

# Modeling Human Suboptimal Control: A Review

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This review paper provides an overview of the approaches to model neuromuscular control, focusing on methods to identify nonoptimal control strategies typical of populations with neuromuscular disorders or children. Where possible, the authors tightened the description of the methods to the mechanisms behind the underlying biomechanical and physiological rationale. They start by describing the first and most simplified approach, the reductionist approach, which splits the role of the nervous and musculoskeletal systems. Static optimization and dynamic optimization methods and electromyography-based approaches are summarized to highlight their limitations and understand (the need for) their developments over time. Then, the authors look at the more recent stochastic approach, introduced to explore the space of plausible neural solutions, thus implementing the uncontrolled manifold theory, according to which the central nervous system only controls specific motions and tasks to limit energy consumption while allowing for some degree of adaptability to perturbations. Finally, they explore the literature covering the explicit modeling of the coupling between the nervous system (acting as controller) and the musculoskeletal system (the actuator), which may be employed to overcome the split characterizing the reductionist approach.

**Keywords:** muscle control, optimization methods, stochastic approach, EMG informed, feedback control

To produce controlled movements, the human central nervous system (CNS) sends excitation signals to the skeletal muscles in the form of motoneurons action potentials, causing their contraction in a timely fashion. Traditionally, neurophysiologists focus on the control unit (the nervous system) rather than on the actuation unit (the musculoskeletal system), while biomechanists do the opposite.

It has been observed experimentally<sup>1,2</sup> that the nervous system of healthy adult subjects who are performing nonmaximal motor tasks, such as level walking, select those muscle activation patterns that, while ensuring instantaneous equilibrium and the desired kinematics, also minimize certain cost functions (eg, the smallest consumption of metabolic energy). For this reason, this particular control strategy is frequently referred to in the biomechanics literature by the term *optimal control*.<sup>3-5</sup> Studying the movement of a human body under optimal control only requires detailed modeling of the dynamics of the musculoskeletal system (MSK system), and the neuromuscular control mechanisms can be represented implicitly by imposing such an optimal control.<sup>6</sup>

Unfortunately, most applied biomechanics research focuses on the movement of nonhealthy, and frequently also nonadult, subjects. A child with cerebral palsy or an elder with an artificial total knee replacement surely does not usually walk by adopting an optimal control strategy. But modeling nonoptimal control is a lot more challenging, and it remains one of the open problems in applied biomechanics research.

This review paper summarizes some of the work done so far on this topic. The review is organized in 3 parts:

- First, we provide some examples of the traditional reductionist approach, with the older neurophysiology literature investigating the neuromuscular control modeling the MSK system

in an oversimplified way and the biomechanics literature investigating human movement assuming optimal control.




- Then, we will look at the more recent literature exploring neuromuscular control as a combination of multiple cost functions, a stochastic process, and a derivation of the uncontrolled manifold theory.
- Last, we will look at the most recent literature, which tries to overcome the reductionist split between biomechanics and neurophysiology and explore the possibility of explicitly also modeling the controller which, depending on the different theories, might rely on voluntary control of the involuntary reflex chain on central pattern generators (CPG), or more complex predictor–corrector controllers (Figure 1).

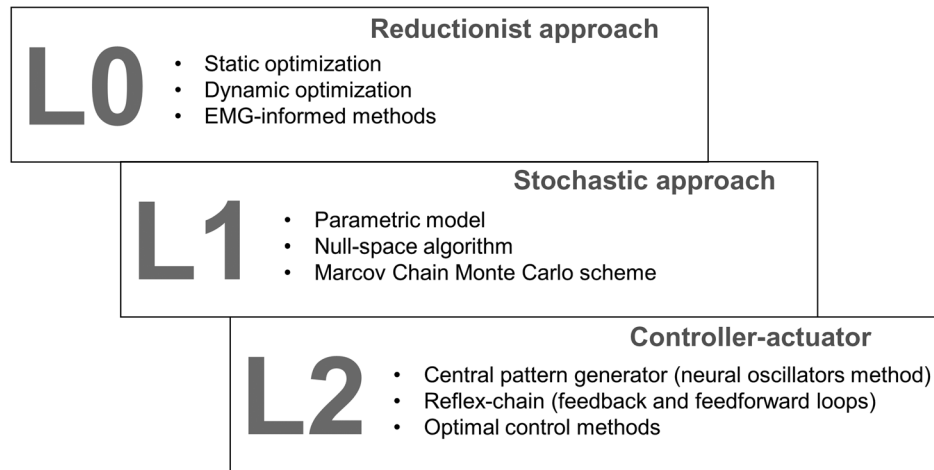
## Reductionism in Action: Separation Between Controller and Actuator

In the mid-60s, biomechanics research dealt with a complex problem: how to unravel the redundancy of the musculoskeletal system, a system with more actuators (the muscles) than degrees of freedom. In other words, if several options (in terms of muscle forces and activations) are available, how can we tell which “strategy” the CNS selects to achieve a specific goal? The so-called muscle redundancy (MR) problem was first introduced by Nikolai Bernstein in 1967.<sup>7</sup> In the decades following, several solutions to the MR problem were proposed, in most cases supported by scientific (physiological) evidence and experimental studies.

## Static and Dynamic Optimization Approaches

Under the assumption that the CNS adopts a single strategy (among infinite available) according to an unspecified physiological criterion (eg, minimization of muscle stresses), an elegant yet simplistic and reductionist approach was theorized. The MR problem could

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**Figure 1** — Summary of the 3 approaches developed and adopted over the years to estimate muscle activations and forces using musculoskeletal models. EMG indicates electromyography.

be described as an optimization problem, where a given cost function (representative of the intended physiological criterion) was to be minimized or maximized. Thus, providing an “optimal” solution to the problem.

In 1973, taking on this concept, Seireg and Arvikar<sup>8</sup> proposed a cost function comprising 2 weighted terms, one for the individual muscle forces and one for the joint moments (Eq. 1). At each time frame, within a simulation, the cost function was minimized, to provide an “optimal” solution that produced nonnegative muscle forces and guaranteed dynamic equilibrium (joint dynamics):

$$J_1 = \sum_{i=1}^n \omega_i \cdot F_i + \sum_{i=1}^n \omega_i \cdot M_i. \quad (1)$$

Thus, the MR problem is reduced to a simple equilibrium problem but disregards the link between neural command (brain and CNS) and muscle activation and force generation.

Despite this, the idea rapidly gained momentum. The same approach was employed to study human and animal<sup>9</sup> musculoskeletal biomechanics in several works, to get insights into the role of muscles in various districts of the body, including the masticatory system,<sup>10</sup> the upper limbs (shoulder, elbow and wrist),<sup>11–20</sup> the spine,<sup>21–24</sup> and the lower limbs (hip, knee, and ankle).<sup>25–33</sup> Variations of the linear cost function proposed by Seireg et al<sup>34</sup> were introduced, for example, which minimized relative muscle forces, discouraging the large muscles in the model from providing the biggest contribution. Formulations not including the second term in (Eq. 1), which is associated with the external joint moments, also began to appear. Of note, the propensity for a linear rather than a nonlinear cost function was primarily due to numerical reasons. Algorithms for efficient and stable solutions were already widely used for linear optimization compared to nonlinear optimization algorithms,<sup>27</sup> with no physiological ground.<sup>32</sup> Traditional approaches (eg, simplex method) to solve the MR problem via the optimization of linear cost functions may lead to the sole recruitment of a limited (minimal) number of muscles (which is not consistent with electromyography [EMG] recordings).<sup>35,36</sup> Moreover, to penalize excessive individual muscle forces, nonlinear cost functions were developed where the sum of squared (relative) muscle forces was minimized. The resulting muscle recruitment strategy (and activation patterns) better approximated the experimental EMG data<sup>13,32</sup> and was associated with a more physiological

load sharing between muscles, compared to those obtained with linear cost functions.

This was just the beginning. Advancements in knowledge, pushed by scientific discoveries in various disciplines, shed new light on the mechanisms behind/governing human motion and the principles underpinning the generation of muscle force.<sup>37,38</sup> Several cost functions were introduced (Table 1), which promised to represent a physiological criterion (eg, minimization of muscle stresses). Some were more task specific (eg, to simulate walking or simple locomotor tasks), and others were district specific (eg, for the upper or lower extremities).

