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Abstract

Biological motion control paradigms can be analyzed from a control theory point of view and translated to control applications. This paper revises and updates important aspects about the neural control of biped gait based on the Central Pattern Generator (CPG) and provides a controller view, including possible artificial implementations of these controllers. A first aspect to consider is the biological sensor-actuation system because the particularities of this system: the mammalian muscle. Many current biped robots are based on symmetrical CPG. However, new evidence suggests that biological CPG is asymmetrical with rhythm generator controlling the flexor half in a kind of feedforward control and the extensor behaving in a feedback fashion controlled by external inputs such as ground contact. A theoretical model of the CPG connections with flexors and extensors is presented.

Keywords	central pattern generator; CPG; gait control; biped robot
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ESCOLA POLITÉCNICA DA UNIVERSIDADE DE SÃO PAULO
Departamento de Engenharia Mecatrônica e de Sistemas Mecânicos

Dear Editor-in-Chief Annual Reviews in Control

We, Jacques Duysens and Arturo Forner-Cordero, would like to submit the manuscript “**A controller perspective on biological gait control: Reflexes and Central Pattern Generators**” by **J. Duysens and A. Forner-Cordero** for consideration for publication in Annual Reviews in Control.

It is our pleasure to submit this review manuscript as we believe that the multidisciplinary nature of this work, already outlined in the past Keynote Lecture from Prof Duysens during the IFAC BMS2018. The field of artificial generation of robotic biped gaits is inspired by ideas from biology. However, these ideas change and therefore it is essential to update the knowledge and provide new insights. This review completes the perspective of biological and robotic biped locomotion focusing on the role of reflexes and mainly Central Pattern Generators.

This manuscript results from the interaction between neuroscience and robotics. It is an original contribution, has not been previously published, is not under consideration for publication elsewhere, and, if accepted, it will not be published elsewhere in similar form, in any language.

Looking forward hearing from you.

Best regards,

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A CONTROLLER PERSPECTIVE ON BIOLOGICAL GAIT CONTROL: REFLEXES AND CENTRAL PATTERN GENERATORS

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ABSTRACT

Biological motion control paradigms can be analyzed from a control theory point of view and translated to control applications. This paper revises and updates important aspects about the neural control of biped gait based on the Central Pattern Generator (CPG) and provides a controller view, including possible artificial implementations of these controllers. A first aspect to consider is the biological sensor-actuation system because the particularities of this system: the mammalian muscle. Many current biped robots are based on symmetrical CPG. However, new evidence suggests that biological CPG is asymmetrical with rhythm generator controlling the flexor half in a kind of feedforward control and the extensor behaving in a feedback fashion controlled by external inputs such as ground contact. A theoretical model of the CPG connections with flexors and extensors is presented.

INTRODUCTION

This paper aims at giving an updated view on current thinking about gait and its application in simulations/robotics. It may help to briefly describe the analogy between gait, as constructed by evolution, and cars as build by engineers.

For a car we first need an engine, which for gait is the spinal CPG (central pattern generator) along with the musculo-skeletal structure supporting movement, as we will see. The engine needs fuel, just as the CPG needs dopamine. The car needs a brake to be able to stop while for biped gait we will encounter cells in the lower brainstem that act as the final common path for stopping. The car engine has a single mode of operation, but one needs a steering wheel for turning and a gear stick to obtain backward driving. For mammalian gait the direction of gait is determined at the brainstem level (pontine reticular formation and MLR, mesencephalic locomotor region). A gear stick is also handy to drive at the appropriate speed (fast on the highway, slow at the intersection). For mammalian gait there is a subpopulation of cells in the MLR that can regulate gait speed while the basal ganglia act as the gas pedal. Now all we need is the car key and an ignition system, which for human gait is present in the prefrontal cortex. One more item is useful: a driver who can judge that the traffic light went on green. In our case we can rely on humans with a visual cortex (for the lucky ones that have color sight) and on parietal cortex to judge where our body is with respect to the environment (soon to be replaced by robotic vision). For gait we use about the same areas to provide the brains decision areas (prefrontal cortex, amygdalae) with the appropriate information for safe walking.

