Muscle squelettique humain : caractérisation multi-échelle et modélisation multiphysique

Human skeletal muscle: multiscale characterization and multiphysics modelling

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RÉSUMÉ. Le muscle squelettique humain est un tissu vivant avec une architecture multi-échelle complexe. La caractérisation et la modélisation du muscle squelettique permettent d'obtenir des données utiles pour une meilleure compréhension de son comportement dans les conditions physiologiques et pathophysiologiques. De plus, de nouveaux biomarqueurs peuvent être extraits à partir de ces données pour l'aide à la décision clinique. Cet article a pour but, premièrement, de synthétiser les techniques expérimentales actuelles pour mesurer les propriétés musculaires à différentes échelles dans les conditions *in vitro* and *in vivo*. Deuxièmement, les modèles *in silico* actuels du muscle squelettique sont aussi présentés et discutés. Cet article fournit un panorama des techniques expérimentales and numériques pour étudier la biomécanique du muscle squelettique.

ABSTRACT. Human skeletal muscle is a living tissue with complex multiscale architecture. The characterization and modelling of skeletal muscle provide useful data for a better understanding of muscle behaviors in physiological and pathological conditions as well as novel biomarkers for clinical decision support. This review paper aims at, firstly, summarizing all cutting-edge techniques used for *in vivo* and *in vitro* characterization of skeletal muscle properties. Secondly, skeletal muscle modeling techniques were also addressed and discussed. This review paper provides an overview of current experimental techniques and numerical methods to study skeletal muscle biomechanics.

MOTS-CLÉS. Muscle squelettique humain, anatomie, physiologie, caractérisation, modélisation, biomécanique du muscle.

KEYWORDS. Human skeletal muscle, anatomy, physiology, characterization, modelling, muscle biomechanics.

1. Introduction to Human Skeletal Muscle

1.1. *Anatomy*

Skeletal muscle is a living material. It belongs to the musculoskeletal system of the human body. The musculoskeletal system of the adult human body includes 206 bones and approximately 640 skeletal muscles [CHI 03]. The skeletal system plays an important role in the protection of vital organs and supports the body structures during movements. Each muscle is attached into the skeleton via the tendon to move the skeleton at one or multiple joints. Each joint is defined by the connection between two adjacent bones. The joint movement allows the body to be moved in a coordination manner. The ligaments and cartilages contribute into the body stability during movements.

Skeletal muscle plays an important role as main motor in the static equilibrium and dynamic movements of the human body. Skeletal muscle has voluntary control while smooth muscle (e.g. blood vessels) and cardiac muscle have involuntary control. Muscle voluntary control mechanism includes activation and contraction states. The contraction patterns of each skeletal muscle depend on its shape. Skeletal muscles have different shapes such as circular (e.g. orbicularis oris muscle), convergent (e.g. pectoralis major muscle), unipennate (e.g. extensor digitorium muscle), non-fusiform parallel (e.g. sactorius muscle), bipennate (e.g. rectus femoris muscle), parallel-fusiform (e.g. biceps brachii muscle), and multipennate (e.g. dettoid muscle) (Figure 1.1). Skeletal muscle has multiscale architecture with fiber arrangement and orientation. Each skeletal muscle is composed of fibers (i.e.

cells). Each fiber is composed of myofirils. Each myofiril includes sarcomere and contractile proteins (actin and myosin) (Figure 1.2).

