HIERARCHICAL MODELLING IN BIOLOGY: SYSTEMATIC BUILDING OF LIMB MODELS

Cs. Fazekas *,2 **Gy. Kozmann** *,** **K.M. Hangos** ***,1

* *Department of Information Systems, University of Veszprém, Veszprém, Hungary*
** *Department of Biomedical Engineering, Research Institute for Technical Physics and Materials Sciences, Budapest, Hungary*
*** *Systems and Control Laboratory, Computer and Automation Research Institute, Budapest, Hungary*

Abstract: A multi-level model, that provides a hierarchically structured description of a complex, multi-scale limb system is proposed in this paper for predicting and analyzing movement patters generated by various activation signals. The levels, the sub-models on each level and their interconnections are developed and described following a systematic modelling procedure.
The computational properties (degree of freedom and differential index) of the developed model have been analyzed and a sub-model has been transformed to meet the index-one requirement for solving the resulting differential algebraic equation (DAE) model by standard methods implemented in MATLAB.
The model is extensively verified against engineering expectations using parameter values found in the literature, and a good agreement was found. Parameter sensitivity analysis has also been performed.

Keywords: Biomedical system, model, hierarchical system, muscle, tendon, aponeurosis, pennation, sarcomere

1. INTRODUCTION

Most of complex biological and medical systems are inherently multi-scale systems. The reason for this is, that the modelling of these systems has its roots in physics, chemistry, biology and biophysics, thus the properties of models reflect the underlying time and length scales on which important phenomena occur. There is no matured way of constructing multi-scale models, but results are emerging in this important modelling paradigm that enable to systematically integrate sub-models of different origin into a multi-scale process modelling framework (Ingram *et al.*, 2004).

Human locomotion is a complex movement of a body. For a successful movement, interactions among muscular-skeletal system and central nervous system (CNS) are needed. Therefore, if one wants to create a realistic model of a limb, a number of different effects must be taken into account. This requires to model different, interrelated processes, such as biochemical processes, the material and structural properties of the muscles, force generation and skeletal system behavior, to mention just a few.

[1] Corresponding author: hangos@scl.sztaki.hu
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As one of the most important parts of any limb model, different muscle models exist in the literature that focus on one or more important aspects of muscle functioning (van der Linden, 1998). Unfortunately, however, most of muscle models deal only with a partial functioning of the muscle such as a force depending on the muscle length or muscle geometry or firing rates of nerves etc.

The other crucial component of limb models is the model that generates the exerting muscle forces, such as in (Hill, 1938), (Huxley, 1957), (Zahalak, 1981), (Duke, 1999).

There is an emerging flow of papers that report limb models based on a well-defined musculoskeletal and neuro-musculo-skeletal systems such as (Lim *et al.*, 2003), (Yakovenko *et al.*, 2004), (Gunter and Ruder, 2003), (Myers and Massone, 1997). The approach taken in (Laczko *et al.*, 1988) and (Laczko *et al.*, 2004) can be regarded as the starting point of our work because this model aims at generating limb movement patterns based on neuronal activity.

Based on the above, the need of integrating the already available partial models arise. Our aim is then to create a general framework for limb modelling that is able to describe the movement pattern based on the neuronal activation, molecular events, and muscle force exertion integrating partial models and defining interfaces between these models. In order to demonstrate the capabilities of our general framework a simple case study is used that integrates models known from the literature.

2. SYSTEM DESCRIPTION

The multi-scale nature of a detailed limb model is a consequence of a wide range of mechanisms that contribute to the movement and can only be described on rather different scales of sizes.

The input of the model consists of the activation signal or stimuling signal of each muscles as a function of time. Activation signal is, for example, the envelope of the EMG signal. Activation signals are normalized, i.e. their values are between zero and one.

The output of the model includes the joint angles, their velocities and accelerations (that together form a so called movement pattern) as a function of time.

2.1 Levels

The proposed hierarchical framework for limb modelling contains four levels that describe one or more important anatomical and/or physiological components of the limb and muscle (Cheng *et al.*, 2000), (Enoka, 2002), (Zatsiorsky, 2002). It is a multilevel model as depicted in Fig.1.

Level of sarcomere is responsible for the force generation according to its state and activation. This level should contain the molecular model of force generation and bio-chemical processes. In living muscle the strength of force depends on the length of sarcomere, velocity of contraction and activation.

Level of motor unit or fiber's function is the generation of force of motor unit from the forces of sarcomeres that are in the given motor unit. This level defines the passive forces of fibers. Here we assume that the motor unit contains the same muscle fibers and sarcomeres. It is why the motor units and fibers are not distinguished.