Given this description one may be inclined to think that evolution works as an engineer. However, that idea is highly misleading, since there are many examples to illustrate that evolution has recycled some old solutions to adapt them to a new task. Hence it is more correct to describe evolution as a tinkerer than as an engineer. In the next sections we will describe the various levels of neural control of gait, with emphasis of bipedal gait but in the context of evolution.

CPG: CENTRAL PATTERN GENERATORS

In vertebrate gait the basic motor output is generated by spinal CPGs (Central Pattern Generators). It is a group of neurons that is able to generate a rhythmic control output, combining “autonomously generated signals” and “control from higher centers” along with “entrainment with the environment”.

These CPGs combine circuits for flexor reflexes with circuits for limb extension reflexes. The first clear demonstration of this was made in 1967 when it was shown that CPGs in spinal cats (cats with transected spinal cord) could be activated to produce locomotor output by injection of L-dopa (Jankowska, Jukes, Lund, & Lundberg, 1967). The locomotor CPGs show striking similarities across species (Goulding, 2009; Kiehn, 2011). This inspired Grillner and colleagues to investigate the function of locomotor CPGs in lamprey, a primitive vertebrate that has been around for some 560 million years (Grillner, 2011). The lamprey uses CPGs to swim by contractions on one side being combined with relaxations on the other side. From there it seems like a big step to walking on land with limbs instead of fins. However, there are several fishes that manage to use fins as legs (Thorsen, Cassidy, & Hale, 2004). In addition there are amphibians that can perform both swimming and walking. It is therefore commonly assumed that walking vertebrates rely on CPGs, originally designed for swimming (Goulding, 2009) but adjusted for gait on land. One major argument for this is that some cell types are common to fish, lamprey and mammals (Grillner, Robertson, & Stephenson-Jones, 2013). These include inhibitory commissural interneurons (connecting CPGs on opposing sides of the body) and V2a neurons in the mouse spinal cord, neurons that are part of the rhythm generating circuitry that have their equivalents in the lamprey.

One feature that relates to this fish heritage is that swimming involves a rostro-caudal sequence of activations and similarly, in walking vertebrates, there is a rostro-caudal sequence of CPG activations with cervical CPGs (controlling forelimbs) leading the lumbosacral CPGs (controlling the hindlegs). Furthermore, in the isolated spinal cord one can investigate the ability of CPGs to generate rhythmic activity and this showed that cervical CPGs are more excitable than lumbosacral ones, actually these generate more easily rhythmic motor output in isolation after some form of chemical facilitation (Deliagina, Orlovsky, & Pavlova, 1983; Kiehn, 2006).

The simplest basic output of the CPG is a burst of neural activity in flexors (supporting the swing phase) and a burst of activity in extensors (supporting the stance phase). The networks generating these bursts are mutually inhibitory. These networks form the pattern generating part of the CPG, a part that is thought to be separate from the rhythm generating circuitry (McCrea & Rybak, 2007, 2008). The latter authors concluded this on the basis of experiments with “spontaneous deletions”, gaps of bursts of activity in locomotor animal models. Others have also noted such deletions (Duysens, 1977; Duysens, 2006; Zhong, Shevtsova, Rybak, & Harris-Warrick, 2012) but they observed that the deletions were highly asymmetric. Flexor deletions

are usually concomitant with sustained ipsilateral extensor activity. In contrast, extensor burst deletions do not affect rhythmic flexor bursting. This was the basis for the proposition of an asymmetric CPG with the rhythm generating part of the CPG primarily activating the flexor circuitry. Generation of extension then originates from the release of inhibition (from this flexor part), aided by gravity and by reinforcing extensor load feedback (Duysens, De Groote, & Jonkers, 2013; Pearson & Duysens, 1976). This idea of an asymmetric CPG has already been included in some biological models as well (Rybak, Shevtsova, Lafreniere-Roula, & McCrea, 2006; Rybak, Stecina, Shevtsova, & McCrea, 2006; Zhong et al., 2012).

