Modeling age-related neuromuscular changes in humans

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Abstract: With aging, motoneurons and muscle tissue undergo significant changes, which influence function in terms of strength, mobility, and overall independence. Mathematical modeling provides a practical method of studying the relationships among recruitment, rate-coding, and force output in motor units, and may be used to predict functional neuromuscular changes related to aging. For this study, the Heckman–Binder model was used to examine changes in human quadriceps motor units. Relationships among current input, firing frequency, and force output were defined for both a younger and an older individual. Included in the model were age-related effects associated with reduced muscle contractile speed; reduced muscle-fibre number, size, and specific tension; reduced gain of the frequency–current relationship; decreased size of motoneurons; and altered motor unit remodeling. Adjustment of this model to reflect age-related changes resulted in a leftward shift of the force–frequency function, lower firing frequency for any given current injected into the motoneuron, and a reduction in maximal force output. The model suggests that older individuals are capable of reaching force levels up to approximately 50% of those attained by younger individuals, with relatively similar or even slightly lower levels of current input. This could mean that the sense of effort and the contribution of factors other than degree of effort from afferent inputs to the pool, including conscious supraspinal centres, might be different in the older adult.

Key words: aging, strength, muscle, motoneuron, force, quadriceps, effort.

Résumé : Des modifications significatives au niveau des motoneurones et du tissu musculaire sont observées au cours du vieillissement; ces changements ont un effet signifiant sur la force musculaire, la mobilité et l'autonomie globale. Les modèles mathématiques sont pratiques quand il s'agit d'analyser la relation entre la sommation spatiale, la sommation temporelle et la production de tension des unités motrices; on peut les utiliser comme prédicteurs des modifications neuromusculaires associées au vieillissement. Pour cette étude, le modèle de Heckman et Binder a été utilisé pour examiner des changements des unités motrices du quadriceps fémoral humain. On détermine tant chez un jeune individu que chez un plus vieux la relation entre l'arrivée du courant, la fréquence des potentiels d'action et la tension produite. On intègre dans le modèle les variables suivants : les effets dus à l'âge concernant la diminution de la vitesse de contraction musculaire, la diminution du nombre de fibres musculaires, de leur calibre et de leur tension spécifique, la diminution du gain dans la relation fréquence-courant, la diminution de la taille des motoneurones et la restructuration des unités motrices altérées. Quand on teste ce modèle en fonction des modifications observées avec l'âge, on observe un déplacement vers la gauche de la fonction tension-fréquence, une diminution de la fréquence des potentiels d'action pour tout courant donné aboutissant au motoneurone et une diminution de la tension maximale produite. D'après ce modèle, les personnes âgées peuvent produire jusqu'à 50 % de la tension maximale produite par les jeunes en envoyant un courant de même intensité ou légèrement affaibli. Cela signifie que la sensation de l'effort et que la contribution des facteurs autres que le courant aboutissant au pool, y compris ceux des centres supramédullaires, pourraient différer chez les personnes âgées.

Mots-clés : vieillissement, tension musculaire, muscle, motoneurone, force, quadriceps, effort.

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Introduction

As our knowledge of the neuromuscular system continues to grow with information gained from basic science and clinical studies, researchers have also developed mathematical models and computer simulations in attempts to further understand aspects of this physiological system. More than 50 years ago, the first theories proposing a sliding filament structure in skeletal muscle were developed (Huxley and Niedergerke 1954; Huxley 1953); since that time, numerous models have been developed to study a variety of different aspects related to muscle and its neurological connection. For example, models have been developed to investigate re-

lationships among force output, recruitment, and rate-coding (Fuglevand et al. 1993; Heckman and Binder 1991; Moritz et al. 2005; Taylor et al. 2002); muscle activation, fatigue, and recovery (Liu et al. 2002); and the effects of electrical stimulation (Davidson et al. 2006; Perumal et al. 2006; Wexler et al. 1997).

A primary purpose of developing simulations is to quantitatively analyze the effects of changing parameters and assumptions of the system being modeled. In studying muscle and motoneuron properties, it is difficult to record information from more than the few motor units in close proximity to electrodes in human and animal studies. Therefore, motor unit models provide a practical method for studying the relative influence of recruitment and rate-coding, and for predicting force output from an entire motor unit pool. Although many studies have identified changes that affect skeletal muscle and its activation with aging (e.g., reduction in size and current threshold of motoneurons, reductions in the number of muscle fibres, atrophy of remaining fast-twitch fibres, and slowing of contractile speed), the relative influences of each of these changes on force production have not been simulated in a comprehensive model.

In 2003, Thelen (2003) developed a model to investigate age-related effects of reduced contraction velocity and increased noncontractile tissue on the force–velocity and force–length properties of muscle during concentric contractions. While this model was found to generate simulated ankle torque results consistent with those measured in healthy older adults, the focus was strictly on muscular changes with aging, and age-related alterations associated with neural activation were not included. In comparison, Barry et al. (2007) incorporated motor unit data gathered from experiments on the first dorsal interosseus muscle in older adults to investigate the relationship between variability in discharge rate and force steadiness with aging. Although this model included some parameters related to muscle activation, few motoneuron properties were represented. Heckman and Binder (1991) developed a model based on motoneuron activation properties and frequency–current relationships for low- and high-threshold motoneurons. The model consisted of a pool of 100 simulated motor units for which steady-state neural and mechanical properties were matched to experimental data for cat medial gastrocnemius motor units. It was designed to predict whole system motor input and force output functions based on single unit data for cats, and has since been modified to describe a similar application in rats (Gardiner 2001). However, it has not been previously used to describe motor unit characteristics in humans. As well, it has not been used to predict age-related changes to motor unit output.

The objectives of this study were to modify the model developed by Heckman and Binder (1991) to make it representative of human neuromuscular properties, based on available literature, and to incorporate typical age-related neuromuscular changes to determine the effects on force output for the aged condition. The quadriceps muscle was used in the model because it is one of the most thoroughly studied in terms of age-related strength and morphological changes (see review by Roos et al. 1997), and it is functionally important in terms of contributing to the ability to sit, stand, walk, and climb stairs, which are fundamental to maintaining mobility.

Materials and methods

The model originally developed by Heckman and Binder (1991) was used as the foundation for this study. It was developed to quantitatively study the relationship between synaptic input and force output for an entire pool of motor units during steady-state conditions. The Heckman–Binder model incorporated motoneuron excitability, tetanic force, twitch/tetanic properties, and contractile speed factors, along with rate-coding and recruitment properties required to generate isometric contractions. Simulations were based on experimental data gained from studying the medial gastrocnemius muscle of the cat. The motoneuron input to force output relationship was modeled for a pool of 100 motor units, based on motoneuronal frequency–current (f-i) and muscle unit force–frequency (F-f) relationships (for examples, see Figs. 1B and 1A, respectively). Motoneuronal f-i functions were modeled using the following parameters: current threshold for repetitive firing at steady state (I_{thres}), firing frequency at current threshold (f_{thres}), gain (slope) of the f-i relationship (G_1 in the primary range of firing and G_2 in the secondary range of firing), and the firing frequency at the transition from primary to secondary firing ranges (f_{trans}). Isometric F-f functions of the muscle unit were described by the following parameters: maximal tetanic force (F_{max}), a frequency constant related to the speed of contraction and the left–right position of the F-f curve (T_f), and an exponent (P) used to transform the exponential F-f function to a sigmoidal function to better describe the relationship between force and frequency (Erim et al. 1996; Kernell 1983; Kernell et al. 1983).