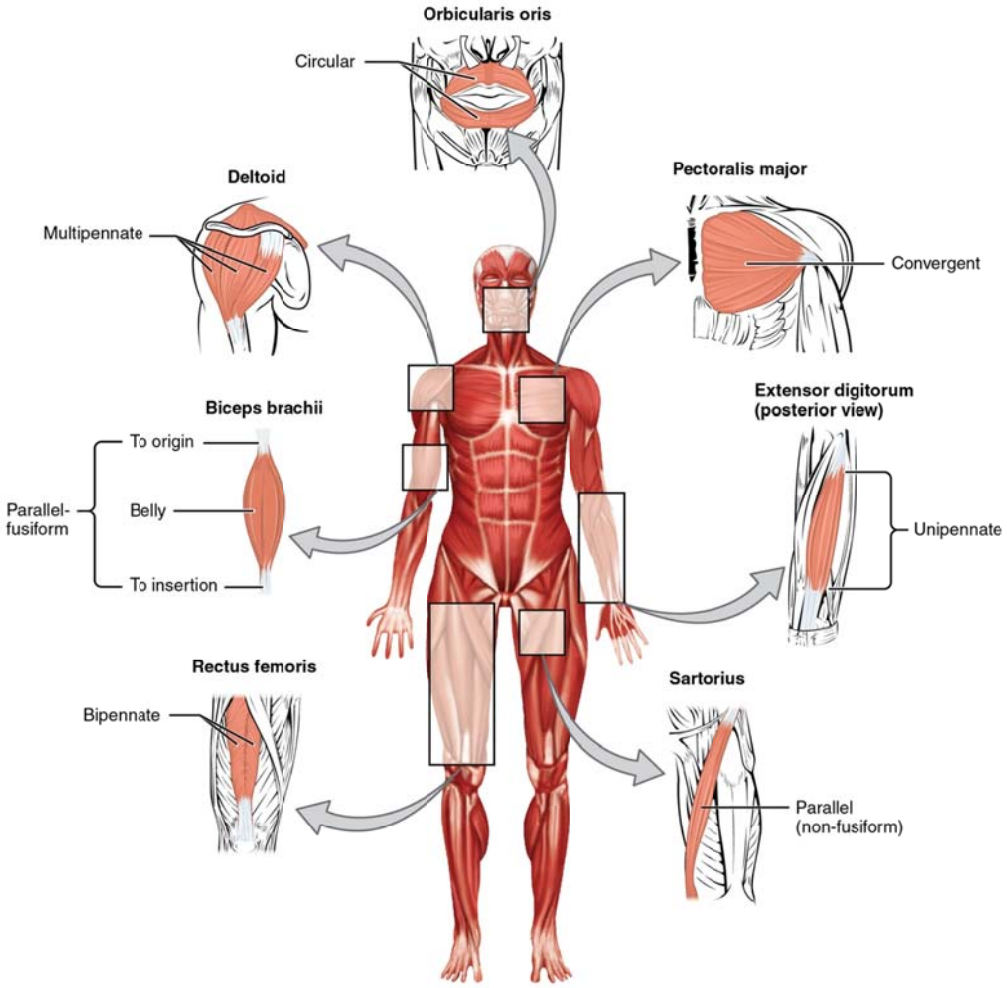

Figure 1.1. *Skeletal muscle shapes [OPE 16].*

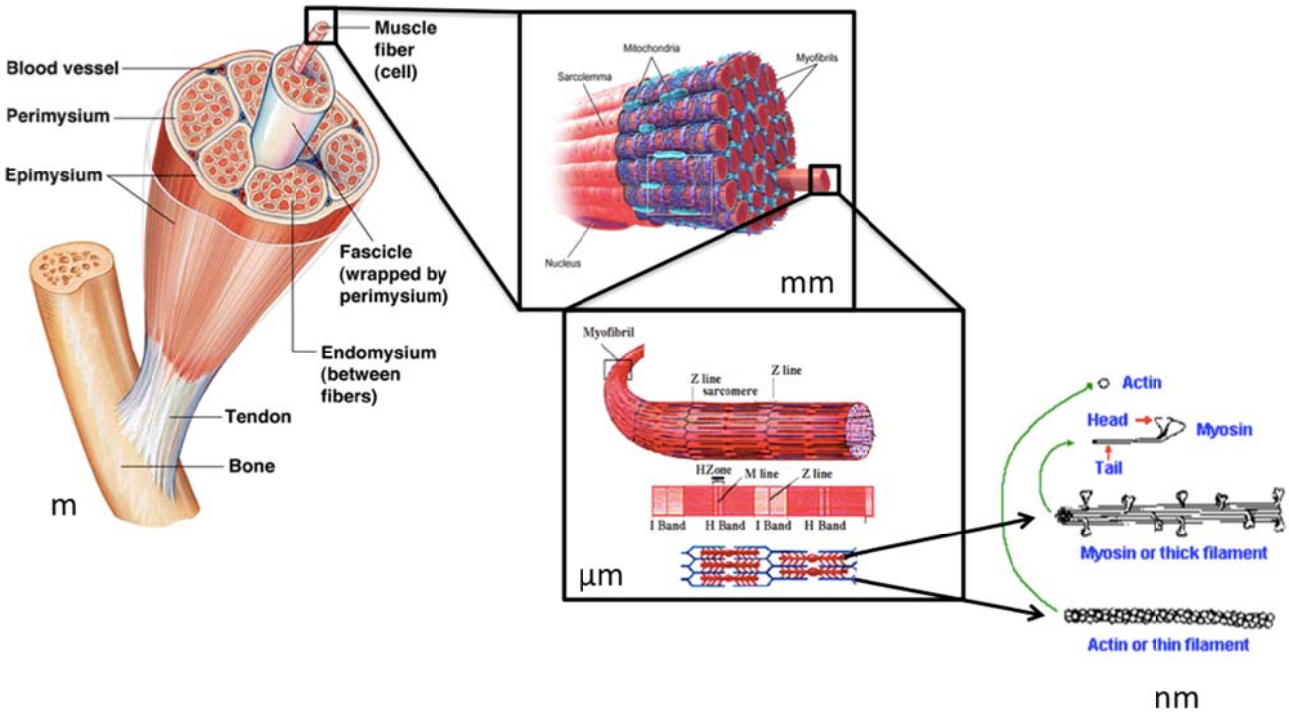

Figure 1.2. *Multiscale architecture of skeletal muscle: fiber, myofibril, sarcomere, and contractile proteins (actin and myosin) (adapted from Pearson Education Inc. 2009, Wikipedia, and [MAN 11]).*

1.2. *Physiology: activation and contraction*

Muscle activation mechanism is commanded and control by the nervous system (Figure 1.3). When a command is generated through motor neuron axons, multiple motor units (MU) are progressively activated to contract the muscle. This progressive recruitment mechanism is appeared in time and in space. The activation level depends on the MU's sizes and morphologies. The muscle force depends on number of recruited MU and their behaviors (e.g. firing rate or patterns). The action potential transmission allows the voltage-sensitive protein to change its shape to open calcium release channel. Then, calcium ions bind to troponin to change its shape allowing tropomyosin move to the actin side to enable the contraction process. Note that actin and myosin are main motorproteins of the skeletal muscle.

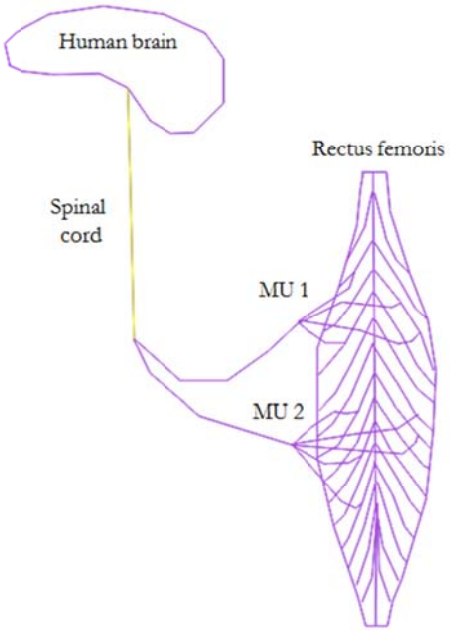

Figure 1.3. *Muscle activation by nervous control system: illustrative example for the rectus femoris muscle.*

Muscle contraction mechanism is appeared at the sacromere level (Figure 1.4(a)). Each myofiril is a contractile unit. According to the cross-bridge theory [NOB 77], muscle contraction arises from an interactive and cycling process between myosin and actine proteins to produce mechanical force. First, myosin reaches forward, binds to actin, contracts, and releases actin. Then, this protein reaches forward again to bind actin in a new cycle. Note that myosin filaments keeps their lenght constant while other regions of the sarcomere shortened (Figure 1.4(b)). There are two contraction types : isometric and anisometric. The muscle lenght is unchanged for isometric contraction while muscle lenght changes for anisometric contraction. If the muscle is shorten, it is a concentric contraction. If the muscle increses its lenght, it is a eccentric contraction.

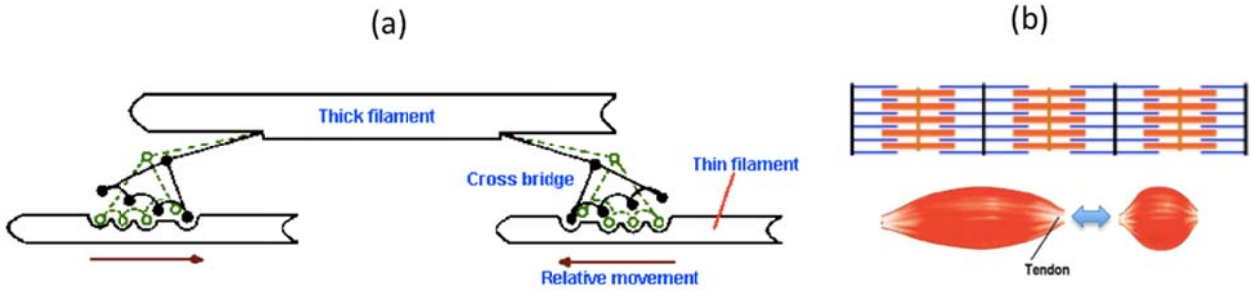

Figure 1.4. *Muscle activation arises from myosin-active interactive and cycling process (a) and its shorten effect on the sarcomere and muscle length change (b) (adapted from [NOB 77]).*

2. Objective

This paper aims at, firstly, reviewing all cutting-edge experimental techniques and numerical methods used for *in vivo* and *in vitro* characterization and modelling of skeletal muscle. Experimental techniques have been commonly used to measure morphological, functional and mechanical properties at entire muscle level, architectural properties at fiber level, micro-architectural properties at sarcomere level and contractile properties at protein level (Figure 2.1).

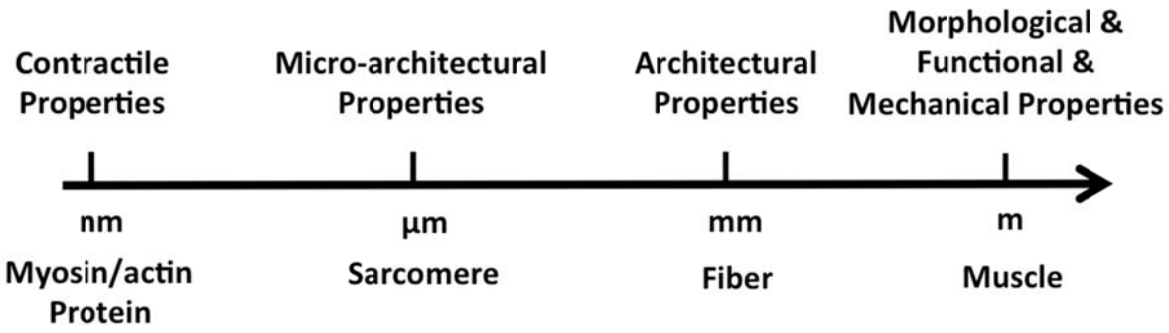

Figure 2.1. *Measurable properties of skeletal muscle across different length scales: morphological, functional and mechanical properties at entire muscle level, architectural properties at fiber level, micro-architectural properties at sarcomere level and contractile properties at protein level.*

In addition to measurable properties, other intrinsic properties (e.g. muscle force) may only be estimated using numerical simulation. Two computational appraoches have been commonly used. The first one relates to the estimation of muscle deformation using finite element method. The second one deals with the estimation of muscle force using rigid body modelling appraoch (Figure 2.2). In fact, the paper reviews also current muscle models and their perspective application.