In humans there are many arguments supporting the view that spinal CPGs contribute to gait, for a summary see (Dimitrijevic, Gerasimenko, & Pinter, 1998; Duysens & Pearson, 1998; Duysens & Van De Crommert, 1998; MacKay-Lyons, 2002). One of the most convincing pieces of evidence comes from the human newborn, who is able to walk when supported, despite the absence of mature connections from the cortical regions. Based on EMG recordings, Dominici and colleagues were able to show that the locomotor output in such neonates consist of only 2 primitives, one for flexion and one for extension, exactly as one would predict from the animal CPG work (Dominici et al., 2011). As gait matures, the pattern gets more complex, with increasing involvement from higher centers located in the brain, in particular since there is an increase in balance requirements when walking occurs unsupported. One way to study human CPG output is to look at the locomotor output in people paralyzed by spinal cord injury undergoing epidural spinal cord stimulation (Danner et al., 2015). Although a basic activation pattern was generated, which is compatible with the idea of spinal burst generators, there seems to be a need for a high-level controller that maintains bipedal balance. In a review of the animal and human literature a model for the human CPG has been advanced (Duysens & Forner-Cordero, 2018).

FEEDBACK

Most experiments showing that CPGs can produce locomotor output in the absence of sensory input are highly artificial since under normal conditions gait is an interactive process between centrally generated activities and afferent input from body sensors that are activated by the movements. Hence it is commonly assumed that in the cat- and presumably also in humans, locomotion is controlled by CPGs in interaction with sensory feedback from the environment (Duysens, Clarac, & Cruse, 2000; Pearson, 2004; Rossignol, 2006). When CPGs are active under fictive motor output pattern without afferent input the motor output often shows

important differences (Fleshman, Lev-Tov, & Burke, 1984; Grillner & Zangger, 1975; Grillner & Zangger, 1984; Markin, Lemay, Prilutsky, & Rybak, 2012).

Under natural condition, the most important feedback consists probably of signals from the limb loading or unloading. In insects, Keir Pearson and colleagues discovered that load receptors enhanced leg extension and blocked flexion. It was suggested that a similar mechanism could exist in mammals that are equipped with load sensors: the Golgi Tendon Organs (GTOs), placed at the muscle-tendon junctions and connected to Ib afferent fibers. They are optimally placed to record the contractions of the muscles as confirmed by recordings from single Ib dorsal root afferents in walking cats (Loeb & Duysens, 1979).

By stimulating these afferents during walking on a treadmill it was shown in the cat that indeed the load feedback could increase extension and suppress flexor activity (Duysens & Pearson, 1980; Duysens et al., 2000). Hence the load signals during the stance phase provide reinforcing feedback and simultaneously suppress the onset of swing. Inversely, at end stance, the load signals from extensors decrease and the swing can start. Similar results were later obtained in fictive locomotion, induced by administration of nialamide (a monoamine oxidase inhibitor) and L-DOPA in cats (Conway, Hultborn, & Kiehn, 1987). The contribution of afferent feedback to extensor burst generation was estimated in the cat by Hiebert and Pearson (Hiebert & Pearson, 1999). They allowed one hind leg to step into a hole in the treadmill belt on which the animal was walking. The unloading caused the extensor EMG to be reduced to 70% of normal. It is likely that humans rely on load receptors in the same way as has been extensively reviewed (Dietz & Duysens, 2000). In infants, it was shown that sudden loading of the leg prolongs the stance phase and produces some delay in the ensuing swing phase (Yang, Stephens, & Vishram, 1998). In adults the reflex effects of Ib afferents are inhibitory when subjects are seated but this inhibition is suppressed during standing or walking (Faist et al., 2006). In that study, Ib reflexes were investigated during sitting, lying supine, lying supine with 300 N pressure applied to the foot sole, standing, and a rhythmic loading and unloading task called "reduced" gait. The Ib inhibition, as seen during sitting and lying supine, was significantly reduced or disappeared during standing and when lying supine but loaded (Faist et al., 2006). During the stance phase of "reduced" gait, the inhibition disappeared in most subjects, and even a facilitation was observed in some subjects. Similar results were obtained by Stephens and Yang (Stephens & Yang, 1996). Hence, during walking the Ib effects may be facilitatory (as in cats). Natural stimulation of these afferents yields similar results since Grey and colleagues (Grey, Nielsen, Mazzaro, & Sinkjær, 2007) found that brief plantar flexion