F-f curves were generated for each motor unit using the following formula (Heckman and Binder 1991):

$$F = F_{max} \times \left(1 - e^{(-\text{frequency}/T_f) \times P} \right)$$

Readers are directed to review the original work of Heckman and Binder (1991) for a more detailed explanation of the model.

The model applied to a human motoneuron pool

Existing experimental human data were used (when available) to generate a human application representative of the quadriceps muscle in a younger person. The model was run in Microsoft Excel 2003. Justifications for adjustments to model parameters are explained below.
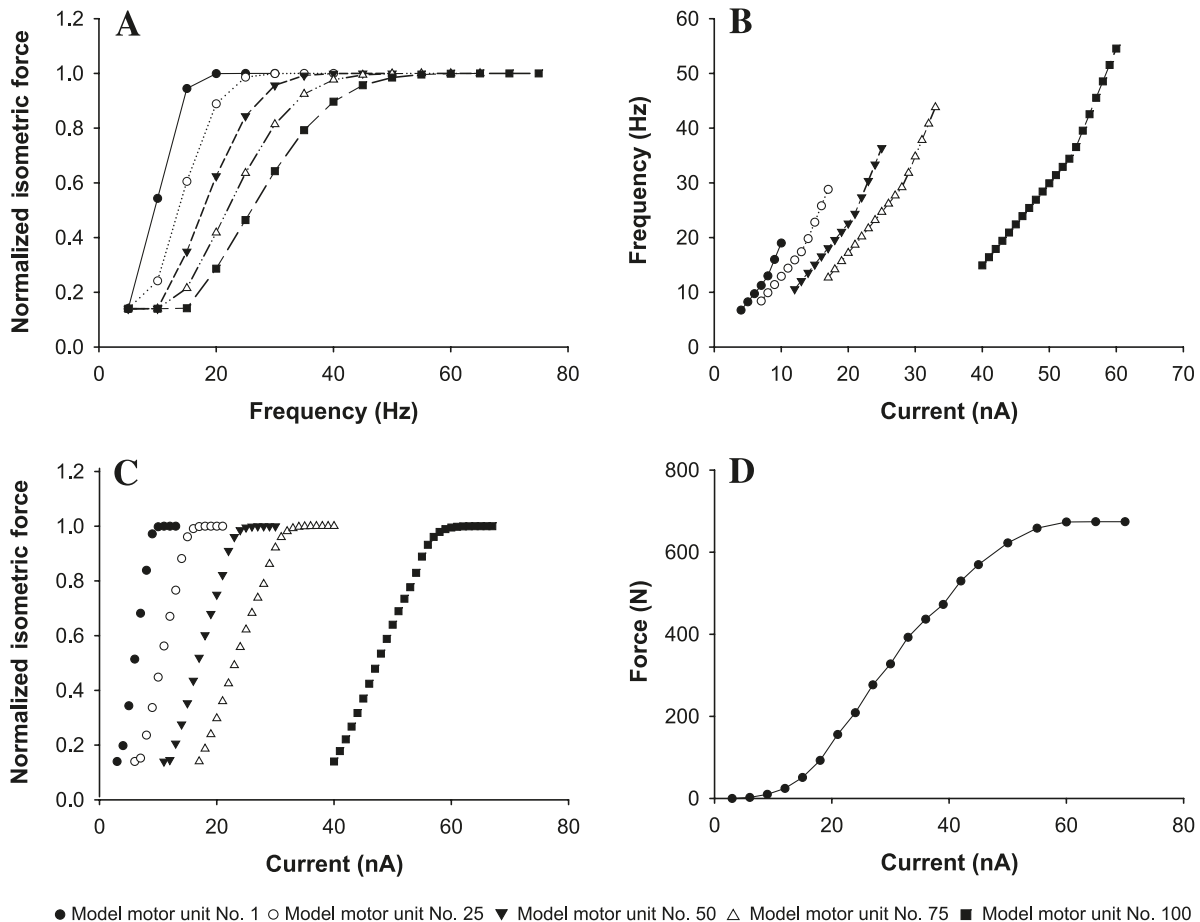
I_{thres}

Because there are no human data available describing rheobase or rhythmic firing thresholds of motoneurons, current threshold values in the younger human model were not modified from those used in the cat motoneuron model. The current threshold was set to vary from 3.5–40 nA, in agreement with experimental results from the cat and rat (Bakels and Kernell 1994; Baldissera et al. 1987; Munson et al. 1997).

f_{thres}

In the human model, the frequency threshold was set to increase linearly with recruitment threshold, but values were set slightly lower (approximately 6–15 Hz.) than those found in the cat model. This is consistent with the firing rates ob-

Fig. 1. Representative force–frequency relationships (A), frequency–current relationships (B), and force–current relationships (C) for model motor units. Force was normalized to maximum tetanic force for each motor unit (A and C). (D) Whole muscle force (N) vs. current (nA) injected into the entire motoneuron pool.

● Model motor unit No. 1 ○ Model motor unit No. 25 ▼ Model motor unit No. 50 △ Model motor unit No. 75 ■ Model motor unit No. 100

served in tibialis anterior motor units in younger people (Erim et al. 1996; Van Cutsem et al. 1997). To our knowledge, no data are available describing frequency thresholds for low- and high-threshold motor units in the quadriceps.

G_1 and G_2

Because there is no evidence to suggest that the gain on the excitatory drive–firing rate relationship differs in humans, G_1 and G_2 values from the cat model were used.

f_{trans}

In the cat motoneuron model, the firing frequency at the transition between primary and secondary firing ranges occurred at 80% of maximum force levels for individual motor units (Kernell 1979). For the human model, values for f_{trans} were set to 50% of the cat values (12.5–35.3 Hz.) to account for the lower mean firing rates in humans than in cats (Hornby et al. 2002).

F_{max}

Absolute tetanic force levels were scaled in increasing proportion exponentially to create a 100-fold range between the tetanic force produced by the lowest threshold motor units and force produced by the highest threshold motor units, as has been supported by work in humans (Milner-Brown et al. 1973; Stephens and Usherwood 1977; Van Cut-

sem et al. 1997). Values were adjusted so maximal stimulation of the entire motoneuron pool would result in a force output close to 650 N, which has been measured for the quadriceps muscle in younger people (Allman and Rice 2004; Roos et al. 1999). For simplicity, the model was generated for a pool consisting of 100 motor units, but in actual fact, the 4 muscles that constitute the quadriceps group likely each consist of a few thousand motor units (Lexell et al. 1988; Ling et al. 2007).

T_f and P

The T_f and P formulae include a value for the twitch/tetanus ratio. This constant was set at 0.08 in the cat model, but was changed to 0.14 for the human model, based on data from human quadriceps muscle (Scott et al. 2006).