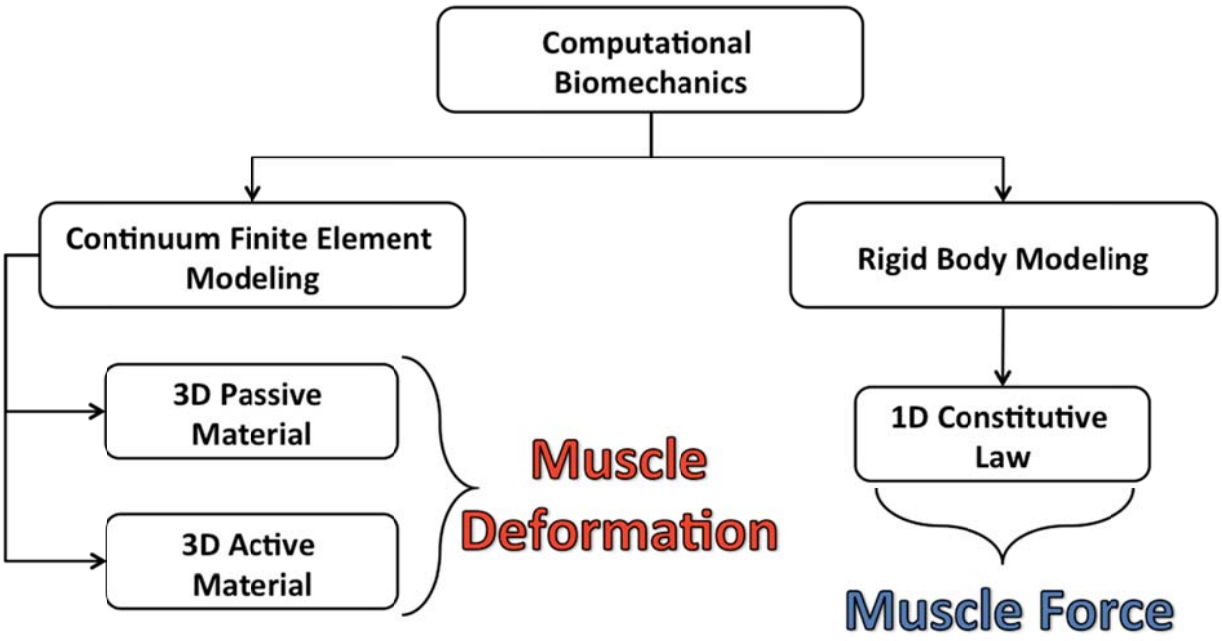

Figure 2.2. *Skeletal muscle modelling using computational biomechanics approaches.*

The next section summarizes all cutting-edge techniques used for *in vivo* and *in vitro* characterization of skeletal muscle properties. Then, skeletal muscle modeling techniques were addressed and discussed in section 4. Future research directions will be addressed in section 5. Finally, the conclusions will be given in the section 6.

3. Multiscale Characterization

3.1. *Morphological, functional and mechanical properties at entire muscle level*

3.1.1. *Morphological properties*

At the entire muscle level, morphological characterization of skeletal muscle has been studied in a important number of research projects. Muscle volume, muscle length, muscle thickness and physiological cross-sectional area (pCSA) are common morphological properties to be measured [ABE 15], [ALB 08], [DEB 11a], [HAS 11], [HOR 07] (Figure 3.1). Data ranges of values are reported for *in vivo* normal and pathological subjects as well as *ex vivo* cadaveric specimens. Medical imaging techniques like ultrasound, computer tomography (CT) and magnetic resonnace imaging (MRI) have been usually used for *in vivo* measurements. The *in vivo* measuring chain includes different steps: 1) image data acqusition, 2) image processing (filtering, segmentation and reconstruction), and 3) property extraction and computing. Manual or semi-automatic seggmentation has been commonly performed for skeletal muscle. Consequently, the image processing step is time-consuming for skeletal muscle. Note that due to complex nature of biological tissues, experimental and processing errors exist and need to be considered within the characterization process. For muscle disorders, a decreasing behavior of muscle volume is generally noted. Recent study showed evident non-uniform hypertrophy patterns of muscle volume for fast sprinting [HAN 16]. These data have been used for clinical decision support [GIL 16] and especially served as input data for numerical models [MOD 16].

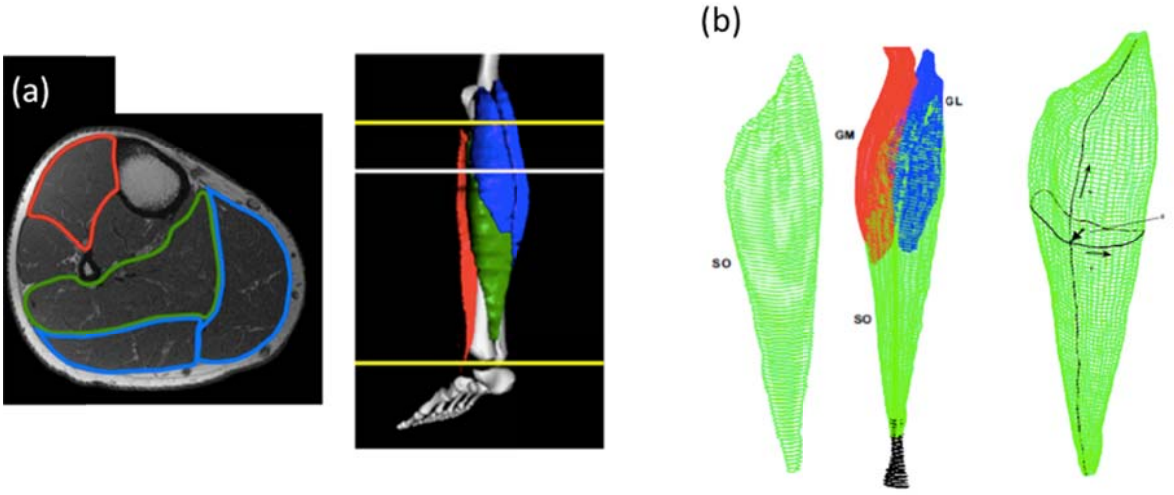

Figure 3.1. *Common morphological properties of skeletal muscle derived from medical imaging techniques (ultrasound, CT, MRI): volume (a) and pCSA (b) (adapted from [ALB 08], [HAS 11]).*

3.1.2. *Functional properties*

Muscle moment arm and contraction velocity are two common functional properties of the skeletal muscle (Figure 3.2). The *in vivo* measurement of these properties needs the development of specific advanced medical imaging sequences like dynamic MRI (dMRI) or real-time cine phase contrast MRI [ASA 03], [BLE 07], [CLA 15]. The muscle moment arm is defined by the length between the center of rotation at the joint spanned by the muscle of interest and the line of force along side this muscle. Note that this property may be estimated using numerical models [ARN 00]. Muscle contraction velocity is a quantitative indicator of skeletal muscle motion. This information may be used for analyzing muscle function in neurologic and musculoskeletal disorders. Moreover, motor unit recruitment patterns and amplitudes have been measured using electromyography (EMG) technique. Surface EMG allows a non-invasive measurement while intramuscular EMG allows a better precision but in an invasive manner [DEL 97].