Level of muscle computes the forces and torques of muscles by integrating the forces of motor units belonging to the given muscle and computes the activation state of muscle from the input activation signal. Furthermore, this level models the effect of tendon, aponeurosis and pennate muscles. Three sub-levels are identified therein:

- Sub-level of muscle: this sub-level integrates the effects of motor units.
- Sub-level of tendon: this sub-level computes the effect of tendon.
- Sub-level of aponeurosis: this sub-level computes the effect of aponeurosis.

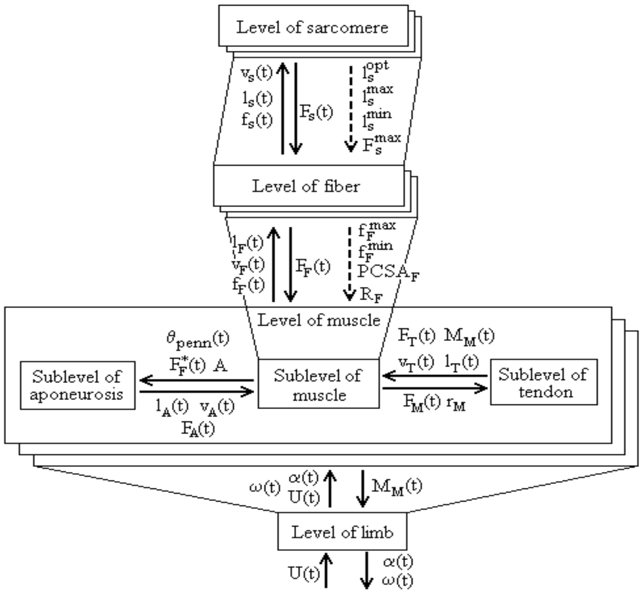
Level of limb is responsible for the computation of the movement of the limb if the torques of muscles of every joint are known. This level computes the joint angles, their velocities and their accelerations. It is also responsible for the realization of the intersegmental dynamics and gravitational effect.

2.2 Interfaces

In a multilevel model the interfaces between levels play a crucial role.

The interface between the level of sarcomere and the level of fiber contains four equations: the transformations of length, contraction velocity and activation of fiber into the length, contraction velocity and activation of sarcomere, and the transformation of force of sarcomere into the force of fiber. In addition, some parameters are also defined here: the computation of minimal, maximal, optimal length of fiber from the minimal, maximal and optimal length of sarcomere or vice versa, and the computation of maximal force of fiber from the maximal force of sarcomere or vice versa belong to this level, too.

The interface between the level of fiber and level of muscle contains four equations: the transforma-



Sarcomere	$v_s(t)$	[m/s]: contraction velocity of sarcomere
	$l_s(t)$	[m]: length of sarcomere
	$f_s(t)$	[Hz]: frequency of action potential in the level of sarcomere
	$F_s(t)$	[N]: exerted force of sarcomere
	l_s^{opt}	[m]: optimal length of sarcomere
	l_s^{max}	[m]: maximal length of sarcomere
	l_s^{min}	[m]: minimal length of sarcomere
	F_s^{max}	[N]: maximal force of sarcomere
Fiber	$l_F(t)$	[m]: length of fiber
	$v_F(t)$	[m/s]: contraction velocity of fiber
	$f_F(t)$	[Hz]: frequency of action potential in the level of fiber
	$F_F(t)$	[N]: exerted force of fiber
	f_F^{max}	[Hz]: maximal exciting frequency of the fiber
	f_F^{min}	[Hz]: minimal exciting frequency of the fiber
	$PCSA_F$	[m²]: physiological cross section area of the fiber
	R_F	[1]: recruitment order of fiber
Muscle	$\theta_{penn}(t)$	[rad]: pennate angle of muscle
	$F_F^*(t)$	[N]: force of muscle at the line of fibers
	A	[m]: area of the muscle
	$l_A(t)$	[m]: length of aponeurosis
	$v_A(t)$	[m/s]: contraction velocity of the aponeurosis
	$F_A(t)$	[N]: force of aponeurosis
	$F_T(t)$	[N]: force of tendon
	$v_T(t)$	[m/s]: contraction velocity of tendon
	$l_T(t)$	[m]: length of tendon
	$F_M(t)$	[N]: force of muscle
	r_M	[m]: moment arm of the muscle
	$M_M(t)$	[Nm]: torque of the muscle
Limb	$\alpha(t)$	[rad]: joint angle
	$\omega(t)$	[rad/s]: joint velocity
	$U(t)$	[1]: activation signal

Fig. 1. The structure of the hierarchical framework and the list of model variables

tion of length, contraction velocity and frequency of muscle into the length, contraction velocity and frequency of fiber, and the transformation of the force of fiber into the force of muscle. There are some parameter transportation equations in this level, too. The level of muscle has to know the physiological cross sectional area and the recruitment order of the fiber.