Specific age-related changes incorporated into the model

Based on physiological changes associated with aging, model parameters were adjusted in simulations of the motoneuron pool to represent properties that would be found in an older adult (70–80 years of age).

Reduced muscle contractile speed

For the entire pool of motor units, values for the frequency constant related to the speed of contraction (T_f) were reduced to account for slowing in contractile speed

and changes in the *F-f* relationship that have been demonstrated to occur with aging (Allman and Rice 2004; Roos et al. 1999). The majority of researchers have reported longer contraction and half-relaxation times in older adults (see review by Roos et al. 1997), although not all researchers have found this (Trappe et al. 2003). Results vary substantially, with contraction duration reportedly being 3%–72% slower in older adults. One study that specifically examined properties of the quadriceps muscle from older men demonstrated that time to peak tension lengthened by 11% in men 73–91 years of age, compared with the younger group (19–35 years of age) (Roos et al. 1999).

Reduced muscle unit strength

Maximal force generation capabilities for individual motor units were reduced in a linear fashion; there was a 2% reduction in maximal force potential for each successive group of 5 motor units to represent changes related to loss of numbers of muscle fibres, reductions in size of fibres (preferentially affecting fibres in the high threshold motor units), and reductions in specific tension levels.

Studies have demonstrated that muscle-fibre numbers are reduced with age (Lexell et al. 1983, 1988). In comparing quadriceps vastus lateralis total muscle-fibre number between individuals in their 20s and 70s, Lexell et al. (1988) found a 40% reduction with age, which increased to 50% when younger individuals were compared with those in their 80s. Because preferential loss of a specific type of muscle fibre would result in altered fibre-type proportions with age, studies have examined relative changes in numbers of slow- and fast-twitch muscle fibres. However, while a number of biopsy studies have examined fibre-type proportions in the vastus lateralis muscle in younger and older subjects, the results are conflicting (Grimby et al. 1984; Larsson et al. 1979; Lexell et al. 1988; Trappe et al. 2003). Fibre-type proportions can be influenced by changes in fibre size, histochemical profile, and fibre number. As summarized in review papers by Porter et al. (1995) and Roos et al. (1997), at least part of the reason for the reportedly variable effect of age on muscle-fibre numbers may be related to the fact that biopsy results are not always representative of changes across the entire muscle. However, data from cross-sectional analyses of whole muscle suggest that the loss in number of muscle fibres does not differ between fibre types (Lexell et al. 1988; Lexell and Downham 1992).

Along with declining muscle-fibre numbers, muscle-fibre sizes also decrease with age, with type II fibres demonstrating the most significant reductions. As summarized in reviews by Vandervoort (2002) and Porter et al. (1995), a large range of quadriceps muscle-fibre size reductions has been noted in the literature. While type I fibres have demonstrated size reductions in the range of 1%–25%, type II fibres have shown greater atrophy, in the range of 10%–60%.

The majority of studies, although not all (Trappe et al. 2003), have found that specific tension (force expressed relative to muscle physiological cross-sectional area) also decreases with age. Studies have demonstrated that for the quadriceps muscle, specific tension is 14%–34% lower for people aged 65–85 years than for those aged 20–43 years (Frontera et al. 2000; Larsson et al. 1997; Yu et al. 2007). Contrary to these findings, Trappe et al. (2003) found similar force per cross-sectional area results among younger and older women and men, and suggested that changes in specific tension with age may be limited to those with a particular activity profile. Despite possible debate about changes in specific tension with age, reductions in overall strength with age are well established. Although changes in absolute total muscle strength seem to be relatively minor until approximately 50 years of age, strength decreases at a rate of 1.0%–1.5% per year as people continue to age (Larsson et al. 1979; Vandervoort and McComas 1986). Peak isometric force levels for the quadriceps have been reported to be 31%–48% lower in older men (aged 70 years and older) than in younger men (Allman and Rice 2004; Roos et al. 1999; Young et al. 1985).

Reduced motoneuron gain

For the older model, G_1 and G_2 were reduced by 36% and motoneuron current threshold was reduced by 25%, as has been suggested by rat experimental data. No data are currently available to describe age-related changes in gain of the *f-i* relationship in humans because of the invasive nature of this measure. However, studies on rat motoneurons suggest that values for G_1 and G_2 are 36% lower in older animals (Kalmar et al. 2008). As well, older motoneurons are smaller and exhibit approximately 25% lower current thresholds in experiments on rats (Kalmar et al. 2008) and cats (Morales et al. 1987); however, human data are not available.

Loss and sprouting of motor units

To represent changes related to loss of motor units and re-innervation of some fast-type muscle fibres with low-threshold motoneurons, the model was adjusted so that 30% of the motoneurons were lost. As well, based on the work by Pettigrew and Gardiner (1987), low-threshold motor units were made larger (i.e., capable of producing greater amounts of force) and high-threshold motor unit size was not changed. Although denervation, axonal sprouting, and re-innervation of muscle occur throughout life as part of a regular motor unit remodeling process at neuromuscular junctions, with age this process is modified. While some motor units are simply lost, it is believed that some type II muscle fibres may be re-innervated by sprouting axons from low-threshold motoneurons, with subsequent conversion of muscle-fibre types from fast to slow (Howard et al. 1988; Kanda and Hashizume 1989; Stalberg et al. 1989). The overall result is a reduction in total motor unit number, with the possibility that remaining motor units consist of a greater number of muscle fibres in older people than in younger people (Doherty et al. 1993). Human studies have estimated the motor unit number loss to be about 50% in subjects over 60 years of age (Brown et al. 1988; Tomlinson and Irving 1977). As well, it has been demonstrated in the quadriceps muscles of older men that there are unusually high incidences of muscle fibres containing more than 1 myosin heavy chain isoform, which is consistent with the process of denervation and re-innervation (Klitgaard et al. 1990).

Table 1. Key model parameters representative of younger human quadriceps motoneuron pool.

Motor unit No.	I_{thres} (nA)	G_1	G_2	Frequency threshold (Hz)	Frequency transition (Hz)	Force max (N)	T_f	P
1	3.50	1.5	3.0	6.00	12.50	0.28	10.79	3.23
5	3.96	1.5	3.0	6.36	13.42	0.34	11.55	3.17
10	4.54	1.5	3.0	6.81	14.58	0.43	12.51	3.11
15	5.17	1.5	3.0	7.26	15.73	0.54	13.46	3.06
20	6.00	1.5	3.0	7.71	16.88	0.68	14.42	3.02
25	6.83	1.5	3.0	8.16	18.03	0.86	15.37	2.99
30	7.89	1.5	3.0	8.61	19.18	1.09	16.33	2.96
35	9.00	1.5	3.0	9.06	20.33	1.37	17.28	2.93
40	9.91	1.5	3.0	9.51	21.48	1.73	18.24	2.91
45	10.82	1.5	3.0	9.96	22.64	2.19	19.19	2.89
50	11.89	1.5	3.0	10.41	23.79	2.76	20.15	2.87
55	13.00	1.5	3.0	10.86	24.94	3.48	21.10	2.85
60	13.91	1.5	3.0	11.32	26.09	4.40	22.06	2.83
65	14.82	1.5	3.0	11.77	27.24	5.55	23.01	2.82
70	15.89	1.5	3.0	12.22	28.39	7.00	23.96	2.81
75	17.00	1.5	3.0	12.67	29.54	8.83	24.92	2.80
80	18.43	1.5	3.0	13.12	30.70	11.14	25.87	2.78
85	20.50	1.5	3.0	13.57	31.85	14.06	26.83	2.77
90	25.00	1.5	3.0	14.02	33.00	17.74	27.78	2.77
95	31.00	1.5	3.0	14.47	34.15	22.38	28.74	2.76
100	40.00	1.5	3.0	14.92	35.30	28.24	29.69	2.75