In 1981, Crowninshield and Brand<sup>27</sup> introduced a new physiological property in the cost function: the muscle physiological cross-sectional area, that is, the cross-sectional area of muscle multiplied for its cosine of fiber pennation angle. More specifically, they divided the force term by the muscle physiological cross-sectional area, defining a cost function that minimized the overall muscle stress (force over surface). Interestingly, increasing the power to 2<sup>14,43</sup> or 3,<sup>27</sup> the identified “optimal” solution was representative of a recruitment strategy that minimizes the overall muscle activation or maximizes muscle endurance to contraction<sup>44</sup> (typical in prolonged and repetitive activities<sup>27</sup>) respectively. Along the same line, other authors<sup>30</sup> suggested adding some physiological constraints to the optimization (eg, to minimize the total mechanochemical power of muscles with similar function/role)<sup>30</sup>; however, it was noticed that the higher the power in the cost function the lesser the need for additional constraints.<sup>13,36</sup> An et al,<sup>11</sup> on the other hand, preferred to treat muscles as independent from one another (as they are independent in terms of energy stock and blood provision) and looked for a solution that minimized the cost function independently for each muscle. Noteworthy, the cost function suggested by An et al<sup>11</sup> and a polynomial cost function with a high exponent<sup>36</sup> produce substantially equivalent solutions.

Indeed, healthy individuals tend to minimally activate their muscles while performing simple locomotor tasks<sup>27</sup> in an attempt to save energy and/or sustain the activity for long periods of time. However, the same may not hold true for pathological populations who may present with spastic (permanently contracted) muscles or individuals performing strenuous tasks requiring a different metabolic demand (ie, to generate a large amount of muscle force/power in a short timeframe).<sup>45</sup> Furthermore, it is not uncommon in the

**Table 1 Summary of the Cost Function Proposed to Solve the Muscle Redundancy Problem as an Optimization Problem**

Physiological rationale	Cost function	Specific references
Minimize muscle forces	$\sum_{i=1}^n \omega_i \cdot F_i + \sum_{i=1}^n w_i \cdot M_i$	Seireg and Arvikar <sup>8</sup>
Minimize muscle activations	$\sum_{i=1}^n F_i / F_{\max, i}$	Pedotti et al <sup>32</sup>
Minimize muscle fatigue	$\sum_{i=1}^n (F_i)^2$	Pedotti et al <sup>32</sup>
Minimize muscle activations More physiological results	$\sum_{i=1}^n (F_i / F_{\max, i})^2$	Pedotti et al <sup>32</sup>
Minimize muscle stresses	$\sum_{i=1}^n F_i / \text{PCSA}_i$	Crowninshield et al <sup>26</sup>
Increased endurance	$\sum_{i=1}^n (F_i / \text{PCSA}_i)^3$	Crowninshield and Brand <sup>27</sup>
Minimize muscle stresses Consider each muscle as individual	Min $\sigma   \frac{F_i}{\text{PCSA}_i} \leq \sigma$	An et al <sup>11</sup>
Joint stability	$\sum_{i=1}^n (F_i - F_s)^2$	Forster et al <sup>39</sup>
Minimize joint contact force joint	$\frac{\ \vec{F}(\vec{a}, t)\ }{\ \vec{F}_{\text{act}}(\vec{a}_{\text{act}}, t)\ } + \omega_2 R(\vec{a}, t)$	van Veen et al <sup>40</sup>
Track experimentally measured joint contact force	$\omega_1 \left( \frac{\ \vec{F}_{\text{exp}}(t) - \ \vec{F}(\vec{a}, t)\ }{\ \vec{F}_{\text{exp}}(t)\ } \right)^2 + \omega_2 R(\vec{a}, t)$	van Veen et al <sup>41</sup>

Note: For a more comprehensive list of cost functions, the reader is referred to the appendix in the study of Tzirakos et al.<sup>42</sup> The cost functions are reported in chronological order. PCSA indicates physiological cross-sectional area of a muscle. References are provided for completeness.

older adults or in subjects who underwent joint arthroplasty to observe the synchronous activation of both agonist and antagonist muscles in the attempt to stabilize their joints, which is probably related to their self-sense of weakness. Any cost function aiming to favor (metabolic) efficiency discourages cocontractions and cannot be considered representative of any such situation. Additional terms may be required, as suggested in the study of Forster et al.<sup>39</sup>

Extensive research has been conducted to define more suited cost functions able to capture abnormal responses or atypical (not optimal) activation patterns that characterize pathological populations.<sup>39,40</sup> By minimizing or maximizing specific internal biomechanical quantities (eg, joint torques or articular loads), one can induce (therefore mimic) muscle cocontraction or joint overloading and predict contact force profiles that better approximate in vivo data.<sup>40</sup> Nonetheless, discrepancies between predicted muscle activations and EMG data remain.

The source for this can be found in the way muscle dynamics is commonly (not properly) implemented. Classical inverse dynamics (optimization based) approaches fail to model the physiological behavior of a muscle.<sup>46</sup> The MR problem is commonly solved separately at each timeframe, resulting in a solution that respects the physiological constraints at the single time frame but is independent of the previous or following instant. Time history is not accounted for. Static optimization algorithms may generate muscle activation patterns exhibiting sudden bursts, which are not physiologically plausible. A suggested solution to avoid this unwanted outcome was the Physiological Inverse Approach<sup>46</sup> based on a combination of inverse dynamic analysis—the musculoskeletal kinematics is fixed—and dynamic optimization to estimate muscle forces together with activation and contraction dynamics. An alternative method where continuity in the solution was ensured through time integration (over time windows) were implemented is the Computed Muscle Control,<sup>47,48</sup> which combines static optimization to compute muscle activations and time integration (employing proportional–derivative controllers). However, there is conflicting evidence regarding this method. Computed Muscle Control predictions were found to overestimate the muscle and joint contact forces compared to static optimization,<sup>49</sup> casting some doubts on the reliability of this approach. In addition,

ensuring continuity in the solution through time integration—although computationally expensive<sup>50</sup>—was not shown to improve predictions in gait analysis.<sup>51</sup>

## EMG-Informed Approaches

In the early 90s, with a series of studies by McGill<sup>52</sup> and McGill and Norman,<sup>53</sup> the use of EMG data to inform or drive the models became a reality. Abnormal muscle activation patterns (including, but not limited to, muscle cocontractions) could finally be accounted for, enabling to investigate and study the effect of neuromuscular disorder on human biomechanics (eg, causes behind gait disorders in cerebral palsy,<sup>54,55</sup> or poststroke patients<sup>56</sup>).

In an EMG-informed model, muscle activations and forces are predicted through forward dynamics simulations directly from a limited number of EMG signals recorded in vivo (and properly elaborated), while the multibody dynamics (joint kinematics and kinetics) are computed using an inverse paradigm based on experimental data. For the above reason, the EMG-informed method has also been referred to as *forward-inverse* approach.<sup>57</sup> The EMG signals can further be used to tune the parameters defining the behavior of the modeled muscles so that these could reproduce the experimentally derived linear envelopes (surrogate of muscle activations), while generating the required joint torques.<sup>58,59</sup> This process, conceptualized by Hatze Herbert,<sup>60</sup> is referred to as model calibration and influences the overall predictive accuracy of a model.<sup>61</sup>

The relationship between EMG signal and muscle force, which plays a key role in an EMG-driven model, was initially simplified to a linear function (ie, muscle force was proportional to the excitation level) and later refined by Lloyd and Besier,<sup>61</sup> who presented a new model able to describe (1) the second-order filtering with damping response that links EMG signal to muscle excitation and (2) the nonlinear (exponential) activation-to-force relationship.<sup>61</sup>

Over the years, the methods were further refined (ie, the development of an EMG-assisted approach) to enhance the dynamic consistency of EMG-driven models, thus ensuring more physiologically plausible estimates.<sup>62</sup> The cost function now includes 3 weighted terms governing the model's ability (and of the neural solution) to generate estimates in line with experimental joint moments and EMG

data. In the last decades, EMG-informed models have been used for both clinical<sup>54,55,63–65</sup> and sport-related applications.<sup>66</sup>

Although presenting some limitations—primarily connected to the nature of the EMG signals and to the methods to acquire these, the EMG-informed approach represented a step forward toward modeling suboptimal muscle control. While the number of sensors (electrodes) that can be placed on the subjects is limited (typically between 8 and 16)—especially in children, the number of modeled muscles driven by EMG data can be expanded. Muscles sharing the same innervation (same motoneuron) show similar excitation patterns.<sup>67</sup> In addition, synergy-based methods now enable the reconstruction of missing EMG signals from primitives and weights extracted from normative data sets combined with those (few) collected on the patient himself.<sup>68,69</sup> For more details on synergy-based methods, the reader is referred to the review written by Taborri et al.<sup>70</sup> Complementary information may be extracted from signals recorded with an array and/or matrices of electrodes (instead of bipolar or fine wire electrodes).<sup>71</sup> High-density EMG traces (HD-EMG), processed and decomposed,<sup>71–73</sup> provide insights on the motor neurons firing (rate) and activity and may be employed to drive or inform MSK models.<sup>72,74,75</sup>

Indeed, the development and use of EMG-informed approaches contributed to shifting the paradigm from searching for the optimal solution to searching for a more real(istic) solution in line with experimental data. The solution represents the specific task performed in a specific environment (typically a lab). The generalization of other everyday activities or environments is not straightforward. Intrasubject variability is also not accounted for. Alternative methods were thus explored.