The interface between the level of muscle and level of limb contains twice as many equations as joints that describe the transformation of joint angles and joint velocities into the sum of joint angles and joint velocities and vice versa. It also contains the transportation of joint torque from the sub-level of muscle to level of limb and the transportation of activation signal from the level of limb to the sub-level of muscle.

Intra-level interfaces are within the level of muscle, the sub-levels have inter-level interfaces, too. The interface between the sub-level of muscle and the sub-level of tendon contains the transportation of the force of muscle and its moment arm from the sub-level of muscle to the sub-level of tendon and the transportation of the force of tendon, the torque of muscle, the length of tendon and the contraction velocity of tendon from the sub-level of tendon to the sub-level of muscle. The interface between the sub-level of muscle and the sub-level of aponeurosis contains the transportation of the pennate angle, the sum of force of muscle's fibers, the length of the fiber and the area of the muscle from the sub-level of muscle to the sub-level of aponeurosis and the transportation of the length, the contraction velocity and the force of aponeurosis from the sub-level of aponeurosis to the sub-level of muscle.

Our framework can handle limbs containing any segments, any number of muscles that rotate a given joint and any different kinds of fibers that belong to one muscle.

3. CASE STUDY: A SIMPLE LIMB MODEL

In order to demonstrate the capabilities of our general hierarchical framework for limb modelling, a simple case study is used that integrates the following models known from the literature:

- model of recruitment of motor units from (Cheng *et al.*, 2000),
- model of sarcomere, force-velocity relationship from (Dernyi and Vicsek, 2000),
- model of active force generation, force-length relationships from (Cheng *et al.*, 2000) that are similar to (Epstein and Herzog, 1998), (Huijing, 1998), (Laczko *et al.*, 2004), (van der Linden, 1998), (Yakovenko *et al.*, 2004), and force-frequency relationship being sigmoid function,
- model of passive force as in (van Soest, 1992) that is similar to (Laczko *et al.*, 2004),
- model of viscoelastic properties of tendon from (Epstein and Herzog, 1998),
- model of aponeurosis and pennate effect based on (van der Linden, 1998),
- model of limb dynamics by using well-known limb dynamic equations (Enoka, 2002), (Zatsiorsky, 2002).

In this case study the functions and the structure of the levels are the following:

Level of sarcomere gives the force-velocity relationship of the active force generation. This relationship depends on the concentration of P, ADP, ATP and their dissociation and association rates. It contains only algebraic equations.

Level of motor unit realizes the force-length and the force-frequency relationships since the used sarcomere model does not deal with them. It also realizes the passive force characteristic of the fibers. It contains only algebraic equations.

Level of muscle computes the joint torques and the properties of fibers belonging to the given muscle.

- Sub-level of muscle: It computes the exciting frequency of the fibers based on the recruitment order and the PCSA of the fibers. Joint torque is computed by integrating the torque of the muscle belonging to the same joint.
- Sub-level of tendon: realizes a viscoelastic tendon. It computes the torque of the given muscle.
- Sub-level of aponeurosis: a quadratic force-length characteristic is used. It is responsible for the computing of the uni-pennate effect of the muscle.

This level contains three differential equations (DE) for the length of the tendon, the length of the aponeurosis and the pennate angle.

Level of limb deals with the inertia properties of segments, the intersegmental dynamics and the gravitational effect using the following set of differential equations:

$$\theta \frac{d^2\alpha}{dt^2} = \mathbf{M} - \mathbf{V}(\alpha, \dot{\alpha}) - \mathbf{G}(\alpha) \tag{1}$$

where α is the vector or joint angles as a function of time, $\mathbf{M}$ is the vector of joint torques, θ is the chain inertia matrix, $\mathbf{V}$ is the vector of centrifugal and Coriolis terms and $\mathbf{G}$ is the vector of gravity terms.

Space limitation does not allow to present the simple limb model in its full details but it can be found (Fazekas *et al.*, 2004).