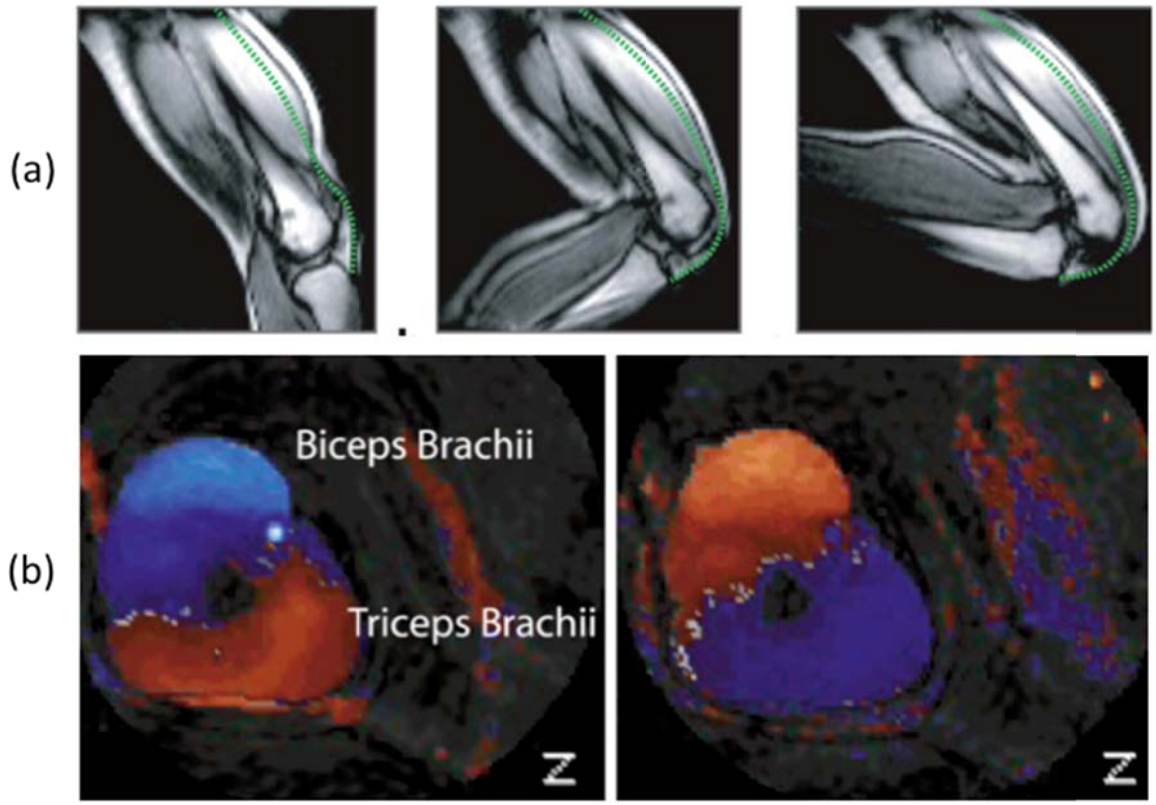

Figure 3.2. *Common functional properties of skeletal muscle derived from advanced medical imaging techniques: dynamic MRI for muscle moment arm (a) and real-time cine phase contrast MRI for muscle contraction velocity (b) (adapted from [ASA 03] and [BLE 07]).*

3.1.1. *Mechanical properties*

Mechanical properties of the skeletal muscle have ben commonly measured using ergometer and elastography techniques (Figure 3.3). In particular, ultrasound and magnetic resonance elastography have been used to quantify muscle anisotropy, viscocity and large deformation effects in passive and active states [BAS 02], [BAR 11], [DEB 11b], [BIL 15].

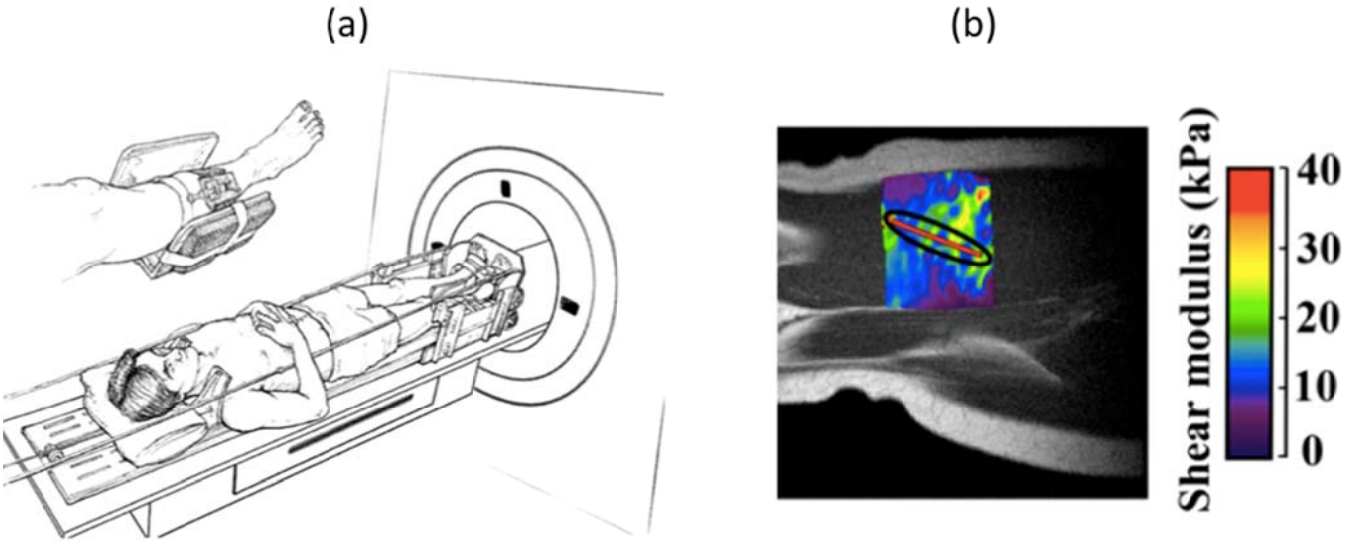

Figure 3.3. *Set up of a magnetic resonance elastography measurement (a) and an example of shear modulus map of the vastus medialis muscle) (adapted from [BAS 02] and [DEB 11b]).*

3.2. *Architectural properties at fiber level*

The *in vivo* quantification of archirectural properties of muscle fiber arrangement and orientation plays an important role in the development of accurate numerical models of the skeletal muscle. Current research studies have focused on the measurement of fiber length and fiber orientation angle using ultrasound technique [DEB 11a] (Figure 3.4). In particular, diffusion tensor imaging (DTI) has been used to track and visualize the muscle fiber distribution of the skeletal muscle [BLE 07], [HEE 09] (Figure 3.4). Recently, numerical methods like Laplacian vector field simulation may be also used to reconstruct skeletal muscle fascicle arrangements [CHO 13].

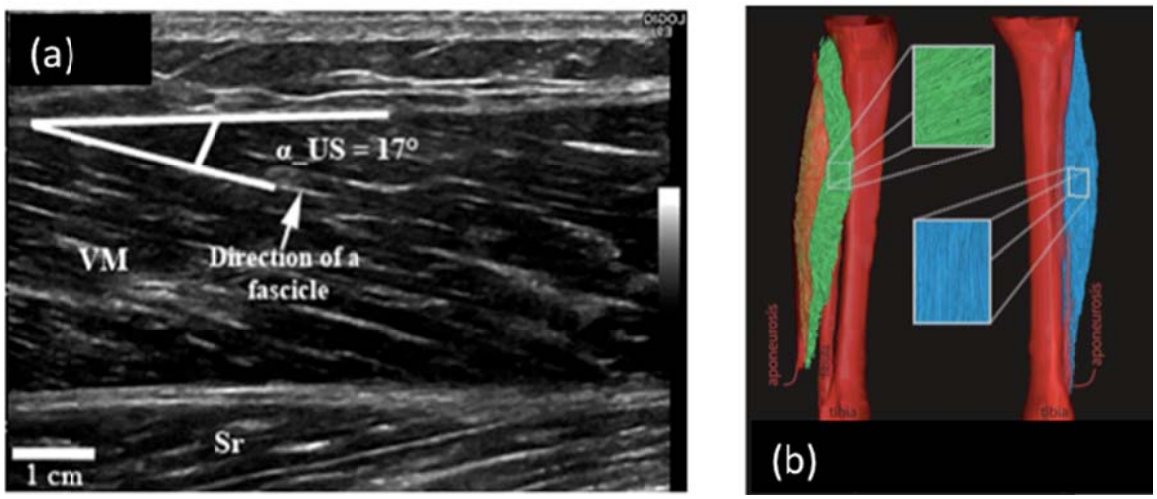

Figure 3.4. *Fiber-based architectural properties of skeletal muscle: ultrasound measurement of fiber pennation angle (a) andtensor diffusion MRI measurement of fiber distribution pCSA (b) (adapted from [DEB 11a] and [BLE 07]).*

3.3. *Micro-architectural properties at sarcomere level*

The *in vivo* measurement of the micro-architectural properties of the skeletal muscle at sarcomere level is particularly challenging. While sarcomere length in cadaveric specimen may be measured by laser diffraction technique [HOR 07], *in vivo* measurement may not be currently performed in a non-invasive manner. Recently, optical microendoscopy has been developed and used for measuring of sarcomere length in a minimally invasive manner [LLE 08] (Figure 3.5).