## Neuromotor Control as a Stochastic Process

Toward the end of the 20th century, scientists started looking at the MR problem from a different perspective. The multitude of possible neural solutions (combinations of muscle forces and activations to produce a specific motion and dynamics) were interpreted as motor abundance (with a positive connotation) other than redundancy (negative connotation).<sup>76</sup>

Observing how workers used to perform repetitive tasks, Scholz et al<sup>77</sup> and Scholz and Schöner,<sup>78</sup> theorized that the CNS is not constantly selecting an optimal solution (in a reductionist sense), rather it controls only those muscles and degrees of freedom that need to be controlled to achieve the set goal.<sup>79</sup> Motor control was thus considered a stochastic process aimed at identifying a “good enough” solution that allows for some variability to provide stability to sudden changes or perturbations. This is known as the uncontrolled manifold theory.

At first, an exploration of natural biological variations in muscle forces (not yet attributable to a stochastic approach) was introduced through the parametric variation of the relative contributions of individual muscles, which were grouped based on their physiological function and role.<sup>80,81</sup> The activation level of each actuator within a specific agonistic muscle group could vary between 0 (minimum) and 1 (maximum), while the activations of all antagonist muscles were determined a priori. Solutions were checked to be physiologically feasible with physiological constraint equations.<sup>81</sup> Such implementation, however, did not account for any goal variation (change in cost function) in response to external environmental factors that was observed experimentally.

In 2011, Martelli et al<sup>82</sup> suggested expanding the solution space to an  $m$ -by- $n$  hyperspace of possible and physiologically plausible

muscle force combinations (where  $m$  is the number of degrees of freedom, and  $n$  is the number of modeled muscles), delimited by the combinations resulting in minimal and maximal joint loading. The solution space was then sampled by randomly perturbing the set of muscle forces corresponding to an optimal solution (ie, null-space algorithm). This method was later refined to ensure that all sampled solutions were within the realm of combinations able to produce the observed kinematics and dynamics (ie, that respected the dynamic equilibrium).<sup>83</sup> A Bayesian approach was implemented that interpreted the vector of the unknown (muscle forces) as a multivariate random variable characterized by a probability density function. The solutions were sampled using the Markov Chain Monte Carlo scheme, which provided a more uniform sampling of the full spectrum of possible recruitment strategies. This results in a band of plausible solutions (in contrast to a single solution identified by more traditional optimization approaches), the width of which is representative of the intrasubject variability in the movement execution, further accounting for experimental data uncertainties.

The stochastic approach was first used to explore the probability of spontaneous hip fractures due to severe osteoporosis and severely suboptimal muscle control.<sup>84</sup> The same has also been used to explain and quantify the variability in the recruitment strategies adopted by individuals with osteoarthritis following a total knee replacement surgery while walking<sup>41</sup> and to explore possible effects of knee joint overloading (eg, due to Parkinson disease) on implant wear.<sup>85</sup> A similar approach was employed where the initial solution was identified through EMG-assisted simulations<sup>86</sup> as opposed to static optimization. Current implementations of the stochastic approach suffer from the same limitations of static optimization approaches in that the solution is solved at each time frame, independently of the past and the future.

Alternative applications of the uncontrolled manifold theory have been proposed over the years. With a focus on highly dynamic tasks, specifically parkour motion (jumping and landing techniques); in 2018, Maldonado et al<sup>87</sup> presented an extension of the uncontrolled manifold theory based on the task function approach used in robotics. They showed that the CNS hierarchizes and controls (sub)tasks to coordinate complex movements.

## Explicit Modeling of the Controller–Actuator Coupling

Providing a systematic review of the current knowledge on the neurophysiology bases of motor control is beyond the scope of this review. For the sake of simplicity, we can idealize the current understanding in 3 separate layers that operate in concert: a reflexes layer, a CPG layer, and a voluntary control layer.

Reflexes are muscle contractions that occur unconsciously. Specific sensory organs (eg, the muscle spindle, which senses the elongation of each skeletal muscle, or the Golgi organs, which sense the tendons force) produce afferent signals that the motoneurons in the spine directly translate into a coordinated pattern of efferent activation signals to selected muscles, according to some predetermined schemes.<sup>88</sup>

Voluntary movements always involve the CNS. But for stereotypical movements such as level walking, the involvement may be limited to initiating the task. Once in motion, a cluster of motoneurons in the spine is responsible for sustaining it by generating precodified activation patterns,<sup>89</sup> even in the absence of descending inputs from the higher level centers (ie, supraspinal). It can be considered a low-level (ie, in spinal cord) controller.<sup>90</sup>

This is the essence of the CPG theory proposed by Grillner in 1975.<sup>91</sup>

The control of nonstereotypical movements requires continuous control by the CNS. There are many theories on how this works exactly, but a generalization of some of these theories is that of predictor–corrector control. Because of the nonnegligible latency in the transmission of nervous signals, the brain needs to decide not what to do now but what to do in some hundred milliseconds, when the muscles will contract in response to the CNS signaling. To do so, the brain maintains a predictive model of how the body interacts with the physical world, which provides an estimate of the best possible activation pattern to achieve the desired motor target. This estimate is inaccurate for several reasons. Thus, as the movement develops, the CNS use all afferent signals to control and update its prediction and, where necessary, perform some corrections.<sup>88</sup>

Modeling such mechanisms is not trivial. In general, this is achieved by adding feedback and feedforward<sup>92–94</sup> loops triggered by external factors such as muscle elongation (over stretch),<sup>95–100</sup> joint angles<sup>97–102</sup> or rate of force development.<sup>92,95,97–101</sup> While more complex to implement than traditional approaches, the inclusion of explicit controller–actuator mechanisms within the models enables predictive simulations, which are useful for investigating cause–effect relationships, gait abnormalities, and neuromuscular deficits.

In the following, we will review the existing literature, clustering it around these 3 separate control layers.

## Central Pattern Generator for Stereotypical Movements

One of the first controller-based MSK models implementing a CPG mechanism was introduced in 1991 by Taga et al,<sup>103</sup> who developed a torque-actuated model whose movements were based on the phase of the gait cycle through neural oscillators.<sup>104</sup> Later, this model was improved by adding muscles to actuate joints.<sup>105</sup> Stance and swing phases were identified by a foot contact mechanism that accounted for gait speed and other factors. Accordingly, a series of neural oscillators (one per joint)—coupled to one another—alternatively activated agonist and antagonist muscles. As a result, the MSK model was able to walk normally, in line with experimental data from motion capture systems. The model presented an early and primitive feedback-based behavior based on joint angle, which could modulate (enhance or suppress) the work/action of adjacent neural oscillators. In 2001, Ogihara and Yamazaki<sup>96</sup> suggested a model with both a rhythmic pattern from a CPG mechanism and feedback loops from proprioceptive information. The parameters characterizing the whole controller–actuator system were tuned to minimize the energy expenditure (per distance traveled).

## The Role of Reflexes: Feedback and Feedforward Loops

In 2010, Geyer and Herr<sup>99</sup> introduced a different level of the physiological controller, an alternative to a CPG controller, to mimic the role of both the Golgi organs and the muscle spindles; thus, adding muscle reflexes modulation (similarly to the way spinal reflexes send sensory information to alpha motoneurons). The walking pattern was guaranteed by length and force feedback specific for each muscle, depending on the gait phase. A force-sensor acted as an inhibitor, while a controller acted in response to muscle fiber (over)stretch and contraction velocity. Positive and negative feedback were introduced to ensure stability (of leg and trunk segments) and to prevent joint

overextension during the execution of the task. In the same years, similar (or slightly more advanced) models stemmed from this work, for example, that implemented a feedforward control to stabilize further the gait<sup>92</sup> or neural oscillators driven by synergies extracted via nonnegative matrix factorization methods to control the activation of muscle actuators.<sup>106</sup> Other authors<sup>107,108</sup> proposed ways to model the stretch reflex instead, which is responsible for muscle hyperresistance and hyperexcitability in children with cerebral palsy (eg, in spastic muscles), linking the excitations of specific muscles to the velocity and acceleration at which their fibers were contracting<sup>107</sup> and the muscle force produced.