Note: I_{thres}, current threshold (nA); G_1 and G_2, gain on the frequency–current relationship in the primary and secondary firing ranges, respectively; force max, maximum tetanic force; T_f, frequency constant related to the speed of contraction and the left–right position of the force–frequency curve; P, exponent used to transform the exponential force–frequency function to a sigmoidal function. See text for formulae used to determine motor unit forces from currents and the resultant motoneuronal firing frequencies.

Results

Model of younger human quadriceps motoneuron pool

A model of 100 motor units representative of motoneuron and muscle properties from the quadriceps muscle of a younger person was generated using the parameters in the Heckman–Binder model (Table 1). As outlined in Table 1, current thresholds ranged from 3.5–40 nA and frequency thresholds ranged from 6–14.92 Hz. All motor units in this model were recruited when 40 nA of current was delivered. At this current level, when all motor units reached firing threshold, the force output was equal to approximately 75% of maximum isometric force generation, similar to published data for the tibialis anterior muscle (Van Cutsem et al. 1997).

Simulated *F-f* relationships were generated for representative motor units, ranging from No. 1 to No. 100 (Fig. 1A). The *f-i* relationship is depicted in Fig. 1B, and the force–current (*F-i*) relationship is shown in Fig. 1C. It is evident that higher-threshold motoneurons had higher frequency thresholds and reached higher maximal firing rates. Variable levels of input current were simulated in the model to measure the resultant whole muscle force output (Fig. 1D). Maximal isometric force for the young quadriceps muscles rose steadily, with increasing current reaching peak values of approximately 675 N, which is consistent with previous studies of knee extension strength in humans (Allman and Rice 2004; Roos et al. 1999).

Figure 2 illustrates the relationship between the number of motor units activated and the resultant force per motor unit

(in absolute and normalized terms), when different levels of input current were injected into all motoneurons in the pool. Figures 2A, 2B, and 2C represent increasing levels of current (15, 25, and 35 nA, respectively). When 15 nA of current was injected into the motoneuron pool, approximately 25% of the motor units were fully activated (i.e., 100% maximum force was reached by 25 motor units in this diagram). The overall resultant force was 52.5 N (approximately 8% of total maximum isometric force). Approximately 65% of the motor units were recruited, with the lower-threshold motor units contributing relatively little absolute force (in the range of 0.25–0.65 N each), despite being maximally activated. Many of the slightly larger motoneurons were not fully rate-coded; yet, because of their size and the types of muscle fibres they innervate, they contributed relatively more force toward the total. In Fig. 2B, when 25 nA was injected into the model, a greater number of motor units were activated (approximately 90% were activated to some extent, with the total force output of 239.5 N, or 35% of maximum). Although motor unit Nos. 60–90 were not fully rate-coded, they generated much larger forces than the lower-threshold smaller motor units. Figure 2C demonstrates the system when the current was set to 35 nA and the total force output was 425.2 N, or 63% of maximum. This current was sufficient to recruit 95% of motor units in the pool, with the majority (80%) being fully rate-coded.

Model of older human quadriceps motor unit

The model for the younger human motoneuron pool was

Fig. 2. Generated sample relationships between the number of motor units activated and the resultant force (in absolute units on the left and normalized terms on the right) when different levels of current were injected into the model. (A, B, and C) Increasing levels of current (15, 25, and 35 nA, respectively). Each dot represents 5 motor units.
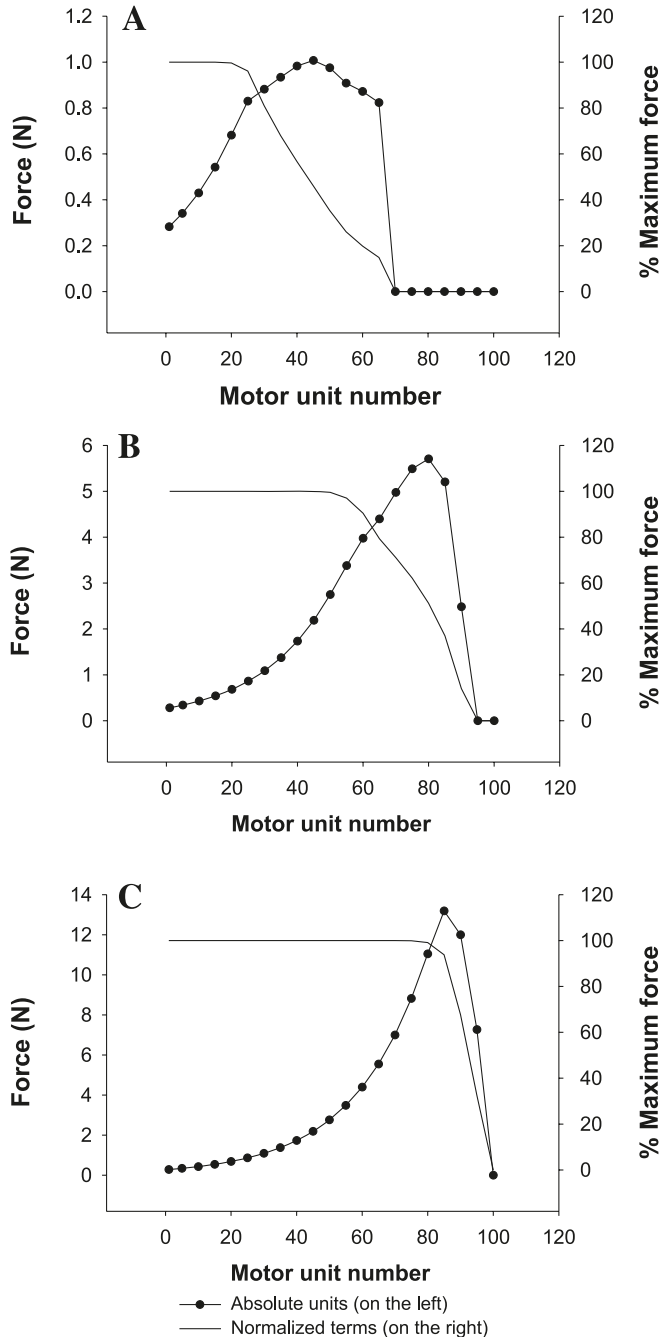
systematically modified to reflect changes in the neuromuscular system with aging. That is, specific changes in motoneuron and (or) muscle properties related to aging were first modeled individually to determine their effects on frequency and force output from the system. A composite model that incorporated all individually modeled changes was then generated to determine the overall effect of aging on force production.