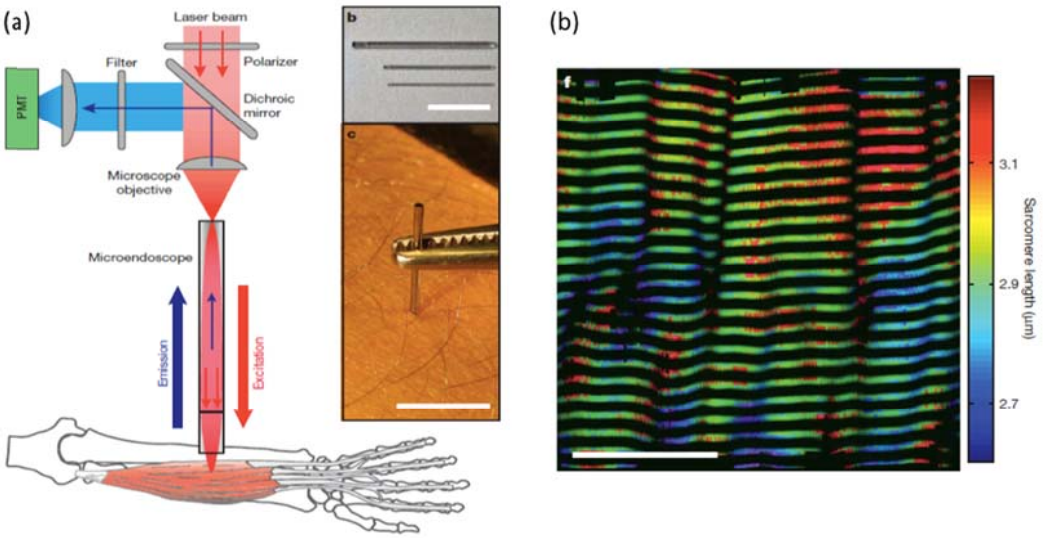

Figure 3.5. *Experimental set up for measuring sarcomere length using optical microendoscopy (a) and a map of measurement outcome (b) (adapted from [LLE 08]).*

3.4. *Contractile properties at protein level*

In vivo characterization of the skeletal muscle at the protein level is particuparly challenging. Recently, the motion of myosin protein has been visualized using high-speed atomic force microscopy (HS-AFM) technique [KOD 14] (Figure 3.6). This technique opens novel perspective to explore the mechanism underlying the myosin-actin interaction leading to a better understanding of muscle force generation capacity.

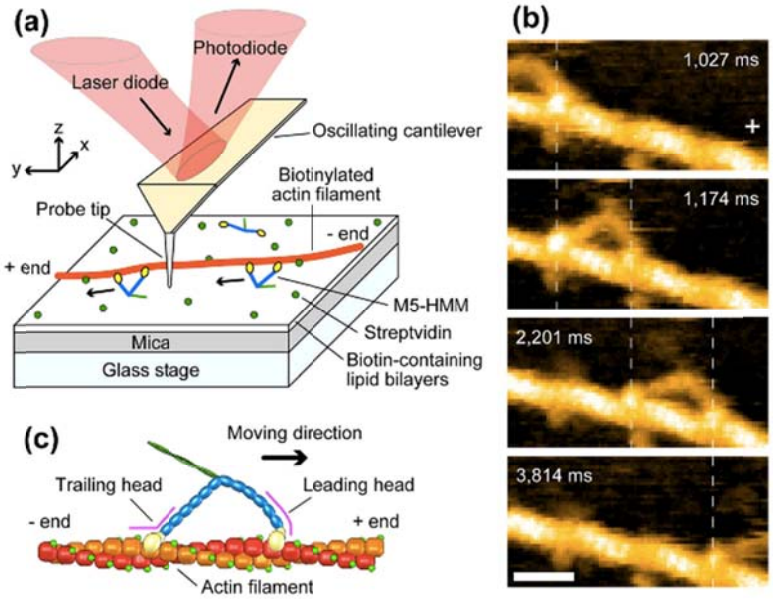

Figure 3.6. *Visualization of motion of myosin V protein using high-speed atomic force microscopy (HS-AFM) technique [KOD 14].*

3.5. *Genome editing for improving muscle function*

The development of the clustered regularly interspaced short palindromic repeat (CRISPR)/Cas9 tool opens new avenue for the study of muscle function in pathophysiological condition. In particular, genome may be cut at a specific location. Thus, existing genes may be removed and replaced by the new ones. The Cas9 nuclease delivering and appropriate RNAs guiding into a cell are essential steps to achieve this objective. This powerful tool was recently used to edit and manipulate the genome of the Duchenne muscular dystrophy (DMD) diease [NEL 16] (Figure 3.7). By modifying the dystrophin gene, the authors noted an improvement in muscle biochemistry and an enhancement in muscle force production capacity. This amazing biological toolbox will help to the reserve skeletal muscle diease symptom in a near future.

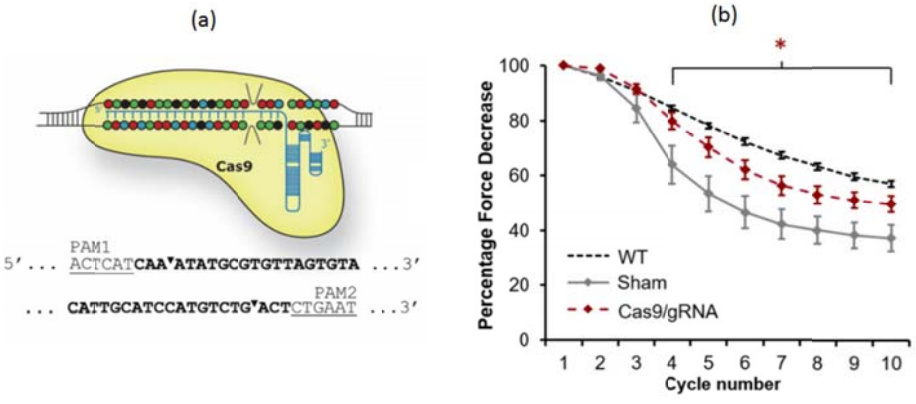

Figure 3.7. *Visualization of Cas9 nuclease targeting process (a) and muscle force enhancement outcome (b) [NEL 16].*

3.6. *Nanomachine: molecular muscle*

The development of advanced chemical processes leads to the creation of specific molecules with controllable motions as nanomachines. Thus, when adding appropriate energies, these nanomachines perform specific tasks. This original works related to the design and synthesis of these nanomachines has been recognized by the 2016 Nobel Prize in Chemistry[1]. In particular, a molecular muscle was synthesed (Figure 3.8) to mimics the contraction of muscle by allowing binding process between the myosin and actine proteins [JIM 00]. This biological molecular motor opens new and challenging avenue for the use of bionic systems in a large range of applications (e.g. healthcare, robotics)