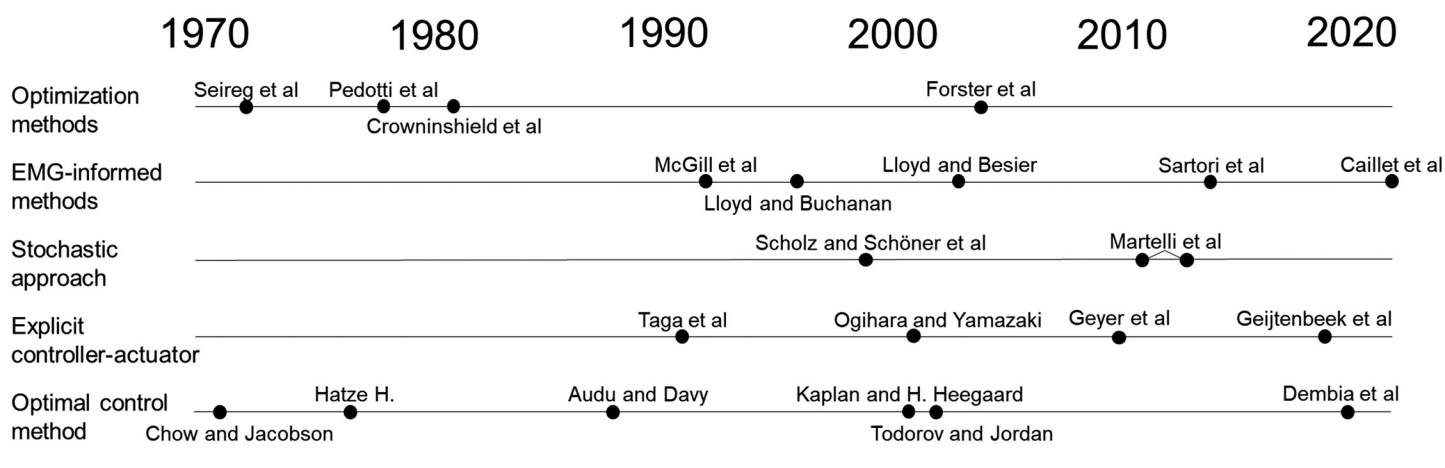
Indeed, modeling muscle reflexes, combined with new approaches typical of optimal control methods, enables to run predictive simulations combining constraints and model modifications typical of pathological conditions such as age-related modifications,<sup>109</sup> weakness of specific muscle groups,<sup>98,102</sup> to evaluate model transition to different gait speeds or to different terrain slope simply using the foot contact information to update the global state and oscillator working frequency,<sup>103,110</sup> or to explore a different combination of performance criteria to predict healthy gait.<sup>111</sup> A combination of Computed Muscle Control and biologically inspired feedback controls has also been suggested to evaluate the effects of surgery on balance recovery in patients with cerebral palsy.<sup>112</sup> Of note, in 2019, the SCONE software was released, based on work from Geijtenbeek<sup>113</sup> and Geijtenbeek et al,<sup>114</sup> with the specific aim to enable the generation of reflex-based models and simulations.<sup>113</sup> Thanks to SCONE, the high complexity of this method has been partially overcome.<sup>98,100,111,115</sup>

## Optimal Control Methods

Considering our actions, the result of a continuous refinement operated by the CNS to achieve the desired motor goal, the motor control problem can be seen as an optimal control problem. Hence, it is suitable to be described and solved using optimal control methods, commonly employed in other fields of science to model complex systems<sup>116</sup> and resolve highly nonlinear (differential) equations.<sup>117</sup>

Optimal control problems require the definition of an initial (tentative but plausible) solution, which gets iteratively optimized to meet predetermined tolerance and convergence criteria. At each iteration, the last or best-performing solution (in a batch of simulations) serves as a starting point for the subsequent round of optimization (ie, a predictor–corrector scheme). In an optimal control problem, the cost function describes the task to be performed, its complexity and its purpose through the definition of subgoals. For example, healthy gait could be seen as a combination of criteria to optimize metabolic energy rate, muscle fatigue, joint accelerations, passive torques, and upper body muscle's excitations.<sup>118</sup> Optimal control problems can be defined as tracking or predictive problems. In a predictive simulation, task-specific (sub)goals are optimized independently of experimental data, representing—for a tracking simulation—the overarching objective to follow or to tend to.<sup>6</sup>

The first examples of optimal control applied to human gait were proposed by Chow and Jacobson in 1971<sup>119</sup> and, a few years later in 1976, by Hatze<sup>120</sup> who included the work of individual muscles in the optimal control problem. Due to the high computational costs associated with modeling both the motor task(s) and physiologically consistent muscles, until the late 90s, optimal control methods were rarely employed to simulate human locomotion. With the introduction of direct-shooting methods, such as gradient-based algorithms, simulated annealing and sequential quadratic programming,<sup>4,121,122</sup> the computational time was drastically reduced but remained prohibitive for most applications. In the early 2000s, direct



**Figure 2** — Chronological overview of the approaches to model suboptimal muscle control. The list is not exhaustive but contains the works that in the authors' view contributed to the advancement of the field. EMG indicates electromyography.

collocation methods disrupted this trend,<sup>117,118,123</sup> enabling the solution of large-scale problems with several unknowns. Combinations of various performance criteria have been tested since,<sup>3,118,124–127</sup> for example, to model pathological gait.<sup>128</sup> Alternative algorithms, such as the Adams-type predictor–corrector algorithms,<sup>129</sup> have been proposed to address the problem of muscle control, with limited following.<sup>130</sup>

In the last decades, alternative uses of optimal control methods to solve neuromuscular control problems gained visibility. In 2004, Scott<sup>131</sup> and Todorov<sup>132</sup> suggested employing optimal control methods to iteratively correct the gains of feedback controllers,<sup>133</sup> based on an index of performance. Only those variations that are considered relevant to perform the intended task are thus optimized, enabling the identification of “the best possible control scheme for a given task.” This approach, known as optimal feedback control, allows the exploration of the redundancy accumulated in task-irrelevant dimensions while correcting deviations that impact the task (according to the “minimal intervention principle”).<sup>133</sup> Optimal feedback control is also strictly connected to another optimal control method: the stochastic optimal control,<sup>133</sup> aimed to introduce into simulations physiological noise to predict a more realistic control strategy.<sup>134</sup> More recently, deep reinforcement learning method has been tested out to solve the optimal control problem. The adoption of this method was related to synthesizing physiologically based human motions based either on a kinematic reference motion<sup>135</sup> or without it.<sup>136</sup> For more details, authors suggest the review article written by Song et al<sup>137</sup> (Figure 2).

## Conclusion

This paper reviewed the literature to date on the modeling of neuromuscular control. The work done so far can be clustered into 3 groups: models based on the classic reductionist approach, which assumes optimal control; the modeling of neuromuscular control as a stochastically optimal process, consistently with the uncontrolled manifold strategy; and a third group of papers that attempt to explicitly model the voluntary control through reflex chains, CPGs, or more complex predictor–corrector controllers.

Optimal control plays still an important role in the solution of many biomechanics problems; however, to be clinically relevant in several problems, biomechanics models must be able to handle also suboptimal control.

Assuming a stochastically optimal control can be a very effective approach to model patients with mild degradation of the neuromuscular control; however, it is important that the current approach, where each instance is assumed independent from the following one, may cause unrealistic predictions and should be extended to include some smoothness constraints over time.

The explicit modeling of motor control still remains extremely challenging. Each author focuses on one of the layers (voluntary control of the reflex chain, CPG for repetitive stereotypical tasks, and direct control with predictor–corrector). In contrast, it is probably true that all 3 mechanisms coexist, combined and overlapped. Modeling this complexity is one of the grand challenges of computational biomechanics in the years to come.