perturbation produced a short-latency decrease in soleus EMG that varied directly with the treadmill inclination. It was suggested that Golgi tendon organ feedback was reduced due to the unloading. The data are consistent with the stance phase soleus activity being enhanced by positive force feedback. In general, in engineering, positive feedback has the reputation of being unstable, but it was shown to be operational in some parts of the brain. In particular, Houk and colleagues proposed that positive feedback, regulated by inhibition from cerebellar Purkinje cells, distributes commands throughout the limb premotor network (Houk, Keifer, & Barto, 1993). Similarly, for Ib afferents, positive load feedback was shown to be feasible in model studies performed by Prochazka and colleagues (Prochazka, Gillard, & Bennett, 1997). In that case the stabilization of the typically unstable positive force feedback was achieved by inherent properties of the neuromuscular system.

Another important proprioceptor organ in mammals is the muscle spindle. These receptors consist of a special type of muscle fibers and they are positioned in parallel with the other muscle fibers. They are innervated by special motoneurons (gamma fibers) and they provide information about muscle length and rate of change in muscle length (velocity).

The Ia afferents make monosynaptic contacts with motoneurons and produce stretch reflexes in the parent muscle. In the resting animal the reflex is ideally suited to compensate for the yield produced by muscles when muscle passive elasticity fails (Nichols & Houk, 1976). Hence Ia reflex action compensates for variations in the inherent stiffness of the muscle. Note that this mechanism can implement a position/velocity feedback that in combination with the gamma coactivation results in a position/velocity reference tracking. In this way, the spindle feedback can be used to correct errors or deviations from the intended movement. Actually, the combination of the force (GTO) and position (spindles) signals in a realistic musculoskeletal model showed improved control performance (Kistemaker, Van Soest, Wong, Kurtzer, & Gribble, 2013).

To investigate the role of the muscle spindles in locomotion it is useful to look at experiments in which locomotion is studied in the absence of feedback from these receptors (Mayer et al., 2018). This was recently possible, for example through experiments with the *Egr3*^{-/-} 122 mice, in which muscle spindles fail to develop postnatally (Tourtellotte & Milbrandt, 1998). According to Mayer and colleagues (Mayer et al., 2018), the role of spindle input relates to 3 aspects. First, muscle spindle feedback, signaling hip extension at the end of the stance phase in walking, is used to switch automatically to the swing phase (Andersson & Grillner, 1981; Grillner & Rossignol, 1978; G. Hiebert, Whelan, Prochazka, & Pearson, 1996).

The stretch of hip flexor muscles at the end of the stance phase is the important factor (Hiebert et al., 1996). This role of the hip flexors is not so easy to demonstrate since there is also unloading at end stance, which initiates swing since it yields a release of suppression of activity in the swing generator part of the CPG. Nevertheless, there is good evidence obtained by Andersson and Grillner (Andersson & Grillner, 1983), who demonstrated that it was possible to induce entrainment of the locomotion central pattern generators by sinusoidal hip movements during “fictive locomotion” (CPG output induced in a paralyzed animal). This feedback system implies that the stretch reflexes are more pronounced as gait speed increases and stretch is larger.

Second, muscle spindle afferent input is crucial in shaping the activity in some muscles in the first extension period at end swing. In the study of Grillner and Zanger (Grillner & Zangger, 1975) it was shown that deafferentation tended to eliminate the EMG burst in Semitendinosus muscle (St) in this period. At end swing the knee is extended and thereby stretches this muscle. It was later argued that in humans the same occurs and that the EMG burst in St at end swing is generated by reflexes (Duysens, van Wezel, van de Crommert, Faist, & Kooloos, 1998). Akay and colleagues (Akay, Tourtellotte, Arber, & Jessell, 2014) studied changes in mouse locomotor pattern under conditions in which spindle feedback is attenuated genetically and biomechanically. They found that patterning of the flexor muscles activity, such as St, was severely affected after elimination of proprioceptive feedback from Group Ia/II afferents. Again, we encounter a very efficient feedback system since at increasing speed of gait the stretch reflex is enhanced thereby creating stronger activation of hamstrings activity (as needed in their function as hip extensors in early stance).

Third, in early stance there is a brief period of yield in extensor muscles and it was suggested that this yield results in a stretch of extensor muscles thereby reinforcing by means of a stretch reflex the ongoing extensor EMG in that phase (Duysens et al., 2000). This system provides another optimal feedback system since yield increases with speed of gait while higher muscle activation is required at higher speeds (Prilutsky, Herzog, & Allinger, 1994).