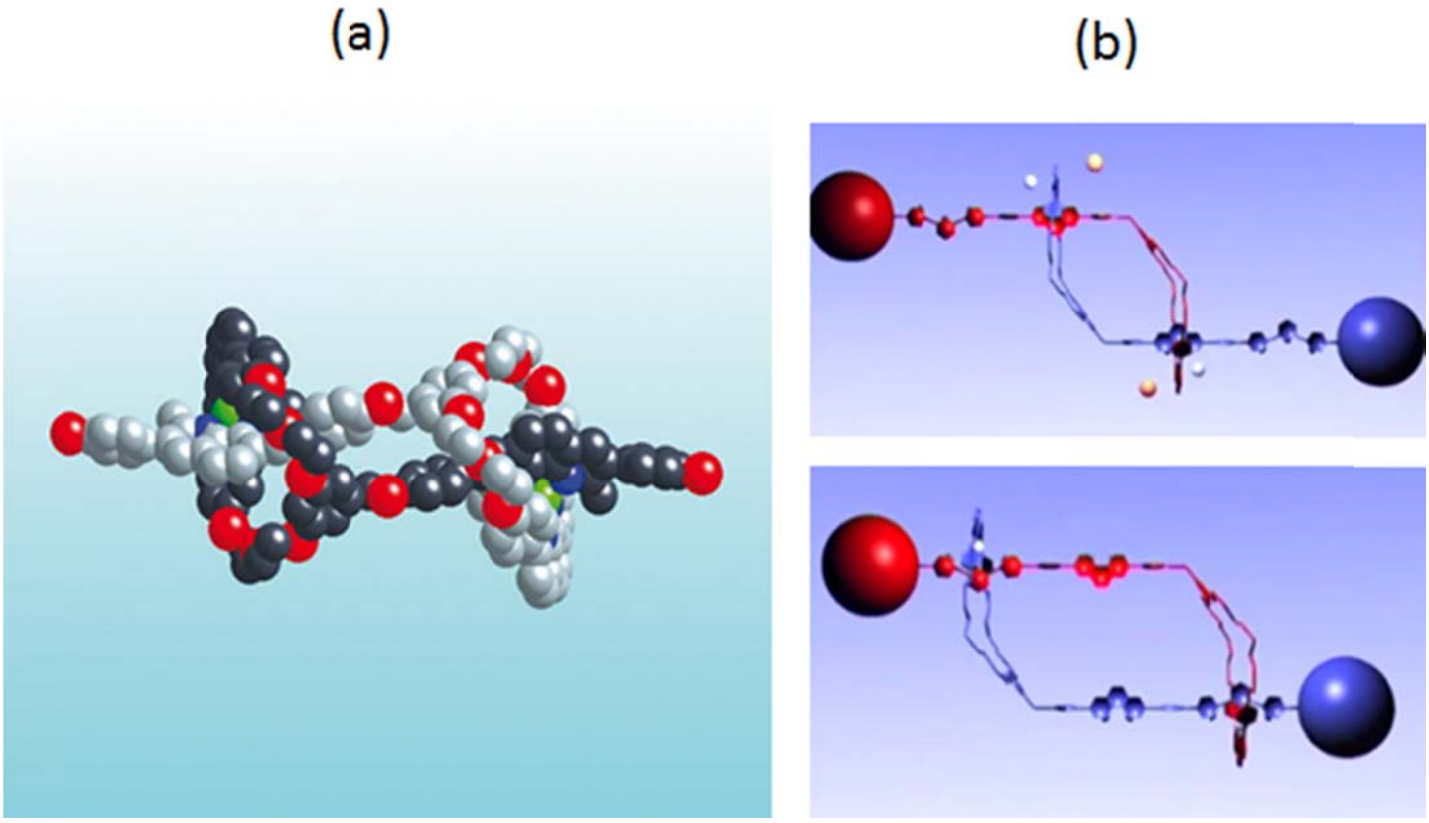

Figure 3.8. *Structure of a molecular muscle (a) and actin-myosin binding process (©Jean-Pierre SAUVAGE/CNRS photo).*

4. *In silico Multiphysics Modelling*

4.1. *Muscle force estimation using Hill-type model*

The estimation of skeletal muscle forces is a engineering challenge during the last two decades due to the lack of non-invasive experimetal technique to measure this mechanical indicator [DAO 12]. Different numerical approaches like inverse dynamics coupled with static optimization, forward dynamics coupled with static or dynamic optimization, and EMG-driven estimation have been developed to achieve such challenging objective. Hill-based rheological muscle model [HIL 38], [ZAJ 89] has been commonly used to describe the muscle behavior (Figure 4.1). Hill-type muscle model has 3 behavior curves such as the tendon Force-Length curve, muscle Force-Length curve, and muscle Force-Velocity curve. F_M and F_T are the muscle and tendon forces respectively. l_M and l_T are the muscle and tendon lengths respectively. l_{MTU} is the muscle tendon unit length. α is the muscle pennation angle, which is the angle between the muscle fibers and the tendon. An example of rigid musculoskeletal model to estimate muscle force using Hill-type muscle model is shown in Figure 4.2.

[1] https://www.nobelprize.org/nobel_prizes/chemistry/laureates/2016/press.html

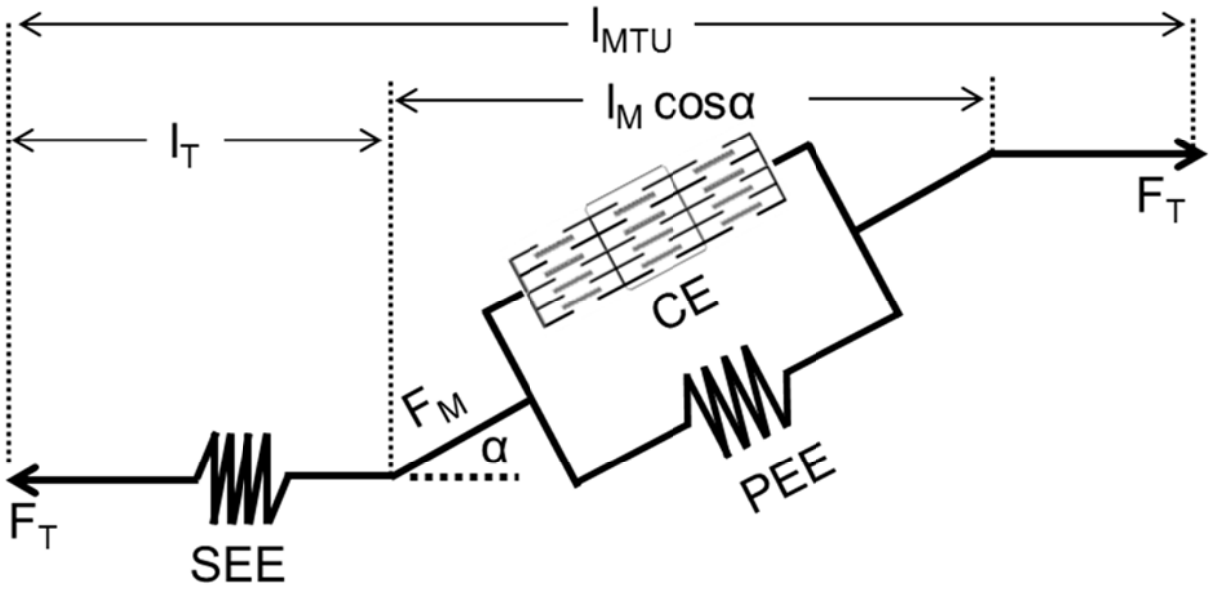

Figure 4.1. *Graphical representation of a Hill-based muscle model.*

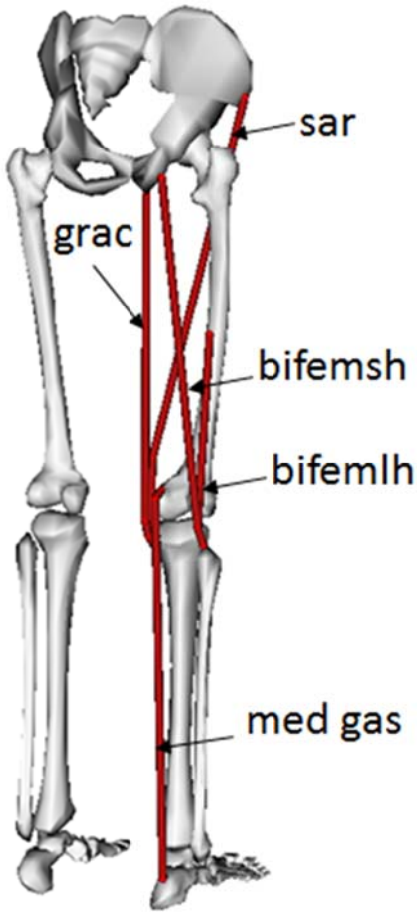

Figure 4.2. *Illustration of rigid musculoskeletal model of the lower limb to estimate muscle forces using Hill-type muscle models (e.g. Sartorius, biceps femoris).*

4.2. *Muscle stress and strain estimation*

To estimate skeletal muscle deformation and stress, finite element modeling has been used to study the 3D passive and active behaviors of the skeletal muscles.