The first modification made to the model involved reducing the frequency constant related to the speed of contraction (T_f) to account for slowing in contractile speed with aging. The resultant *F-f* plot and *F-i* plots are portrayed in Figs. 3A and 3B, respectively. *F-f* data are displayed for representative motor units (Nos. 1, 50, and 100). Plots for the representative motor units from the older individual are steeper and shifted to the left, relative to the younger motor units (Fig. 3A), and the overall force/current ratio is slightly elevated in the older model (Fig. 3B). Figure 3C depicts the change in *F-i* that occurred when the older motoneuron model was adjusted to simulate changes related to decreased specific tension, loss of muscle fibres, and decreased size of muscle fibres within individual motor units (and the resultant decrease in maximum force capacity for individual motor units). Maximal force generation capabilities of individual motor units were reduced by a factor that increased in a linear fashion, so that force production was reduced to a greater extent in the higher-threshold motor units than in the lower-threshold motor units (to reflect changes in numbers of muscle fibres and specific tension, which affect all motor units, and atrophy of type II muscle fibres that preferentially affect higher-threshold motor units). The younger motoneuron pool was capable of generating greater total force with lower input current, compared with the older motoneuron pool. Whereas maximal total muscle force reached approximately 675 N in the younger model, maximal force in the older simulation was 440 N.

Data obtained from experiments on rats suggest that G_1 and G_2 (the gain of the *f-i* function in the primary and secondary ranges, which reflects the excitatory drive–firing rate relationship) may decrease with aging (Kalmar et al. 2008). Reducing the values for G_1 and G_2 resulted in a significant reduction in the slope of the *f-i* relationship (Fig. 4A). To simulate age-related changes in motoneuron size that affect current threshold, I_{thres} was reduced by 25% for all motoneurons. This resulted in a greater slope in the *F-i* relationship and larger forces per given current for older motor units until a similar maximum force was reached (Fig. 4B).

The model was then adjusted to represent loss of motor units (low- and high-threshold units), with some re-innervation of type II muscle fibres by low-threshold motoneurons (Fig. 5). In this model, the total number of motor units represented was reduced by 30%, incorporating relatively equal loss of both low- and high-threshold motor units. Without adjustment for sprouting from low-threshold motoneurons (Fig. 5A), total force output was reduced to nearly half of what was available in the younger model. However, when motor units associated with the smallest motoneurons were given greater force potential (to represent a greater number of innervated muscle fibres), the total force generation capability for the quadriceps increased by approximately 100 N (Fig. 5A). A motoneuron model was then generated, incorporating all age-related factors, to determine the combined effect of reducing contractile speed (T_f); reducing muscle-fibre number, size, and specific tension; reducing the gain on the frequency–current (*F-i*) relationship; decreasing the size of motoneurons; and altering motor unit remodeling (Fig. 5B). Maximum isometric force levels and their associated current requirements are listed in Table 2 for both the younger and composite older moto-

Fig. 3. (A) Changes in the force–frequency relationship associated with slowing in contractile speed with aging in motor units Nos. 1, 50, and 100. The force–current relationship is depicted in (B). (C) Whole muscle force vs. current when the older model accounted for changes in the size of muscle fibres, the loss of muscle fibres, and the reduction in specific tension.
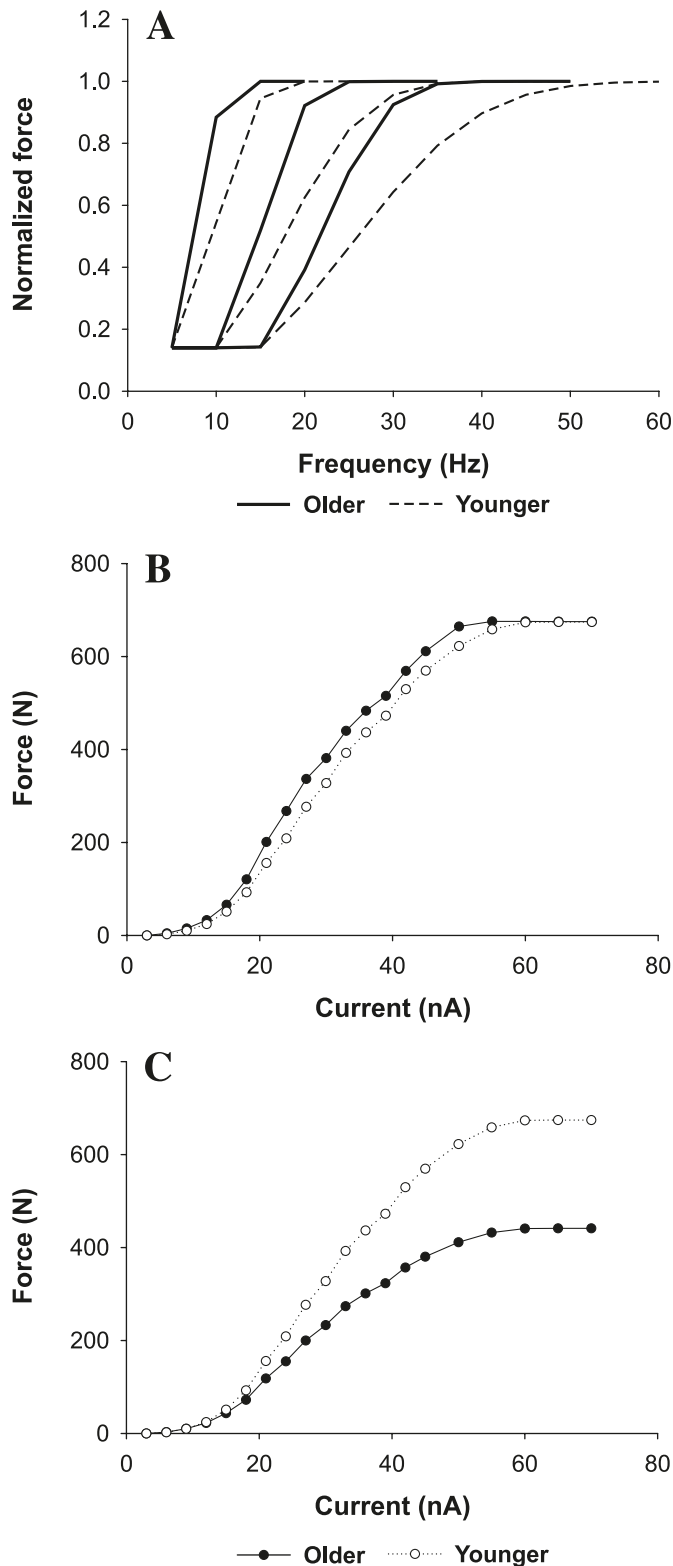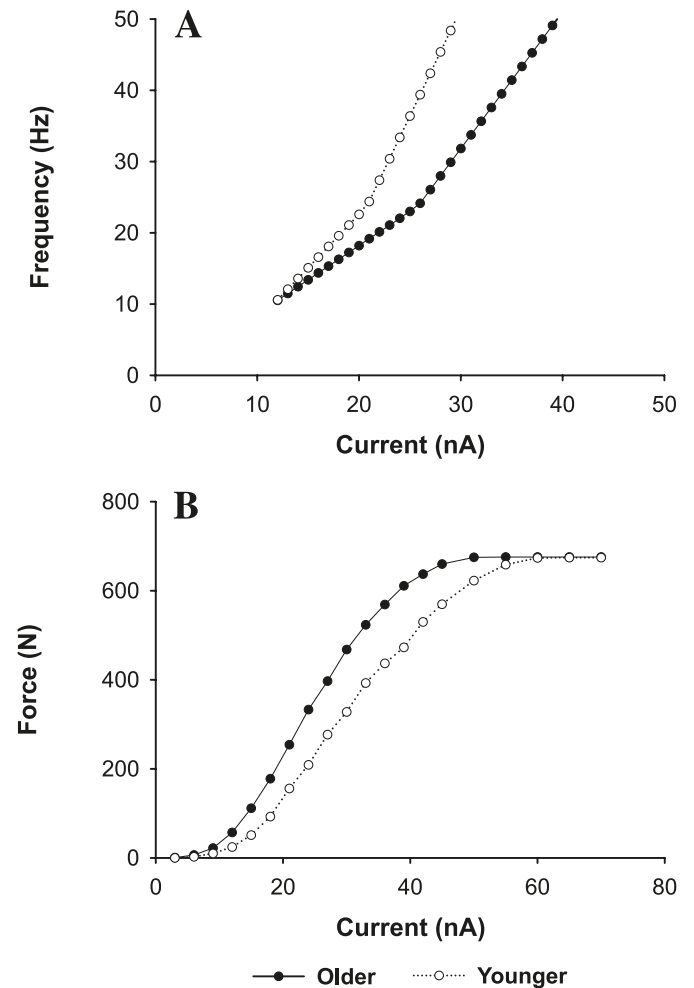