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## References

1. Beckett R, Chang K. An evaluation of the kinematics of gait by minimum energy. *J Biomech.* 1968;1(2):147–159. PubMed ID: 16329302 doi:10.1016/0021-9290(68)90017-1
2. Waters RL, Mulroy S. The energy expenditure of normal and pathologic gait. *Gait Posture.* 1999;9(3):207–231. PubMed ID: 10575082 doi:10.1016/S0966-6362(99)00009-0
3. De Groote F, Kinney AL, Rao AV, Fregly BJ. Evaluation of direct collocation optimal control problem formulations for solving the muscle redundancy problem. *Ann Biomed Eng.* 2016;44(10):2922–2936. PubMed ID: 27001399 doi:10.1007/s10439-016-1591-9
4. Neptune RR, Hull ML. Evaluation of performance criteria for simulation of submaximal steady-state cycling using a forward dynamic model. *J Biomech Eng.* 1998;120(3):334–341. PubMed ID: 10412400 doi:10.1115/1.2797999
5. Zajac FE. Muscle coordination of movement: a perspective. *J Biomech.* 1993;26:109–124. PubMed ID: 8505346 doi:10.1016/0021-9290(93)90083-Q

6. Umberger BR, Miller RH. Optimal control modeling of human movement. In: Müller B, Wolf SI, Brueggemann GP, et al, eds. *Handbook of Human Motion*. Springer International Publishing; 2017:1–22. doi:10.1007/978-3-319-30808-1\_177-1
7. Bernstein NA. *The Co-Ordination and Regulation of Movements*. Pergamon Press; 1967.
8. Seireg A, Arvikar RJ. A mathematical model for evaluation of forces in lower extremities of the musculo-skeletal system. *J Biomech*. 1973;6(3):313–326. PubMed ID: 4706941 doi:10.1016/0021-9290(73)90053-5
9. Prilutsky BI, Herzog W, Allinger TL. Forces of individual cat ankle extensor muscles during locomotion predicted using static optimization. *J Biomech*. 1997;30(10):1025–1033. PubMed ID: 9391869 doi:10.1016/S0021-9290(97)00068-7
10. Trainor PGS, McLachlan KR, McCall WD. Modelling of forces in the human masticatory system with optimization of the angulations of the joint loads. *J Biomech*. 1995;28(7):829–843. PubMed ID: 7657681 doi:10.1016/0021-9290(94)00128-Q
11. An KN, Kwak BM, Chao EY, Morrey BF. Determination of muscle and joint forces: a new technique to solve the indeterminate problem. *J Biomech Eng*. 1984;106(4):364–367. PubMed ID: 6513533 doi:10.1115/1.3138507
12. Brook N, Mizrahi J, Shoham M, Dayan J. A biomechanical model of index finger dynamics. *Med Eng Phys*. 1995;17(1):54–63. PubMed ID: 7704345 doi:10.1016/1350-4533(95)90378-O
13. Challis JH, Kerwin DG. An analytical examination of muscle force estimations using optimization techniques. *Proc Inst Mech Eng H*. 1993;207(3):139–148. PubMed ID: 8117365 doi:10.1243/PIME\_PROC\_1993\_207\_286\_02
14. Happee R. Inverse dynamic optimization including muscular dynamics, a new simulation method applied to goal directed movements. *J Biomech*. 1994;27(7):953–960. PubMed ID: 8063845 doi:10.1016/0021-9290(94)90267-4
15. Karlsson D, Peterson B. Towards a model for force predictions in the human shoulder. *J Biomech*. 1992;25(2):189–199. PubMed ID: 1733994 doi:10.1016/0021-9290(92)90275-6
16. Penrod DD, Davy DT, Singh DP. An optimization approach to tendon force analysis. *J Biomech*. 1974;7(2):123–129. PubMed ID: 4837546 doi:10.1016/0021-9290(74)90050-5
17. Pierce JE, Li G. Muscle forces predicted using optimization methods are coordinate system dependent. *J Biomech*. 2005;38(4):695–702. PubMed ID: 15713289 doi:10.1016/j.jbiomech.2004.05.016
18. Raikova R. A model of the flexion—extension motion in the elbow joint—some problems concerning muscle forces modelling and computation. *J Biomech*. 1996;29(6):763–772. PubMed ID: 9147973 doi:10.1016/0021-9290(95)00072-0
19. Raikova R. A general approach for modelling and mathematical investigation of the human upper limb. *J Biomech*. 1992;25(8):857–867. PubMed ID: 1639830 doi:10.1016/0021-9290(92)90226-Q
20. Yeo BP. Investigations concerning the principle of minimal total muscular force. *J Biomech*. 1976;9(6):413–416. PubMed ID: 932055 doi:10.1016/0021-9290(76)90119-6
21. Brown SHM, Potvin JR. Constraining spine stability levels in an optimization model leads to the prediction of trunk muscle cocontraction and improved spine compression force estimates. *J Biomech*. 2005;38(4):745–754. PubMed ID: 15713295 doi:10.1016/j.jbiomech.2004.05.011
22. Goel VK, Kong W, Han JS, Weinstein JN, Gilbertson LG. A combined finite element and optimization investigation of lumbar spine mechanics with and without muscles. *Spine*. 1993;18(11):1531–1541. PubMed ID: 8235826 doi:10.1097/00007632-199318110-00019
23. Nussbaum MA, Chaffin DB, Rechten CJ. Muscle lines-of-action affect predicted forces in optimization-based spine muscle modeling. *J Biomech*. 1995;28(4):401–409. PubMed ID: 7738049 doi:10.1016/0021-9290(94)00078-I
24. Schultz A, Haderspeck K, Warwick D, Portillo D. Use of lumbar trunk muscles in isometric performance of mechanically complex standing tasks. *J Orthop Res*. 1983;1(1):77–91. PubMed ID: 6679579 doi:10.1002/jor.1100010111
25. Brand RA, Pedersen DR, Friederich JA. The sensitivity of muscle force predictions to changes in physiologic cross-sectional area. *J Biomech*. 1986;19(8):589–596. PubMed ID: 3771581 doi:10.1016/0021-9290(86)90164-8
26. Crowninshield RD, Johnston RC, Andrews JG, Brand RA. A biomechanical investigation of the human hip. *J Biomech*. 1978;11(1):75–85. doi:10.1016/0021-9290(78)90045-3
27. Crowninshield RD, Brand RA. A physiologically based criterion of muscle force prediction in locomotion. *J Biomech*. 1981;14(11):793–801. PubMed ID: 7334039 doi:10.1016/0021-9290(81)90035-X
28. Hardt DE. Determining muscle forces in the leg during normal human walking—an application and evaluation of optimization methods. *J Biomech Eng*. 1978;100(2):72–78. doi:10.1115/1.3426195
29. Li G, Kaufman KR, Chao EY, Rubash HE. Prediction of antagonistic muscle forces using inverse dynamic optimization during flexion/extension of the knee. *J Biomech Eng*. 1999;121(3):316–322. PubMed ID: 10396698 doi:10.1115/1.2798327
30. Patriarco AG, Mann RW, Simon SR, Mansour JM. An evaluation of the approaches of optimization models in the prediction of muscle forces during human gait. *J Biomech*. 1981;14(8):513–525. PubMed ID: 7276011 doi:10.1016/0021-9290(81)90001-4
31. Pedersen DR, Brand RA, Davy DT. Pelvic muscle and acetabular contact forces during gait. *J Biomech*. 1997;30(9):959–965. PubMed ID: 9302620 doi:10.1016/S0021-9290(97)00041-9
32. Pedotti A, Krishnan VV, Stark L. Optimization of muscle-force sequencing in human locomotion. *Math Biosci*. 1978;38(1):57–76. doi:10.1016/0025-5564(78)90018-4
33. Röhrle H, Scholten R, Sigolotto C, Sollbach W, Kellner H. Joint forces in the human pelvis-leg skeleton during walking. *J Biomech*. 1984;17(6):409–424. PubMed ID: 6480617 doi:10.1016/0021-9290(84)90033-2
34. Seireg A, Arvikar RJ. A mathematical model for evaluation of forces in lower extremities of the musculo-skeletal system. *J Biomech*. 1973;6(3):313–326. PubMed ID: 4706941 doi:10.1016/0021-9290(73)90053-5
35. Dul J, Townsend MA, Shiavi R, Johnson GE. Muscular synergism—I. On criteria for load sharing between synergistic muscles. *J Biomech*. 1984;17(9):663–673. PubMed ID: 6501326 doi:10.1016/0021-9290(84)90120-9
36. Rasmussen J, Damsgaard M, Voigt M. Muscle recruitment by the min/max criterion—a comparative numerical study. *J Biomech*. 2001;34(3):409–415. PubMed ID: 11182135 doi:10.1016/S0021-9290(00)00191-3
37. Nelson WL. Physical principles for economies of skilled movements. *Biol Cybern*. 1983;46(2):135–147. PubMed ID: 6838914 doi:10.1007/BF00339982
38. Prilutsky BI, Zatsiorsky VM. Optimization-based models of muscle coordination. *Exerc Sport Sci Rev*. 2002;30(1):32. PubMed ID: 11800497 doi:10.1097/00003677-200201000-00007
39. Forster E, Simon U, Augat P, Claes L. Extension of a state-of-the-art optimization criterion to predict co-contraction. *J Biomech*. 2004;37(4):577–581. PubMed ID: 14996571 doi:10.1016/j.jbiomech.2003.09.003