4.2.1. *Skeletal muscle as a 3D passive material*

Hyperelastic and viscoelastic laws have been used to describe the passive behavior of the skeletal muscle [LLE 08], [DAO 14]. Constitutive equations of Neo-Hookean, Mooney-Rivlin and standard linear solid (SLS) materials are expressed as follows:

Neo-Hookean: $$U = C_{10}(I_1 - 3) + \frac{1}{D}(J-1)^2 \quad (1)$$

Mooney-Rivlin: $$U = C_{10}(I_1 - 3) + C_{01}(I_2 - 3) + \frac{1}{D}(J-\mathbf{1})^2 \quad (2)$$

SLS: $$\frac{d\varepsilon(t)}{dt} = (E_1 + E_2)^{-1}.\left[\frac{\sigma(t)}{dt} + \frac{E_2}{\eta}\sigma(t) - \frac{E_1 E_2}{\eta}\varepsilon(t)\right] \quad (3)$$

where U is the strain energy density function; I_1&I_2 are the first and second invariants of the left Cauchy–Green deformation tensor; C_{10}&C_{01}&D are material constants; J=det(F) is the gradient deformation tensor. σ is the stress and ε is the strain. E_1 & E_2 & η are the elastic modulus and the viscosity coefficients.

4.2.2. *Skeletal muscle as a 3D active material*

Description of active behavior of the skeletal muscle needs the developement of advanced muscle constitutive laws. Different formulations of transversely isotropic hyperelastic material have been proposed. Two common used formulations were established by [MAR 98] and [BLE 98] (Figure 4.3) (Tableau 4.1). Note that the homogeniation of sarcomere length and shortening velocities is a strong assumption for these models [HEI 14].

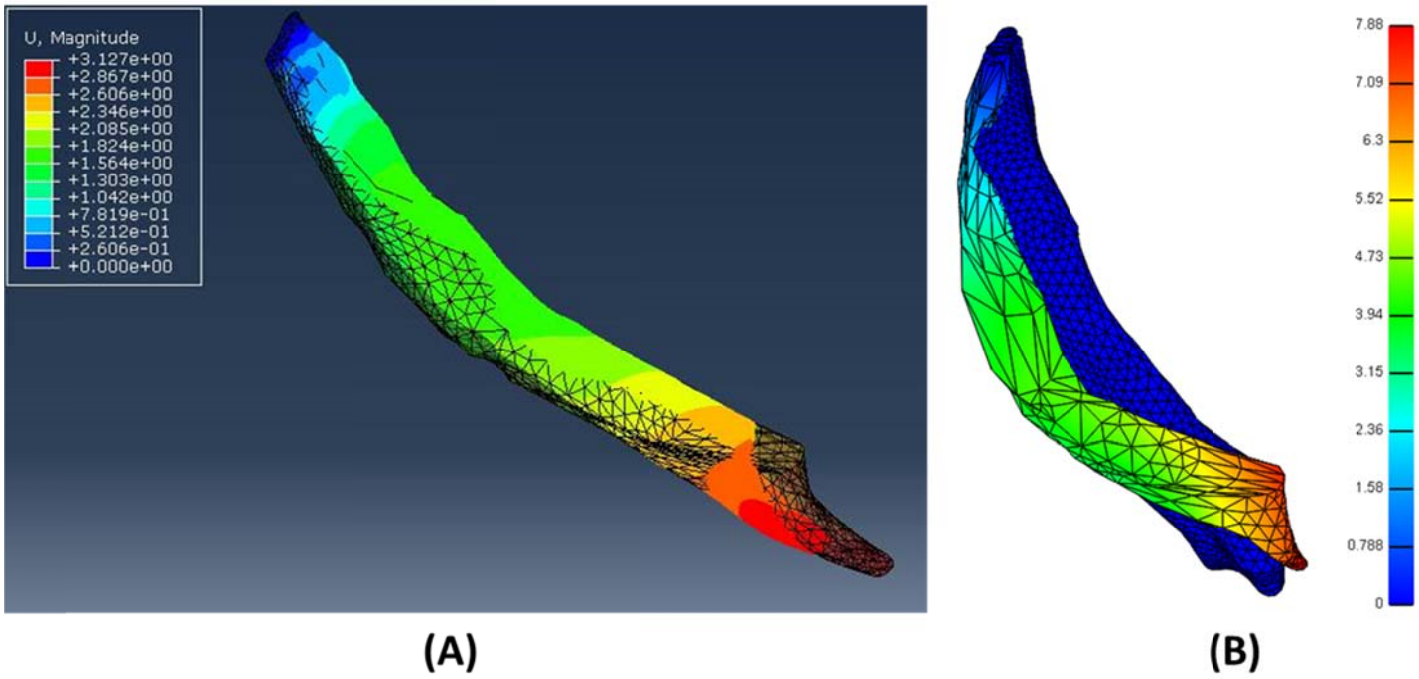

Figure 4.3. *Illustrations of zygomaticus major muscle contraction for smile expression from neutral position using Martins' law (A) vs. Blemker's law (B).*

	Constitutive equations and main parameters
artins model [MAR 98]	$U = C(e^{b(\overline{I_1}-3)} - 1) + U_f + \frac{1}{D}(J-1)^2$ $U_f = U_{PE} + U_{SE}$ $\alpha = 100; b = 1.79; D = 10^{-5} MPa^{-1};$ $C = 8.21 \times 10^{-4}\, MPa;\ \sigma_0 = 0.6688\, Mpa$ λ_f is the elongation of the muscle fiber ζ^{CE} is the contraction amplitude reflecting the muscle activation level
Blemker model [BLE 98]	$U = U_1(B_1) + U_2(B_2) + U_3(\lambda, \alpha) + \frac{K}{2} ln(J)^2$ $U_1(B_1) = G_1(\frac{\overline{I_5}}{\overline{I_4^2}} - 1)$ $U_2(B_2) = G_2(cosh^{-1}(\frac{\overline{I_1}\,\overline{I_4} - \overline{I_5}}{2\sqrt{\overline{I_4}}}))^2$ $P_1 = 0.05; P_2 = 6.6; \lambda^* = 1.4; \sigma_{max} = 3 \times 10^5 Pa; \lambda_{ofl} = 1.4$ $L_1 = 2.7 \times 10^6 Pa; L_2 = 46.4;\ \lambda^*_{tendon} = 1.03$ $G_1^{muscle} = G_2^{muscle} = 500\ Pa; K^{muscle} = 10^7 Pa$ $G_1^{tendon} = G_2^{tendon} = 50000\ Pa; K^{tendon} = 10^7 Pa$ P_3 and P_4 are defined so that $f^{fiber}_{passive}(\lambda)$ is C_0 and C_1 continuous at $\lambda = \lambda^*$; L_3 and L_4 are defined so that $\sigma^{tendon}(\lambda)$ is C_0 and C_1 continuous at $\lambda = \lambda^*_{tendon}$ λ is the along-fiber stretch α is the muscle activation level

Tableau 4.1. *Constitutive equations of the transversely isotropic hyperelastic material proposed by [MAR 98] and [BLE 98].*

Recently, a new formulation of constitutive law of the skeletal muscle has been proposed to couple mechanical behavior into electrical behavior for the excitation-dependent contraction of skeletal muscle [BOL 11]. Note that only a weak coupling with separate simulations has been performedfor this model [BOL 11] (Figure 4.4(a)). Moreover, a multiscale chemo-electro-mechanical skeletal muscle model has been also proposed [HEI 14] Figure 4.4(b). These novel models open new perspectives for the multiphysical modeling of the skeletal muscle. However, these models need too many paramters (> 50), which should be properly identified.