Fig. 4. (A) Frequency–current relationship for motor unit No. 50 in the model for younger and older motor units when G_1 and G_2 were reduced for the older simulation. (B) Force–current relationship for younger and older motor units when the older model was adjusted for lower current thresholds with age.


neuron pool models. Comparisons of current levels required to reach similar absolute force levels (10%, 25%, 50% maximum younger isometric force, 50 N, 300 N) are also listed for both models.

Discussion

Morphological changes in skeletal muscle with age result in loss of muscle mass caused by a combined reduction in total muscle-fibre number and fibre sizes (Porter et al. 1995). Motoneurons are not immune to the effects of aging, and also demonstrate age-related altered functional properties (Kalmar et al. 2008). Taken together, these result in significant age-related changes in the neuromuscular system, which may threaten an older individual's mobility and independence. Because aging affects both the motoneuron and the muscle fibres it innervates, models attempting to simulate changes in strength with aging need to be capable of manipulating both motoneuron and muscle properties. For this study, the simulation originally described by Heckman and Binder (1991) was utilized in a novel way to model changes in neuromuscular function with aging in human

Fig. 5. (A) Force–current relationship for younger motor units (MU), older simulation when motor units were lost, and older motor units when lower-threshold motor units were given greater force potential related to innervating a greater number of fibres with re-modeling. (B) Force–current relationship for the entire motoneuron pool for younger and older motor units when all age-related factors were incorporated in the model.
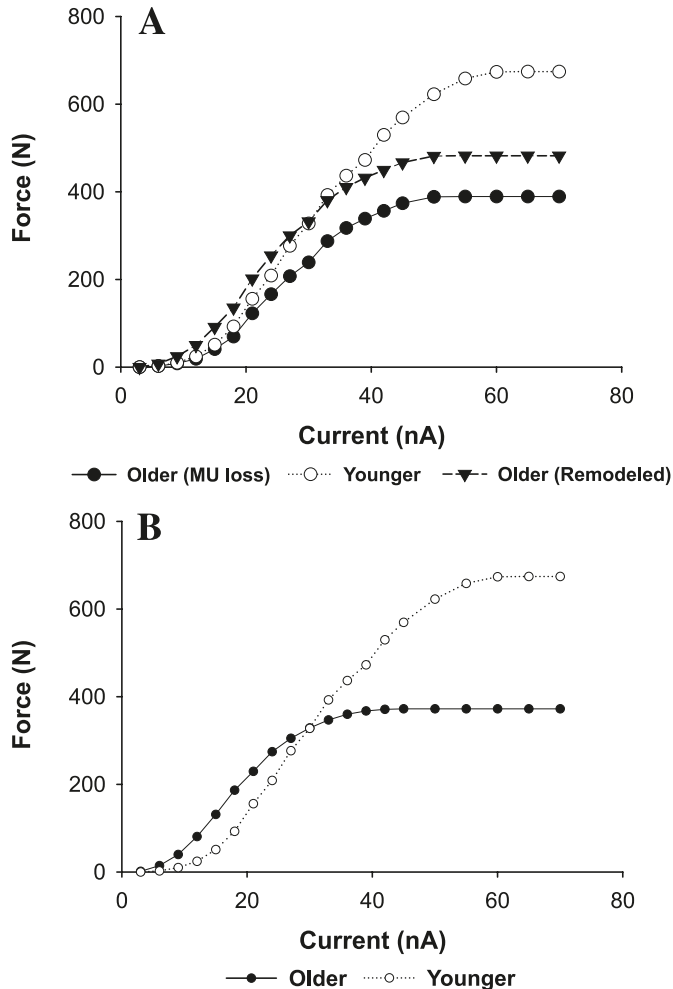
quadriceps motor units. The Heckman–Binder model was chosen for this application because it was designed to be used to determine mechanical force output in response to different levels of current input.

Both human models (the younger and older motoneuron pools) developed in this study were built on the foundations described by Heckman and Binder (1991) and Gardiner (2001). In comparing the model for the younger human motoneuron pool with that previously published for the cat and rat, it is evident that a number of differences and similarities exist. Because the twitch/tetanus ratio is greater in humans (0.14) than in cats (0.08), minimum normalized isometric forces were slightly higher in the human model. Otherwise, the shape of the normalized *F-i* and *F-f* relationships were very similar between the human and cat models. Although the *F-i* functions were not truly sigmoidal in shape in the human models, cat data from the Heckman–Binder model demonstrated a similar finding. Heckman and Binder (1991) stated that because the frequency threshold for each motor

unit was relatively high, the lower parts of the curves were missed (i.e., the sigmoidal shape would be more apparent if lower currents were capable of activating the muscle at lower forces). As well, they proposed that the existence of secondary firing ranges (influenced by G_2) resulted in relatively steep approaches to maximum force. It is expected that this reasoning also applies to the newly developed human models.

Although the frequency threshold and range of firing frequencies were set slightly lower in the human model, and values for T_f and P were adjusted for human data, these modifications did not appreciably change the isometric *F-f* relationship from that previously demonstrated for the cat and rat. Although the magnitude of maximal isometric force generation varies substantially among the species, depending on the amount of contractile protein available to be activated, the shape of the *F-f* relationship was similar.