40. van Veen B, Montefiori E, Modenese L, Mazzà C, Viceconti M. Muscle recruitment strategies can reduce joint loading during level walking. *J Biomech.* 2019;97:109368. doi:10.1016/j.jbiomech.2019.109368
41. van Veen BC, Mazzà C, Viceconti M. The uncontrolled manifold theory could explain part of the inter-trial variability of knee contact force during level walking. *IEEE Trans Neural Syst Rehabil Eng.* 2020;28(8):1800–1807. PubMed ID: 32746299 doi:10.1109/TNSRE.2020.3003559
42. Tsirakos D, Baltzopoulos V, Bartlett R. Inverse optimization: functional and physiological considerations related to the force-sharing problem. *Crit Rev Biomed Eng.* 1997;25(4–5):371–407. PubMed ID: 9505137 doi:10.1615/CritRevBiomedEng.v25.i4-5.20
43. Herzog W. Individual muscle force estimations using a non-linear optimal design. *J Neurosci Methods.* 1987;21(2):167–179. doi:10.1016/0165-0270(87)90114-2
44. Praagman M, Chadwick EKJ, van der Helm FCT, Veegeer HEJ. The relationship between two different mechanical cost functions and muscle oxygen consumption. *J Biomech.* 2006;39(4):758–765. PubMed ID: 16439246 doi:10.1016/j.jbiomech.2004.11.034
45. Lin YC, Dorn TW, Schache AG, Pandy MG. Comparison of different methods for estimating muscle forces in human movement. *Proc Inst Mech Eng H.* 2012;226(2):103–112. PubMed ID: 22468462 doi:10.1177/0954411911429401
46. De Groote F, Pipeleers G, Jonkers I, et al. A physiology based inverse dynamic analysis of human gait: potential and perspectives. *Comput Methods Biomech Biomed Engin.* 2009;12(5):563–574. PubMed ID: 19319704 doi:10.1080/10255840902788587
47. Thelen DG, Anderson FC. Using computed muscle control to generate forward dynamic simulations of human walking from experimental data. *J Biomech.* 2006;39(6):1107–1115. PubMed ID: 16023125 doi:10.1016/j.jbiomech.2005.02.010
48. Thelen DG, Anderson FC, Delp SL. Generating dynamic simulations of movement using computed muscle control. *J Biomech.* 2003;36(3):321–328. PubMed ID: 12594980 doi:10.1016/S0021-9290(02)00432-3
49. Wesseling M, Derikx LC, de Groote F, et al. Muscle optimization techniques impact the magnitude of calculated hip joint contact forces. *J Orthop Res.* 2015;33(3):430–438. PubMed ID: 25492510 doi:10.1002/jor.22769
50. Anderson FC, Ziegler JM, Pandy MG, Whalen RT. Application of high-performance computing to numerical simulation of human movement. *J Biomech Eng.* 1995;117(1):155–157. PubMed ID: 7609481 doi:10.1115/1.2792264
51. Anderson FC, Pandy MG. Static and dynamic optimization solutions for gait are practically equivalent. *J Biomech.* 2001;34(2):153–161. PubMed ID: 11165278 doi:10.1016/S0021-9290(00)00155-X
52. McGill SM. A myoelectrically based dynamic three-dimensional model to predict loads on lumbar spine tissues during lateral bending. *J Biomech.* 1992;25(4):395–414. PubMed ID: 1533860 doi:10.1016/0021-9290(92)90259-4
53. McGill SM, Norman RW. Partitioning of the L4-L5 dynamic moment into disc, ligamentous, and muscular components during lifting. *Spine.* 1986;11(7):666–678. PubMed ID: 3787338 doi:10.1097/00007632-198609000-00004
54. Davico G, Lloyd DG, Carty CP, Killen BA, Devaprakash D, Pizzolato C. Multi-level personalization of neuromusculoskeletal models to estimate physiologically plausible knee joint contact forces in children. *Biomech Model Mechanobiol.* 2022;21(6):1873–1886. PubMed ID: 36229699 doi:10.1007/s10237-022-01626-w
55. Veerkamp K, Schallig W, Harlaar J, et al. The effects of electromyography-assisted modelling in estimating musculotendon forces during gait in children with cerebral palsy. *J Biomech.* 2019;92:45–53. PubMed ID: 31153626 doi:10.1016/j.jbiomech.2019.05.026
56. Shao Q, Bassett DN, Manal K, Buchanan TS. An EMG-driven model to estimate muscle forces and joint moments in stroke patients. *Comput Biol Med.* 2009;39(12):1083–1088. PubMed ID: 19818436 doi:10.1016/j.combiomed.2009.09.002
57. Buchanan TS, Lloyd DG, Manal K, Besier TF. Estimation of muscle forces and joint moments using a forward-inverse dynamics model. *Med Sci Sports Exerc.* 2005;37(11):1911–1916. PubMed ID: 16286861 doi:10.1249/01.mss.0000176684.24008.6f
58. Lloyd DG, Buchanan TS. A model of load sharing between muscles and soft tissues at the human knee during static tasks. *J Biomech Eng.* 1996;118(3):367–376. PubMed ID: 8872259 doi:10.1115/1.2796019
59. Thelen DG, Schultz AB, Fassois SD, Ashton-Miller JA. Identification of dynamic myoelectric signal-to-force models during isometric lumbar muscle contractions. *J Biomech.* 1994;27(7):907–919. PubMed ID: 8063841 doi:10.1016/0021-9290(94)90263-1
60. Hatze H. Estimation of myodynamic parameter values from observations on isometrically contracting muscle groups. *Euro J Appl Physiol.* 1981;46(4):325–338. doi:10.1007/BF00422120
61. Lloyd DG, Besier TF. An EMG-driven musculoskeletal model to estimate muscle forces and knee joint moments in vivo. *J Biomech.* 2003;36(6):765–776. PubMed ID: 12742444 doi:10.1016/S0021-9290(03)00010-1
62. Sartori M, Farina D, Lloyd DG. Hybrid neuromusculoskeletal modeling to best track joint moments using a balance between muscle excitations derived from electromyograms and optimization. *J Biomech.* 2014;47(15):3613–3621. PubMed ID: 25458151 doi:10.1016/j.jbiomech.2014.10.009
63. Assila N, Pizzolato C, Martinez R, Lloyd DG, Begon M. EMG-assisted algorithm to account for shoulder muscles co-contraction in overhead manual handling. *Appl Sci.* 2020;10(10):3522. doi:10.3390/app10103522
64. Kainz H, Hoang H, Pitto L, et al. Selective dorsal rhizotomy improves muscle forces during walking in children with spastic cerebral palsy. *Clin Biomech.* 2019;65:26–33. doi:10.1016/j.clinbiomech.2019.03.014
65. Meyer AJ, Patten C, Fregly BJ. Lower extremity EMG-driven modeling of walking with automated adjustment of musculoskeletal geometry. *PLoS One.* 2017;12(7):e0179698. doi:10.1371/journal.pone.0179698
66. Silvestros P, Preatoni E, Gill HS, Cazzola D. Hyperflexion is unlikely to be the primary cervical spine injury mechanism in accidental head-on rugby tackling. *bioRxiv.* 2022, January. doi:10.1101/2022.02.18.481008
67. Sartori M, Gizzi L, Lloyd D, Farina D. A musculoskeletal model of human locomotion driven by a low dimensional set of impulsive excitation primitives. *Front Comput Neurosci.* 2013;7:79. <https://www.frontiersin.org/articles/10.3389/fncom.2013.00079>
68. Ao D, Shourijeh MS, Patten C, Fregly BJ. Evaluation of synergy extrapolation for predicting unmeasured muscle excitations from measured muscle synergies. *Front Comput Neurosci.* 2020;14:588943. <https://www.frontiersin.org/articles/10.3389/fncom.2020.588943>
69. Rabbi MF, Diamond LE, Carty CP, Lloyd DG, Davico G, Pizzolato C. A muscle synergy-based method to estimate muscle activation patterns of children with cerebral palsy using data collected from typically developing children. *Sci Rep.* 2022;12(1):3599. doi:10.1038/s41598-022-07541-5
70. Taborri J, Agostini V, Artemiadis PK, et al. Feasibility of muscle synergy outcomes in clinics, robotics, and sports: a systematic review. *Appl Bionics Biomech.* 2018;2018:3934698. PubMed ID: 29808098 doi:10.1155/2018/3934698