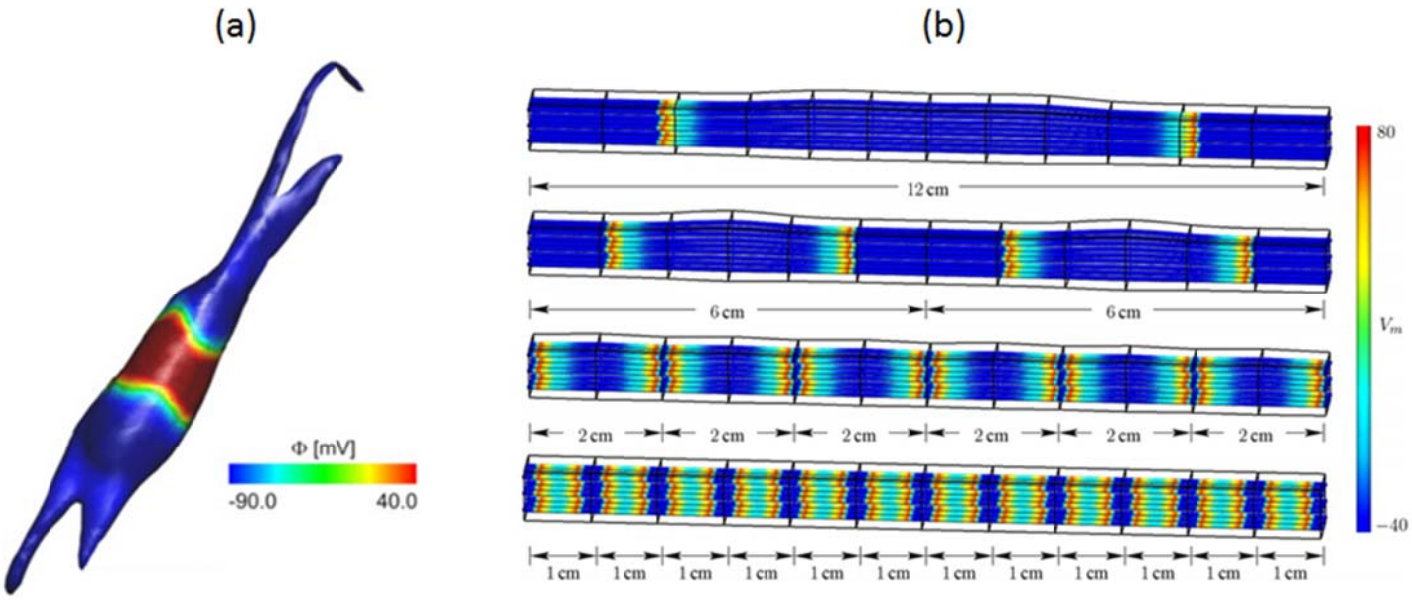

Figure 4.4. *Illustrations of electro-mechanical skeletal muscle model (a) and* multiscale chemo-electro-mechanical skeletal muscle model (b) (adapted from [BOL 11] and [HEI 14]).

5. Future research directions

The characterization of multiscale properties of the skeletal muscle provides evident facts and knowledge about its physiological and pathophysiological behaviors leading to a better understanding of the mecanisms underlying musculoskeletal movement impairments. It is well known that skeletal muscle is anisotropic, viscoelastic, inhomogeneous, nearly incompressible material with large deformation. Experimental techniques like MRI-based ones (conventional, cine phase contrast, dynamic, diffusion tensor, elastography), CT, ultrasound, or optical microendoscopy allows morphological (e.g. fiber and sarcomere length, pCSA, fiber architecture, moment arm), mechanical (e.g. shear modulus, viscosity) and functional (e.g. contraction velocity) properties of this living biomaterial to be quantitatively measured. However, there is no existing experimental technique to measure muscle deformation, stress and forces in a non-invasive manner. *In silico* modeling has been used to estimate such important muscle indicators. To estimate muscle deformation and stress, finite element modeling was used to study the 3D passive and active behaviors of the skeletal muscles. To estimate the muscle forces, rigid body modeling is used with 1D constitutive muscle law (e.g. Hill-based rheological model).

Despite many efforts done, the biomechanics of the skeletal muscle is still an open research challenge from experimental and numerical points of views. The visualization and measurement of the deformation and motion of muscles at entire muscle, fiber and sacromere levels using medical imaging need further developments of advanced imaging sequences and new imaging modes, especially for real time tracking and measurement. Research studies focusing on the measurement, using AFM method, or mimicking, via the design of molecular muscle, of contractile properties of the skeletal muscle at protein level should be done to provide a deeper understanding of the muscle activation and contraction mechanisms under myosin-actin protein interactions, especially in pathophysiological conditions. This information may be used to improve current multiscale chemo-electro-mechanical skeletal muscle model. Moreover, there is still a lack of a systematic multiscale characterization of the skeletal muscle to provide a single coherent and consistent data set. Furthermore, the charaterization of control mechanisms in the spinal cord, peripheral and central nervous system will elucidate the neural excitability characteristics and function. Finally, genome editing using CRISPR/Cas9 biological toolbox will change considerablely our understanding of skeletal muscle diease symptoms and provides a possible way to reserve these symptoms.

For the estimation of the skeletal muscle force using rigid body modelling approach, geometrical representation of the skeletal muscle needs to be improved. The line-of-action representation and one-dimensional rheological model (e.g. Hill-type model) are very limited to model the real biological skeletal muscle. Medical imaging techniques such as magnetic resonance imaging could be used to create 3D geometries of the muscle of interest. However, the time-consuming character of MRI data acquisition and processing needs to be overcome. Hill-type model is commonly used in the musculoskeletal models. This model integrates Force-Length and Force-Velocity relationships to describe the muscle contraction behaviors. Moreover, literature-based values are commonly used leading to inaccurate muscle force estimation. Consequently, experimental imaging techniques such as ultrasound and MRE could be used to compute individualized values for muscle properties. Furthermore, mechanical muscle properties need to be integrated into muscle model to simulate accurately muscle behavior, especially in the case of patient with muscle diseases. Moreover, individualized mono- or multi-objective function will avoid the dilemma of the 'true' choice of an appropriate function for a specific case. Electromyography signal could be integrated to develop EMG-driven musculoskeletal model to describe better muscle activities and behaviors. Another challenging issue will be the integration of 3D muscle constitutive laws to better describe the muscle behavior. Furthermore, the muscle-bone penetration problem needs to be improved. A dynamic muscle action line may be an innovative approach.

For the estimation of the skeletal muscle stress and strain using finite element modelling approach, the validation of novel models (i.e. multiscale electromechanical or chemo-electro-mechanical models) needs to be performed in a systematic way. Thus, novel experiments need to be designed to provide *in vivo* data for model calibration and validation. The coupling between advanced imaging sequence like diffusion tension MRI with transversely isotropic hyperelastic material should be investigated to improve the fiber architecture definition within skeletal muscle. Mechanical properties of the skeletal muscle need also to be integrated into constitutive laws to improve the muscle model accuraccy.

6. Conclusions

Biomechanics of the skeletal muscle is an amazing research topic. The progress of experimental and numerical technology has advanced the understanding of anatomy, physiology and function of the skeletal muscle. This review paper provides an overview of current experimental techniques and numerical methods to study skeletal muscle biomechanics from a multiphysical and multiscale points of view. Possible improvements were also discussed for future research directions. In fact, there are still rooms for improvement of the biomechanics of this interesting living material.

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