Adjusting the human model parameters for changes expected to occur with aging resulted in some predictable findings. For example, accounting for slowing in muscle contractile speed with aging (and, therefore, summation of twitches at lower frequencies), the *F-f* plots for representative motor units demonstrated steeper slopes and were left-shifted, relative to those generated in the younger model (Fig. 3A). This has been found in numerous human studies involving the quadriceps muscle (Allman and Rice 2004; Roos et al. 1999), tibialis anterior (Connelly et al. 1999), and muscles of the hand (Barry et al. 2007). Because firing frequency is directly dependent on input current, the *F-i* relationship for the older model demonstrated a similar leftward shift (Fig. 3B). Taken together, these data suggest that an older individual can attain higher percentages of maximum force for a given current (and, therefore, for a given frequency) than a younger person.

Loss of muscle mass and strength are closely linked to declining function, dependence, and mortality in older adults (Roubenoff 2003). The fact that older individuals are capable of recruiting motor units as effectively as younger people (verified using twitch interpolation by Vandervoort and McComas 1986) suggests that reductions in strength result from changes in the muscle and its nerve supply, rather than from centrally generated motor commands. By the seventh decade, isometric maximum voluntary knee extension torque has been reported to be reduced by 25%–49% (Larsson and Karlsson 1978; Roos et al. 1999; Stalberg et al. 1989; Young et al. 1985). Although loss of muscle mass may be related to loss of muscle-fibre numbers and to atrophy of remaining fibres (largely type II muscle fibres), it is believed that changes in cross-sectional area are more greatly affected by changes to the total fibre number (Lexell and Downham 1992). Figure 3C demonstrates the change in total muscle force demonstrated when the motor unit model was adjusted to account for changes in muscle-fibre number and atrophy of type II muscle fibres with aging. Whereas maximal total muscle force reached approximately 675 N in the younger model, maximal force in the older simulation was 440 N. These results, which represent a 35% reduction in maximal isometric torque, closely agree with previously published findings from experiments involving younger and older individuals (Allman and Rice 2004; Roos et al. 1999; Young et al. 1985). Figure 3C depicts little difference be-

Table 2. Comparison of current requirements in the younger and composite older motoneuron pool models.

Current requirements	Younger model (nA)	Older model (nA)
Current associated with maximum isometric force	64	45
Current associated with 337 N (50% maximum force in younger model)	31	31
Current associated with 168 N (25% maximum force in younger model)	22	17
Current associated with 68 N (10% maximum force in younger model)	16	11
Current associated with 50 N force	15	10
Current associated with 300 N force	28	26

Note: The maximum isometric force is 676 N for the younger model and 376 N for the older model. nA, current.

Table 3. Firing frequencies for given currents in the younger model, older model adjusted for changes in G_1/G_2, and older model modified for changes in I_{thres}.

Input current (nA)	Motor unit No.	Younger model (Hz)	Older model; G_1 and G_2 reduced (Hz)	Older model; I_{thres} reduced (Hz)
12	1	25.0	15.8	27.6
	25	15.9	13.1	18.9
	50	10.6	10.5	15.0
30	1	79.0	50.4	81.6
	25	67.8	42.8	72.9
	50	51.4	31.8	60.3

Note: G_1 and G_2, gain on the frequency-current relationship in the primary and secondary firing ranges respectively; I_{thres}, current threshold (nA).

tween force output for a given current at low levels of current (or during tasks requiring low-moderate effort), but as task difficulty and required current input levels increase, the *F-i* relationship diverges, with older individuals being unable to produce the higher forces reached by younger individuals.

Kalmar et al. (2008), in their studies on rats, demonstrated that the slope of the *f-i* relationship decreases with age, effectively resulting in a lower firing frequency for the same given current in an older animal. They also determined that motoneuron size decreases with age, resulting in lower current thresholds in older rats (i.e., lower rheobase and higher input resistance). Similar findings have been reported in the cat (Morales et al. 1987). These 2 age-related changes have opposite effects on frequency and current (i.e., reducing G_1/G_2 reduces frequency for a given current, and reducing current threshold acts to increase frequency for a given current) (Table 3).

A primary goal of this modeling exercise was to determine the combined effects of age-related changes in motoneuron and muscle properties in terms of input current and force output. Effective synaptic current input may be related to the degree of voluntary effort required to exert force in these human models. Data demonstrated in Fig. 5B and listed in Table 2 show total muscle force levels relative to current input for younger subjects and older subjects (with the older model accounting for reduced muscle contractile speed, reduced muscle-fibre number and size, reduced gain on the *f-i* relationship, decreased size of motoneurons, and altered motor unit remodeling). Although the models suggest that younger individuals are capable of reaching much greater absolute maximal muscle forces (676 N vs. 376 N), the current level required to reach 50% of a younger person's maximal isometric force is the same for both younger and older individuals (31 nA input results in a force output of 337N in both models). As is demonstrated in Fig. 6, 31 nA of current input results in maximal force output for most motor units (55 of 70) in the older model, whereas in the younger model, virtually the same current input results in maximal force output from 70 of 100 existing motor units. In the older model, more force is provided by all activated motor units than in the younger simulation.
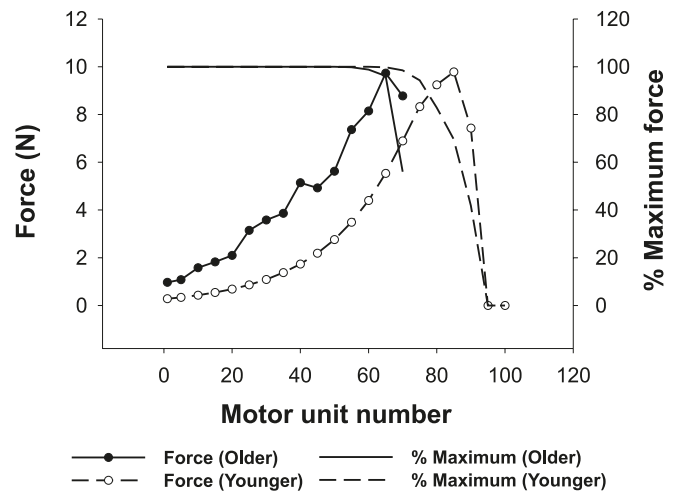
Reducing the gain on the *f-i* relationship (G_1 and G_2) in

Fig. 6. Relationship between the number of motor units activated and the resultant force (in absolute and normalized terms) when 31 nA of current was injected into the older model and younger model.

the older model effectively resulted in lower firing frequencies for any given current. Therefore, as explained in the example above, when virtually the same current (31 nA) was injected into both the younger and older simulations, although the total force output was identical, generation of the force was accomplished at lower frequencies in the older model. This result is in agreement with the study by Barry et al. (2007), who found that although minimal firing rates were similar in the first dorsal interosseus muscle in younger and older people, peak discharge rates were lower in the older group, which resulted in a lower range of rate-coding potential for each motor unit.

