estimated based on Tian et al. (2012) and Hoang et al. (2005). Further evidence for negligible intermuscular force transmission under passive conditions was reported between human thumb and index finger muscles (Diong et al., 2019) and between quadriceps femoris muscles (Freitas et al., 2019; Héroux et al., 2021; Yanase et al., 2021). Regarding other muscles, the reader is referred to a recent scoping review on epimuscular force transmission in humans (Ajimsha et al., 2022) but it should be critically considered which results provide actual evidence of force transmission.

Along with animal studies, there is also some evidence of activation-induced enhancement of epimuscular force transmission. By selectively stimulating gastrocnemius muscle at low activity level and observing movement at both sides of the interface between soleus and gastrocnemius muscles, Bojsen-Møller et al. (2010) observed the same tissue displacement in both soleus and gastrocnemius when knee was flexed. When the selective stimulation was done with the extended knee, or when knee was passively extended, there was relative displacement between muscles. Another study comparing passive and active conditions used a stretch protocol with and without selective electrical stimulation of lateral gastrocnemius muscle. Results showed activity-induced reduction in relative movement between soleus and gastrocnemius muscles, especially at a flexed knee position (Finni et al., 2017). At a longer muscle length with extended knee, it may require a greater force to show the effect because of already stiffer structures. Together these observations seem to suggest that also in humans, activation may facilitate epimuscular force transmission in some conditions (Fig. 7), but its role in normal human movement appears limited. However, other mechanisms should be considered including greater friction between muscles, or pressure-related effects.

5. Future considerations and conclusions

The reviewed research has shown that force transmission and interactions between synergistic muscles can affect force–length properties. Epimuscular pathways seem to be relevant for force production in pathological conditions where it may reduce peak tissue stresses and change force transfer in the presence of scar formation. Scarce evidence suggests a limited role in movement in physiological state. Follow-up experiments in animal models and humans are expected in the upcoming 50 years, specifically with the application of new techniques to estimate individual muscles forces *in vivo*. In addition, it has become clear to us while conducting this review that most of the evidence available has been obtained in experiments involving static muscle conditions, which has led us to focus on the isometric force–length relationship. As the tissues involved are viscoelastic, future experiments should be aimed at effects of epimuscular pathways on force–velocity properties.

Another avenue of research is the influence of adaptation of connective tissue structures on epimuscular force transmission. It is well known that aging, training, and disuse alter stiffness of the connective tissue structures but the associated effects on muscle mechanics via altered force transmission pathways are largely unknown. As an example, stretching is a typical condition that is thought to increase the joint range of motion by reducing passive tension in muscles and connective tissues. If stretching can alter the properties of connective tissues, or tissues associated with the neurovascular tract (e.g. Andrade et al., 2020), it may also have consequences for epimuscular force transmission.

The assumption of muscles as independent motors in the analysis of the mechanics of synergistic muscles crossing a joint was widely

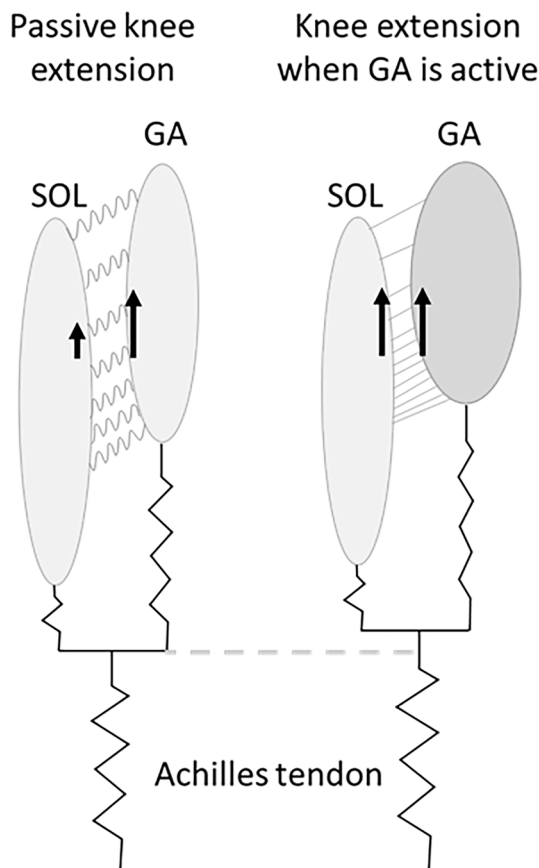


Fig. 7. Representation of the effects of knee extension on movement (vertical arrows) of mono-articular soleus (SOL) and bi-articular gastrocnemius (GA) when both muscles are passive (left) and when GA has been selectively activated via electrical stimulation (right). This phenomenon was observed at a flexed knee when applying 20° knee extension. Activation of GA elongates the tendon and can influence SOL via the shared spring (i.e., common elasticity) and via effects of epimuscular pathways. Bulging of muscle belly alters aponeurosis strain and increases compressive forces that may facilitate epimuscular force transmission (modified based on Finni et al. 2017).

accepted 50 years ago. Today, we know that this assumption is not correct, but the extent to which it leads to errors in the understanding of muscle function within its *in vivo* context is not yet clear. Muscles are, in their natural anatomical situation, intimately interconnected and packed within connective tissues, being subject to epimuscular interactions and to the effects of compression and common elasticity. The extensive connective tissue network in our body and the associated pathways have received increased attention in recent decades, often having implications to force transmission in clinical conditions. With this historical review, the increasing evidence of force transmission and interactions between synergistic muscles has been contemplated and future studies that incorporate these effects in the study of force production and associated applications in biomechanics are likely to have advantage over those that ignore them.

CRediT authorship contribution statement

Tajja Finni: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Resources, Writing - original draft, Writing - review & editing. **Heiliane de Brito Fontana:** Conceptualization, Data curation, Writing - original draft, Writing - review & editing, Visualization, Investigation, Validation, Formal analysis, Methodology, Resources. **Huub Maas:** Conceptualization, Data curation, Formal analysis, Investigation,

Methodology, Project administration, Validation, Visualization, Resources, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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