Whether Ib or Ia afferents are the primary source of excitation in extensors remains an open question. In the cat both muscle spindle and tendon organ afferents can contribute to the increase in extensor nerve activity evoked by group I stimulation intensity during fictive locomotion (Guertin, Angel, Perreault, & McCrea, 1995). Although proprioceptive feedback from GTO and spindles in shaping locomotor output is very important, there is also a contribution from cutaneous afferents, especially those from the paw in cat or footsole in

humans (Duysens et al., 2000). These sensory afferents are well positioned to measure loading and provide load feedback.

Despite the great importance of these various sources of feedback, such input by itself is usually not sufficient to support gait. The sensory feedback generated on a treadmill can assist in generating stepping in spinal cats, mice, and rats but to be effective some other type of tonic stimulation is required, for a recent review see (Hofstoetter, Knikou, Guertin, & Minassian, 2017).

In humans, there are many similarities with the animal studies. Several manipulations provided evidence for the importance of proprioceptive input during gait. By applying small, rapid stretches to the soleus muscle during the stance phase of walking it was estimated that proprioceptive reflexes contribute up to 30% to 60% to the soleus muscle activation during this phase of the step cycle (Yang, Stein, & James, 1991). Whether Ib or Ia afferents are the primary source of excitation in extensors remains an open question here too (Duysens et al., 2000).

Given the importance of proprioceptive input in shaping locomotor activity it has been tempting to use such feedback to elicit rhythmic activity in patients with incomplete spinal cord injury (SCI). This was achieved by the use of treadmill training, in analogy with the animal studies (Dietz, 2008; Dietz, Colombo, & Jensen, 1994; Dietz, Wirz, Curt, & Colombo, 1998; Wernig & Dobkin, 2006). The training was based on the idea that these patients relied on spinal CPGs that needed to be activated (Dietz, 2003), in particular by providing adequate load feedback (Dietz, 2004; Dobkin, Harkema, Requejo, & Edgerton, 1995; Harkema et al., 1997). Limited success was achieved with this training in terms of improved EMG output, even several years after injury (Meyns, Van De Crommert, Rijken, Van Kuppevelt, & Duysens, 2014).

Unfortunately, in patients with complete spinal cord injury, the improvement was less convincing. Dietz and colleagues (Dietz, Müller, & Colombo, 2002) obtained some EMG motor output but there were major differences with the normal activity seen in gait of intact subjects and it appears that some of the activity was reflex generated. It appears that for complete SCI one needs some type of tonic stimulation, much as was observed in the animal work on training of spinal animals (see above). Recently several approaches were taken in this respect.

One of the most promising techniques involves epidural electrical stimulation (EES) of the spinal cord (for review see Mayr et al., 2016). Such stimulation elicits rhythmic output, compatible with activation of spinal pattern generators (Danner et al., 2015). However, the method appeared to have its pitfalls. Epidural electrical stimulation (EES) is not always

selective for the activation of the CPG. Hence it is often not very effective in humans, presumably because it blocks proprioceptive information (Formento et al., 2018). This is particularly true for continuous stimulation but there is hope that other stimulation protocols will give better results (burst stimulation protocol for example). A second method to increase spinal cord excitability is by means of drugs. As mentioned above, in spinal animals it is possible to induce locomotor output by injection of L-dopa (a precursor of dopamine and noradrenaline). In humans there are currently trials with injections of SpinalonTM, a drug that consists of a mixture of L-DOPA, carbidopa and buspirone. This drug is effective in spinal mice (Guertin et al., 2010) and seems quite safe for use in patients (for review, see Hofstoetter et al., 2017) but its introduction must await clinical trials.