The fact that equivalent input current resulted in the generation of 337 N of force in both models suggests that, despite the fact that this represents 90% of maximal force production in the older person, the degree of effort required to exert this force level might not be appreciably different between the 2 age groups. In fact, the models suggest that for resistance tasks requiring <50% maximal voluntary isometric force (relative to the younger individual's capabilities), the degree of input current required by older subjects is actually slightly less than that required by younger individuals (Fig. 5B). This finding is in agreement with the fa-

Table 4. Input current required to generate isometric force (when specific age-related motoneuron and motor unit properties were tested with different values to assess the sensitivity of the model to these specific changes).

Model	Current requirements (nA) for 68 N (10% maximum force in younger model)	Current requirements (nA) for 168 N (25% maximum force in younger model)	Current requirements (nA) for 337 N (50% maximum force in younger model)
Younger model	16	22	31
Older composite model	11	17	31
Older model with G_1 and G_2 unchanged from younger values	10	15	28
Older model with motoneuron current thresholds unchanged from younger values	15	25	48
Older model with 50% of motor units lost	12	21	337 N not possible, maximum force is 280 N

tigue-related literature that has shown that for submaximal repetitive tasks, older individuals may demonstrate greater fatigue resistance than younger subjects on some standardized tasks (Kent-Braun et al. 2002; Lanza et al. 2004). Preferential atrophy of type II muscle fibres, combined with the fibre-type transition from type II to type I, which is thought to occur when fast-twitch fibres are re-innervated by surviving lower-threshold motoneurons, results in an increased percentage of type I muscle fibres (Trappe et al. 2003), which are inherently fatigue resistant. In addition, other factors, such as a lower rate of decline in motor unit firing rate with fatigue (Rubinstein and Kamen 2005), may contribute to fatigue resistance in older adults.

As recognized by Heckman and Binder (1991) and Gardiner (2001), this model is not without its limitations. One of the major shortcomings relates to the fact that the model does not put any upper limits on firing frequencies for motoneurons, allowing the lower-threshold units to reach supratetanic frequencies before the largest motoneurons are activated. In actual fact, studies of voluntary isometric conditions in humans have demonstrated firing frequencies in the range of 15–25 Hz for the triceps brachii (Del Valle and Thomas 2004) and 10–50 Hz for the quadriceps muscle (Knight and Kamen 2008; Pucci et al. 2006) across contractions of different intensities from 25% to 100% maximal voluntary contraction. As well, studies of older adults suggest that maximal firing rates may be reduced with age (Kamen et al. 1995; Kamen and Knight 2004; Nelson et al. 1984); therefore, this model may specifically overestimate older adults' potential to generate force, because maximal firing rates are not restricted.

This model simulates slow isometric contractions, and more extensive modeling would be required to represent rapid contractions where force thresholds of motor units differ (Desmedt and Godaux 1977). It is assumed that remodeled motor units in this model will produce forces scaled relative to the extent of remodeling (i.e., increased innervation ratios). For various reasons (neuromuscular junction failure, distal axonal block, less biomechanical efficiency), this may not be the case during sustained contractions or during rhythmic contraction during exercise. In addition, our model does not account for late adaptation, which can result in reduced motor unit firing rates during sustained constant current injection (Kernell 1979). Results of animal (Kalmar et al. 2008) and human (Erim et al. 1999) studies suggest that motor units in older individuals demonstrate

less adaptation, which may actually benefit older subjects if this results in lower effort requirements to maintain force. Animal research also indicates that the incidence of persistent inward current is greater in older rats (Kalmar et al. 2008). This also could contribute to greater force production with less effort if motoneurons in older adults are more depolarized and require less current to reach firing threshold.

Our model deals with the well-studied isometric condition; however, dynamic concentric and eccentric contractions are often more relevant to human function. Substantial modifications would be required to use the model to predict force in a dynamic task. It is known that relationships among current, frequency, and force vary with different types of contractions. Recruitment thresholds are lower during concentric, as opposed to isometric, contractions, even when the velocity is very low, and initial firing frequencies are dependent on the type of contraction being executed (Tax et al. 1989). Although the simulation sums forces from individual motor units to determine total maximum force, 1 group of researchers has demonstrated in studies on cats that there is actually not a linear relationship between summed tensions and total force (Troiani et al. 1999). As well, our model included only 100 motor units, a small percentage of the actual number of motor units that would be found in the quadriceps. Spreading the same ranges of values for different model parameters over a much larger pool of motor units would result in smoother, steadier force generation. Overall, using this model to estimate force production in humans is also limited by the lack of human data available to represent some parameters in the model.

Although a comprehensive sensitivity analysis was not conducted to illustrate the relative influence of all age-related parameter changes incorporated in the model, analyses were conducted to demonstrate force generation capabilities predicted by the model if certain parameters had not been altered from the younger model. Specifically, the model was adjusted to determine current input levels and subsequent force production when G_1 and G_2 were maintained at younger values, when input current thresholds were unchanged from the younger model, and when a greater percentage (50%) of motor units were lost (Table 4). Preserving the gain on the f-i relationship in the older model predictably had relatively little influence on input current requirements to generate low-, moderate-, and high-level forces (10%, 25% and 50% maximal force levels obtained in the younger model, respectively). Similarly,

in the alternate model, in which 50% of motor units were lost, current requirements did not change substantially to generate low and moderate force levels, but this model indicated that an older person would not be able to reach force levels equal to 50% of maximal values in the younger individual. As illustrated in Table 4, when current thresholds were maintained at levels equal to those used in the younger model, substantially greater amounts of input current were required to generate equal amounts of force. This would be expected, given the reductions in individual motor unit maximum force potential that were incorporated into the model. These analyses demonstrate that the changes in motoneuron current threshold that were incorporated in the composite older model were largely responsible for the changes in the *F-i* relationship with age. Since the parameters tested are those for which comprehensive information is currently lacking, more emphasis should be placed, in future, on these changes with age to better understand alterations in voluntary neuromuscular function in older adults.

In summary, modifying the Heckman–Binder motoneuron model for human data (where available) resulted in the development of *f-i*, *F-f*, and *F-i* functions for the human quadriceps muscle. Adjusting this model to reflect age-related changes in motoneurons and muscle tissue resulted in a leftward shift of the *F-f* function, lower firing frequencies for any given current, and reductions in maximal force output. Interestingly, results generated from the composite model for the older neuromuscular system (which included the combined effects related to reduced muscle contractile speed; reduced muscle fibre number, size, and specific tension; reduced gain on the *f-i* relationship; decreased size of motoneurons; and altered motor unit remodeling) suggest that older individuals may be capable of reaching force levels up to approximately 50% of those attained by younger individuals with relatively similar or even slightly lower levels of current input. This suggests that the degree of effort associated with functional tasks that require lower levels of force output may not be significantly different between younger and older individuals. Because muscle weakness is associated with decreased mobility and morbidity with aging, simulating the effects of these changes and their influence on potential force production may provide further insight into how age-related changes in the neuromuscular system affect functional strength levels, which are important to overall health and well-being in older adults.

Acknowledgements

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