4. MODEL ANALYSIS AND VERIFICATION

Three type of investigations were performed:

- *Solvability analysis* that includes the investigation of degree of freedom and the differential index of the differential-algebraic (DAE) model on each level.
- *Model verification* when we check that the model behaves in a reasonable way, i.e. we check the model against engineering intuition.
- *Sensitivity analysis* to determine which parameters influence significantly the output of the model.

4.1 Solvability Analysis and Model Solution

Solvability analysis has been performed separately on each level. The results of the solvability analysis are as follows.

- The *degree of freedom* of each level is zero that implies a well-posed problem.
- The *differential index* of the DAE models of each level is one, except for the original form of DAE model on the level of limb taken from the literature (Enoka, 2002), (Zatsiorsky, 2002). Therefore, the DAE model on the level of limb was transformed into another algebraically equivalent form shown in Eq. (1) and its index had become one.

Our model has been implemented in MATLAB using the function *ode15s* for solution of the dynamic equations of the limb and function *ode45* for solution of the dynamic equations of tendon and aponeurosis.

4.2 Verification

Verification is completed using three test cases.

1. The verification of the joint torque generation was performed using a simple limb that is a skeleton containing one joint and two muscles as seen in Fig.2 in box *Limb*. The two muscles were excited with different kind of activation signal. We expected that the flexor muscle will increase the joint angle while the extensor will decrease it, and these effects become higher when the corresponding activation signal is higher. As shown in Fig.2 in box *Verification of muscles*, the expected effects were observed.

2. The verification of the gravitational effect was performed using a one-joint limb without muscles. The limb moved like a pendulum. The gravitational acceleration was changed and the frequency of the motion was observed. We expected that the frequency will increase while the gravitational acceleration is increased. Fig.2 in box *Verification of effect of gravitation* shows an example where a good agreement was found with the expectations.

3. Verification of the intersegmental dynamics was performed using a two-joint limb without muscles. In this case the state of one joint was changed and change of the motion of the other joint was observed. Here again, we observed a good agreement with engineering expectations.

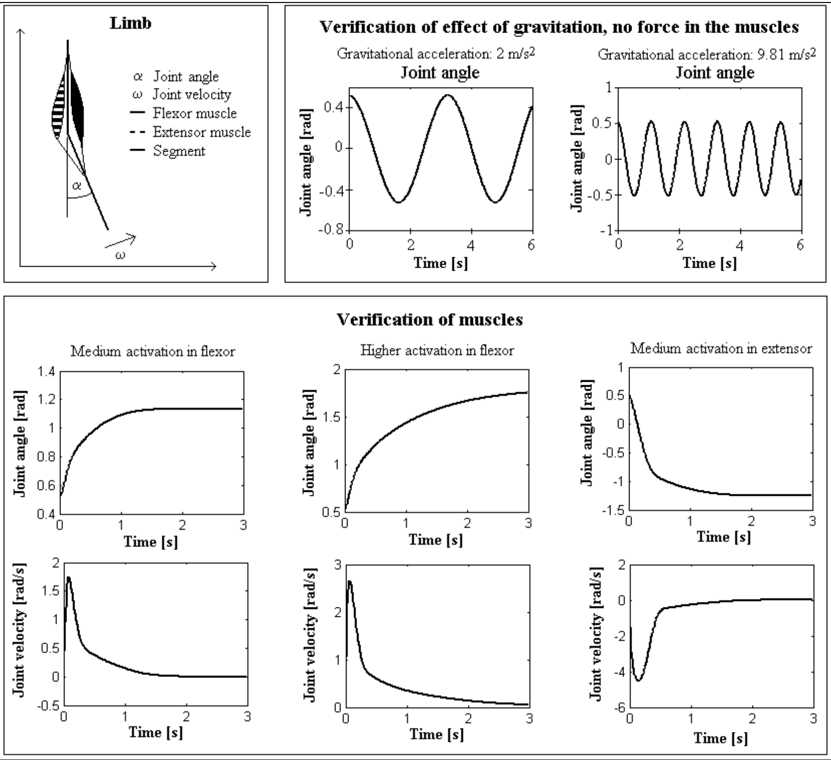


Fig. 2. Model verification results

4.3 Sensitivity analysis

The effect of the model parameters on the model output, i.e. on the movement pattern is investigated using sensitivity analysis. For this purpose we change the value of a parameter with ±10% from its reference value and the deviation of the movement pattern from its corresponding reference pattern was calculated. The change in the joint angle and joint velocity patterns were examined separately.