71. Sartori M. Modelling and simulating human movement neuromechanics. In: Beckerle P, Sharbafi MA, Verstraten T, Pott PP, Seyfarth A, eds. *Novel Bioinspired Actuator Designs for Robotics. Studies in Computational Intelligence*. Springer International Publishing; 2021:13–20. doi:10.1007/978-3-030-40886-2\_2
72. Caillet AH, Phillips ATM, Farina D, Modenese L. Estimation of the firing behaviour of a complete motoneuron pool by combining electromyography signal decomposition and realistic motoneuron modelling. *PLoS Comput Biol*. 2022;18(9):e1010556. doi:10.1371/journal.pcbi.1010556
73. Wen Y, Avrillon S, Hernandez-Pavon JC, Kim SJ, Hug F, Pons JL. A convolutional neural network to identify motor units from high-density surface electromyography signals in real time. *J Neural Eng*. 2021;18(5):056003. doi:10.1088/1741-2552/abead
74. Kapelner T, Sartori M, Negro F, Farina D. Neuro-musculoskeletal mapping for man-machine interfacing. *Sci Rep*. 2020;10(1):5834. PubMed ID: 32242142 doi:10.1038/s41598-020-62773-7
75. Sartori M, Yavuz U?, Farina D. In vivo neuromechanics: decoding causal motor neuron behavior with resulting musculoskeletal function. *Sci Rep*. 2017;7(1):13465. PubMed ID: 29044165 doi:10.1038/s41598-017-13766-6
76. Latash ML. The bliss of motor abundance. *Exp Brain Res*. 2012;217(1):1–5. PubMed ID: 22246105 doi:10.1007/s00221-012-3000-4
77. Scholz JP, Schöner G, Latash ML. Identifying the control structure of multijoint coordination during pistol shooting. *Exp Brain Res*. 2000;135(3):382–404. PubMed ID: 11146817 doi:10.1007/s00221000540
78. Scholz JP, Schöner G. The uncontrolled manifold concept: identifying control variables for a functional task. *Exp Brain Res*. 1999;126(3):289–306. PubMed ID: 10382616 doi:10.1007/s002210050738
79. Latash ML, Scholz JP, Schöner G. Motor control strategies revealed in the structure of motor variability. *Exerc Sport Sci Rev*. 2002;30(1):26. PubMed ID: 11800496 doi:10.1097/00003677-200201000-00006
80. Hurwitz DE, Foucher KC, Andriacchi TP. A new parametric approach for modeling hip forces during gait. *J Biomech*. 2003;36(1):113–119. PubMed ID: 12485645 doi:10.1016/S0021-9290(02)00328-7
81. Lundberg HJ, Foucher KC, Wimmer MA. A parametric approach to numerical modeling of TKR contact forces. *J Biomech*. 2009;42(4):541–545. PubMed ID: 19155015 doi:10.1016/j.jbiomech.2008.11.030
82. Martelli S, Taddei F, Cappello A, van Sint Jan S, Leardini A, Viceconti M. Effect of sub-optimal neuromotor control on the hip joint load during level walking. *J Biomech*. 2011;44(9):1716–1721. PubMed ID: 21497815 doi:10.1016/j.jbiomech.2011.03.039
83. Martelli S, Calvetti D, Somersalo E, Viceconti M, Taddei F. Computational tools for calculating alternative muscle force patterns during motion: a comparison of possible solutions. *J Biomech*. 2013;46(12):2097–2100. PubMed ID: 23791083 doi:10.1016/j.jbiomech.2013.05.023
84. Viceconti M, Taddei F, Cristofolini L, Martelli S, Falcinelli C, Schileo E. Are spontaneous fractures possible? An example of clinical application for personalised, multiscale neuro-musculoskeletal modelling. *J Biomech*. 2012;45(3):421–426. PubMed ID: 22204893 doi:10.1016/j.jbiomech.2011.11.048
85. Viceconti M, Curreli C, Bottin F, Davico G. Effect of suboptimal neuromuscular control on the risk of massive wear in total knee replacement. *Ann Biomed Eng*. 2021;49(12):3349–3355. PubMed ID: 34076785 doi:10.1007/s10439-021-02795-y
86. Bennett KJ, Pizzolato C, Martelli S, et al. EMG-informed neuro-musculoskeletal models accurately predict knee loading measured using instrumented implants. *IEEE Trans Biomed Eng*. 2022;69(7):2268–2275. PubMed ID: 34990350 doi:10.1109/TBME.2022.3141067
87. Maldonado G, Bailly F, Souères P, Watier B. On the coordination of highly dynamic human movements: an extension of the uncontrolled manifold approach applied to precision jump in parkour. *Sci Rep*. 2018;8(1):12219. PubMed ID: 30111843 doi:10.1038/s41598-018-30681-6
88. Latash ML. Features of the system for movement production. In: Latash ML, ed. *Fundamentals of Motor Control*. Academic Press; 2012:25–53. doi:10.1016/b978-0-12-415956-3.00003-8
89. Latash ML. Neurophysiological structures. In: Latash ML, ed. *Fundamentals of Motor Control*. Academic Press; 2012:171–210. doi:10.1016/b978-0-12-415956-3.00010-5
90. Duysens J, Van de Crommert HWA. Neural control of locomotion; part 1: the central pattern generator from cats to humans. *Gait Posture*. 1998;7(2):131–141. PubMed ID: 10200383 doi:10.1016/S0966-6362(97)00042-8
91. Grillner S. Locomotion in vertebrates: central mechanisms and reflex interaction. *Physiol Rev*. 1975;55(2):247–304. PubMed ID: 1144530 doi:10.1152/physrev.1975.55.2.247
92. Dzeladini F, van den Kieboom J, Ijspeert A. The contribution of a central pattern generator in a reflex-based neuromuscular model. *Front Hum Neurosci*. 2014;8:371. doi:10.3389/2Ffnhum.2014.00371
93. Jiang P, Chiba R, Takakusaki K, Ota J. Generation of the human biped stance by a neural controller able to compensate neurological time delay. *PLoS One*. 2016;11(9):e0163212. doi:10.1371/journal.pone.0163212
94. Kaminishi K, Jiang P, Chiba R, Takakusaki K, Ota J. Postural control of a musculoskeletal model against multidirectional support surface translations. *PLoS One*. 2019;14(3):e0212613. doi:10.1371/journal.pone.0212613
95. Kistemaker DA, Van Soest AJK, Wong JD, Kurtzer I, Gribble PL. Control of position and movement is simplified by combined muscle spindle and Golgi tendon organ feedback. *J Neurophysiol*. 2013;109(4):1126–1139. PubMed ID: 23100138 doi:10.1152/jn.00751.2012
96. Ogihara N, Yamazaki N. Generation of human bipedal locomotion by a bio-mimetic neuro-musculo-skeletal model. *Biol Cybern*. 2001;84(1):1–11. PubMed ID: 11204394 doi:10.1007/PL00007977
97. Song S, Geyer H. A neural circuitry that emphasizes spinal feedback generates diverse behaviours of human locomotion. *J Physiol*. 2015;593(16):3493–3511. PubMed ID: 25920414 doi:10.1113/JP270228
98. Ong CF, Geijtenbeek T, Hicks JL, Delp SL. Predicting gait adaptations due to ankle plantarflexor muscle weakness and contracture using physics-based musculoskeletal simulations. *PLoS Comput Biol*. 2019;15(10):e1006993. doi:10.1371/journal.pcbi.1006993
99. Geyer H, Herr H. A muscle-reflex model that encodes principles of legged mechanics produces human walking dynamics and muscle activities. *IEEE Trans Neural Syst Rehabil Eng*. 2010;18(3):263–273. PubMed ID: 20378480 doi:10.1109/TNSRE.2010.2047592
100. Russo AD, Stanev D, Sabnis A, et al. Investigating the roles of reflexes and central pattern generators in the control and modulation of human locomotion using a physiologically plausible neuromechanical model. *bioRxiv*. 2023, January. doi:10.1101/2023.01.25.525432
101. Wang JM, Hamner SR, Delp SL, Koltun V. Optimizing locomotion controllers using biologically-based actuators and objectives. *ACM Trans Graph*. 2012;31(4):1–11. doi:10.1145/2185520.2185521
102. Waterval NFJ, Veerkamp K, Geijtenbeek T, et al. Validation of forward simulations to predict the effects of bilateral plantarflexor weakness on gait. *Gait Posture*. 2021;87:33–42. PubMed ID: 33882437 doi:10.1016/j.gaitpost.2021.04.020
103. Taga G, Yamaguchi Y, Shimizu H. Self-organized control of bipedal locomotion by neural oscillators in unpredictable environment. *Biol*