SIMULATIONS AND ROBOTICS

Many robotics and simulation studies have included feedback to CPG-like structures. Some used force feedback in a neuro-musculo-skeletal model (Ogihara & Yamazaki, 2001; Paul, Bellotti, Jezernik, & Curt, 2005). However, sometimes the feedback was inappropriate, thereby underlining the need for physiological reviews as presented here. For example, (Ogihara & Yamazaki, 2001) implemented force feedback to be suppressive, contrary to suggestions from physiology (Duysens et al., 2000; Grey et al., 2007). On the other hand, Paul and colleagues (Paul et al., 2005) used excitatory force feedback but their model lacked bi-articular muscles, which are very important in locomotor control. Modeling studies which include force feedback are generally very powerful (Geyer & Herr, 2010; Song & Geyer, 2015). Initially it was claimed that this type of feedback was sufficient to evoke locomotion, even in the absence of a CPG, but more recent work showed that the addition of CPG to this model greatly improved its performance (Dzeladini, van den Kieboom, & Ijspeert, 2014; Haeufle, Schmorte, Geyer, Müller, & Schmitt, 2018). More recently, a combination of CPGs with bioinspired sensory feedback was employed to make a complex 3D biped robot (COMAN) walk stably with a straightforward speed control (Van der Noot, Ijspeert, & Ronsse, 2018a; Van der Noot, Ijspeert, & Ronsse, 2018b). This model used a two-level symmetric CPG containing a rhythm generator (RG) and a pattern formation (PF) layer as described previously (Aoi, Ogihara, Funato, Sugimoto, & Tsuchiya, 2010). The latter model used a phase reset of the RG circuit based on the foot contact instants to “entrain” the CPG with the gait rhythm (Aoi et al., 2010). A similar solution consisted of modulating the excitation inputs to the RG circuit at heel-strike (Van der Noot et al., 2018a). While these solutions result in robust gaits, they are not so close to the human CPG that, as we will see in this paper, is probably not symmetric.

Forward modeling has also been used to test load feedback. In one such study it was shown that a better EMG prediction is possible when feedback is added, not only of muscle length but also force (Duysens et al., 2013). For quadrupedal gait, Mazurek and colleagues (Mazurek et al., 2012) compared an open loop CPG model with a hybrid one, having sensory feedback from force plates (representing limb loading), and accelerometers and gyroscopes (representing limb position). The output was used for stimulation applied to hind limb muscles to restore gait in adult anaesthetized cats using intramuscular stimulation. With the sensory feedback added the median number of steps per trial increased and the steps were more successful (in terms of step length and ground reaction force).

FEEDFORWARD CONTROL. THE CPG AS INTERNAL MODEL

Feedback is clearly very useful for locomotion as it adapts the output of the CPG to be appropriate for circumstances (speed of gait, amount of loading). However, feedback takes time and, if a fast reaction is needed, this could be a problem. Take for example the landing of the foot on material that is either harder or softer than expected. It would be a great advantage not to have to rely only on a slow feedback control but instead to anticipate the required stiffness and the expected loads and displacements. Evolution has provided this mechanism which is commonly referred to as feedforward control, a term borrowed from Control Theory.

This was recognized already in the first years of the study of gait. Sherrington, along with Philippon, saw that the building blocks of gait consisted of the circuitry of the flexor and extensor reflex (Philippon, 1905; Sherrington, 1910). These authors also realized the principle of reciprocal inhibition of these networks. Sherrington then went on to highlight the principle of successive induction. When the flexor center is active it suppresses activity in the extensor center. At the end of the flexor period, the suppression decreases, and the extensor center is released from suppression, thereby causing a rebound of extensor activity. Hence, the activation of the flexor center contains already the seeds for the next phase, resulting in a crude example of feedforward control.

A more sophisticated example is given by the way the CPG handles sensory feedback. If a stimulus from the environment tries to elicit a flexor reflex, then it would be disastrous to have a flexor reflex while the limb is in the extensor phase. Inversely, a flexor reflex in early swing would be beneficial since the same circuitry supports both the flexor reflex and swing. Hence, it would be an advantage if the CPG can control these reflex pathways by feedforward gating. Similarly, it would be a great advantage if the CPG would be able to control the phase transition between the two phases. For example, if at the end of the swing phase the foot contact

is earlier than expected then the extensor feedback should be facilitated and there should be a termination of flexor activity. This should only occur when the system is at the appropriate turning point. If contact is made early in swing it is more appropriate to exaggerate the flexion movement as it is likely that an obstacle is encountered.