The results of the sensitivity analysis can be found in Table 1. Sign '-' means that the output is not sensitive to this parameter. (The list of parameters is given in the APPENDIX.) From the table we can conclude that the output is sensitive to

- the molecular events
- the structure of muscle (number of serially and parallel connected sarcomere),
- the activation signals
- most of the parameters of the force generation processes
- the tendons and the aponeurosis (the latter has larger effect)

Table 1. Sensitivity of the output to the parameters

Parameters	Sensitivity	Parameters	Sensitivity
k_{P-}	low	ω	middle
k_{P+}	low	β	middle
k_{ADP-}	high	ρ	middle
k_{ADP+}	low	f_{th}	high
k_{ATP+}	low	k_{tan}	-
$[P]$	low	l_{slack}	(high)
$[ADP]$	low	N_s	very high
$[ATP]$	low	N_p	high
U^{th}	very high	l_T^{slack}	high
r_m	high	D_T	very low
d^{dist}	high	C_T	very low
d^{prox}	high	l_A^{slack}	high
A	middle	$C_A, V_(A)$	low

5. CONCLUSION AND FUTURE WORK

An integrating multi-level hierarchical framework for limb modelling is proposed in this paper that can handle any kind of sub-models of the various mechanical, bio-mechanical and bio-chemical processes. Each level in the hierarchy represents a physiologically and/or anatomically important part of a real limb.

The use and usefulness of the proposed framework has been demonstrated by using a simple yet realistic model of a real two-segment limb. The computational properties of the developed model have been investigated and model verification has been performed. Sensitivity analysis has been used to identify model parameters that influence significantly the output movement pattern.

Further work is directed towards model parameter estimation from static and dynamical measurements. This requires model simplification based on sensitivity results and generating characteristic movement patterns (see Fig. 3) by using the detailed model.

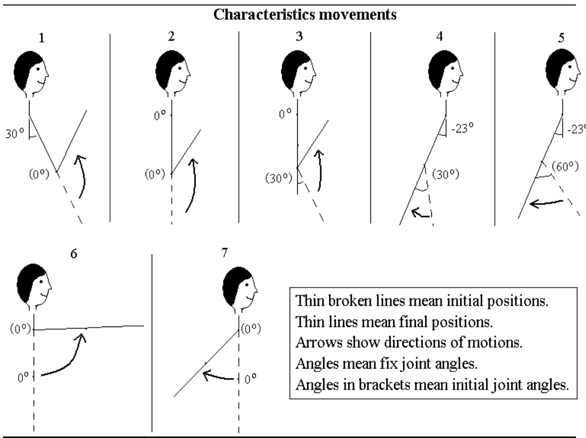


Fig. 3. Characteristic movement patterns

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6. APPENDIX: PARAMETER LIST

- Level of sarcomere
  - k_{P-} [1/s]: dissociation rate constant of P.
  - k_{P+} [1/Ms]: association rate constant of P to the AM complex (actin-myosin complex).
  - k_{ADP-} [1/s]: dissociation rate constant of ADP.
  - k_{ADP+} [1/Ms]: association rate constant of ADP to the AM complex.
  - k_{ATP+} [1/Ms]: association rate constant of ATP to the AM complex.
  - $[P]$ [M]: concentration of P.
  - $[ADP]$ [M]: concentration of ADP.
  - $[ATP]$ [M]: concentration of ATP.
- Level of motor unit
  - N_s [1]: number of serially connected sarcomere in the given fiber.
  - N_p [1]: number of parallel connected sarcomere in the given fiber.
  - ω [1], β [1], ρ [1]: parameters of *force-length of muscle* characteristics.
  - f_{th} [1]: normalized frequency where the half of the maximal force can be produced.
  - k_{tan} [1]: second parameter of *force frequency* characteristic.
  - l_F^{slack} [1]: passive slack length of the fiber.
- Level of muscle
  - U^{th} [1]: threshold activation level of muscle.
  - r_M [m]: moment arm of the muscle.
  - d_M^{dist} [m], d_M^{prox} [m]: distances between the distant or proximal attachment point and the rotated joint.
  - A [m^2]: area (or volume in 3D) of the muscle.
  - l_T^{slack} [m]: slack length of tendon in rest.
  - D_T [N/m]: spring constant of the tendon.
  - C_T [Ns/m]: effect of contraction velocity to the force of tendon. aponeurosis.
  - l_A^{slack} [m]: slack length of aponeurosis.
  - C_A [N/m^2], V_A [Ns/m]: force-length and force-velocity coefficients of the aponeurosis.