- Cybern.* 1991;65(3):147–159. PubMed ID: 1912008 doi:10.1007/BF00198086
104. Matsuoka K. Mechanisms of frequency and pattern control in the neural rhythm generators. *Biol Cybernetics.* 1987;56(5):345–353. doi:10.1007/BF00319514
  105. Taga G. A model of the neuro-musculo-skeletal system for human locomotion. *Biol Cybern.* 1995;73(2):97–111. PubMed ID: 7662771 doi:10.1007/BF00204048
  106. Haghpanah SA, Farahmand F, Zohoor H. Modular neuromuscular control of human locomotion by central pattern generator. *J Biomech.* 2017;53:154–162. PubMed ID: 28126336 doi:10.1016/j.jbiomech.2017.01.020
  107. van der Krogt MM, Bar-On L, Kindt T, Desloovere K, Harlaar J. Neuro-musculoskeletal simulation of instrumented contracture and spasticity assessment in children with cerebral palsy. *J Neuroeng Rehabil.* 2016;13(1):64. PubMed ID: 27423898 doi:10.1186/s12984-016-0170-5
  108. Falisse A, Bar-On L, Desloovere K, Jonkers I, Groote FD. A spasticity model based on feedback from muscle force explains muscle activity during passive stretches and gait in children with cerebral palsy. *PLoS One.* 2018;13(12):e0208811. PubMed ID: 30532154 doi:10.1371/journal.pone.0208811
  109. Song S, Geyer H. Predictive neuromechanical simulations indicate why walking performance declines with ageing. *J Physiol.* 2018;596(7):1199–1210. PubMed ID: 29344967 doi:10.1113/JP275166
  110. Aoi S, Ogihara N, Sugimoto Y, Tsuchiya K. Simulating adaptive human bipedal locomotion based on phase resetting using foot-contact information. *Adv Rob.* 2008;22(15):1697–1713. doi:10.1163/156855308X3689785
  111. Veerkamp K, Waterval NFJ, Geijtenbeek T, et al. Evaluating cost function criteria in predicting healthy gait. *J Biomech.* 2021;123:110530. doi:10.1016/j.jbiomech.2021.110530
  112. Mansouri M, Clark AE, Seth A, Reinbolt JA. Rectus femoris transfer surgery affects balance recovery in children with cerebral palsy: a computer simulation study. *Gait Posture.* 2016;43:24–30. PubMed ID: 26669947 doi:10.1016/j.gaitpost.2015.08.016
  113. Geijtenbeek T. SCONE: open source software for predictive simulation of biological motion. *J Open Source Softw.* 2019;4(38):1421. doi:10.21105/joss.01421
  114. Geijtenbeek T, van de Panne M, van der Stappen AF. Flexible muscle-based locomotion for bipedal creatures. *ACM Trans Graph.* 2013;32(6):206. doi:10.1145/2508363.2508399
  115. Muñoz D, Marchis CD, Gizzi L, Severini G. Predictive simulation of sit-to-stand based on reflexive-controllers. *PLoS One.* 2022;17(12):e0279300. doi:10.1371/journal.pone.0279300
  116. Sharp JA, Burrage K, Simpson MJ. Implementation and acceleration of optimal control for systems biology. *J R Soc Interface.* 2021;18(181):20210241. doi:10.1098/rsif.2021.0241
  117. Kaplan ML, Heegaard JH. Predictive algorithms for neuromuscular control of human locomotion. *J Biomech.* 2001;34(8):1077–1083. PubMed ID: 11448699 doi:10.1016/S0021-9290(01)00057-4
  118. Falisse A, Serrancolí G, Dembia CL, Gillis J, Jonkers I, De Groote F. Rapid predictive simulations with complex musculoskeletal models suggest that diverse healthy and pathological human gaits can emerge from similar control strategies. *J R Soc Interface.* 2019;16(157):20190402. PubMed ID: 31431186 doi:10.1098/rsif.2019.0402
  119. Chow CK, Jacobson DH. Studies of human locomotion via optimal programming. *Math Biosci.* 1971;10(3):239–306. doi:10.1016/0025-5564(71)90062-9
  120. Hatze H. The complete optimization of a human motion. *Math Biosci.* 1976;28(1):99–135. doi:10.1016/0025-5564(76)90098-5
  121. Audu ML, Davy DT. A comparison of optimal control algorithms for complex bioengineering studies. *Optim Control Appl Methods.* 1988;9(1):101–106. doi:10.1002/oca.4660090110
  122. van Soest AJ, Schwab AL, Bobbert MF, van Ingen Schenau GJ. The influence of the biarticularity of the gastrocnemius muscle on vertical-jumping achievement. *J Biomech.* 1993;26(1):1–8. PubMed ID: 8423165 doi:10.1016/0021-9290(93)90608-H
  123. Stelzer M, von Stryk O. Efficient forward dynamics simulation and optimization of human body dynamics. *ZAMM.* 2006;86(10):828–840. doi:10.1002/zamm.200610290
  124. Ackermann M, van den Bogert AJ. Optimality principles for model-based prediction of human gait. *J Biomech.* 2010;43(6):1055–1060. PubMed ID: 20074736 doi:10.1016/j.jbiomech.2009.12.012
  125. Dorn TW, Wang JM, Hicks JL, Delp SL. Predictive simulation generates human adaptations during loaded and inclined walking. *PLoS One.* 2015;10(4):e0121407. PubMed ID: 25830913 doi:10.1371/journal.pone.0121407
  126. Lee LF, Umberger BR. Generating optimal control simulations of musculoskeletal movement using OpenSim and MATLAB. *PeerJ.* 2016;4:e1638. PubMed ID: 26835184 doi:10.7717/peerj.1638
  127. van den Bogert AJ, Hupperets M, Schlarb H, Krabbe B. Predictive musculoskeletal simulation using optimal control: effects of added limb mass on energy cost and kinematics of walking and running. *Proc Inst Mech Eng P J Sport Eng Technol.* 2012;226(2):123–133. doi:10.1177/1754337112440644
  128. Falisse A, Pitto L, Kainz H, et al. Physics-based simulations to predict the differential effects of motor control and musculoskeletal deficits on gait dysfunction in cerebral palsy: a retrospective case study. *Front Hum Neurosci.* 2020;14:40. <https://www.frontiersin.org/articles/10.3389/fnhum.2020.00040>
  129. Hatze H. An efficient simulation method for discrete-value controlled large-scale neuromusculoskeletal system models. *J Biomech.* 2001;34(2):267–271. PubMed ID: 11165293 doi:10.1016/S0021-9290(00)00175-5
  130. Umberger BR, Gerritsen KGM, Martin PE. A model of human muscle energy expenditure. *Comput Methods Biomech Biomed Eng.* 2006;9(5):342–342. doi:10.1080/10255840612331393266
  131. Scott SH. Optimal feedback control and the neural basis of volitional motor control. *Nat Rev Neurosci.* 2004;5(7):532–545. PubMed ID: 15208695 doi:10.1038/nrn1427
  132. Todorov E. Optimality principles in sensorimotor control. *Nat Neurosci.* 2004;7(9):907–915. PubMed ID: 15332089 doi:10.1038/nn1309
  133. Todorov E, Jordan MI. Optimal feedback control as a theory of motor coordination. *Nat Neurosci.* 2002;5(11):1226–1235. PubMed ID: 12404008 doi:10.1038/nn963
  134. Van Wouwe T, Ting LH, De Groote F. An approximate stochastic optimal control framework to simulate nonlinear neuromusculoskeletal models in the presence of noise. *PLoS Comput Biol.* 2022;18(6):e1009338. doi:10.1371/journal.pcbi.1009338
  135. Peng XB, Abbeel P, Levine S, van de Panne M. DeepMimic: example-guided deep reinforcement learning of physics-based character skills. *ACM Trans Graph.* 2018;37(4):143. doi:10.1145/3197517.3201311
  136. Zhou B, Zeng H, Wang F, Li Y, Tian H. Efficient and robust reinforcement learning with uncertainty-based value expansion. December 2019. doi:10.48550/arxiv.1912.05328
  137. Song S, Kidzi?ski ?, Peng XB, et al. Deep reinforcement learning for modeling human locomotion control in neuromechanical simulation. *J Neuroeng Rehabil.* 2021;18(1):126. PubMed ID: 34399772 doi:10.1186/s12984-021-00919-y