The experimental studies confirmed this prediction (Duysens & Pearson, 1976; Duysens, 1977). A cutaneous stimulus given in the early flexor period did indeed enhance flexor activity rather than suppressing it. Work on cats with transected brainstem confirmed that the transition from swing to stance phase is indeed facilitated at the end of the flexor activity while the same stimuli facilitate the onset of swing when given at early swing or end stance (Duysens, 1977). Hence the CPG should be able to some extent to regulate the incoming signals in such a way that appropriate phase transitions occur

The phase-resetting effects described above (Duysens, 1977) were obtained by stimulation of cutaneous afferents from the pads. At onset stance there is also activation of proprioceptors from extensors. Activation of these afferents by brief electrical stimulation during fictive locomotion was also found to produce a reset from flexor to extensor activity (phase transition from swing to stance) or alternatively enhanced extensor activity during stance (Gossard, Brownstone, Barajon, & Hultborn, 1994; P. Guertin et al., 1995).

The observation that afferent activity can induce phase transitions only when the system is “ready” for it is not unique for locomotion. For example, in the respiratory system the stretch receptors in the lung are activated by inspiration and they are able to induce the phase transition to expiration (Herring-Breuer reflex) but only when the vagal afferent input is provided near the end of the inspiration, at a time when the system is ready for a phase switch. The situation is similar to pushing a swing on a playground. It is optimal to add some power to the swing at the end of a cycle to reverse the swing direction. If one would try to do the same in mid-swing cycle the inertia is too large and it is difficult to reverse direction.

The phase-dependent actions of the CPG go beyond control of phase-transitions. The CPG itself determines what the immediate effect is in terms of reflexes to external perturbations. During stance an electrical pulse given to the paw will result in a brief extensor activation while the same stimulus given in early swing yields a flexor response. Hence there is a reversal of reflex effect depending on the phase, “phase-dependent reflex reversal” (Forssberg, Grillner, & Rossignol, 1975). To show that these actions can be caused by the spinal CPG it was essential to perform similar experiments in cats showing so-called “fictive locomotion” (paralyzed cats in which the CPG was activated). Schomburg and colleagues did

indeed demonstrate this type of reversal in such preparations (Andersson, Forssberg, Grillner, & Lindquist, 1978; Schomburg & Behrends, 1978). In normal cats, walking on a treadmill, a phase-dependent modulation of cutaneous reflexes was seen as well (Duysens & Loeb, 1980; Forssberg, 1979). This mechanism was later also demonstrated in humans (Duysens, Trippel, Horstmann, & Dietz, 1990; Yang & Stein, 1990).

The gating of reflexes is made possible by a mechanism called presynaptic inhibition, whereby transmission of afferent terminals is blocked through synapses at the terminal of the afferents, for review of the cat work see (Rossignol, 2006). Of particular interest is the observation that presynaptic inhibition can be produced by the CPG since it is present during fictive locomotion in the cat (Gosgnach, Quevedo, Fedirchuk, & McCrea, 2000; Gossard, Cabelguen, & Rossignol, 1991; Ménard, Leblond, & Gossard, 2002). The work on presynaptic inhibition in human gait has been summarized by Stein (Stein, 1995). Presynaptic inhibition is assumed to underlie phase-dependent modulation of reflexes but it is also thought to be involved in the task-dependent modulation of reflexes in humans, the size of the reflexes depends on the task: seated, standing, walking, running, cycling, see (Duysens, Tax, Trippel, & Dietz, 1993; Edamura, Yang, & Stein, 1991; Katz, Meunier, & Pierrot-Deseilligny, 1988; Zehr et al., 2007)). Reflexes depending on spindles and Ia afferents may be suppressed during gait because they risk disturbing the feedforward output of the CPG (for example, H-reflex amplitude is decreased during walking as compared to standing and a further reduction is seen during running as compared to walking). In contrast foot contact reflexes (depending on cutaneous afferents) may be enhanced by walking and running but are not needed during standing (Duysens et al., 1993).

The CPG modulation of the afferent feedback effects depending on the predictions about the gait state, such as gating of the reflexes, can be regarded as a form of feedforward control. The interesting role of the CPG acting as a hybrid feedback and feedforward model was presented by Kuo using a very simple mechanical model of a one degree of freedom pendulum with a pair of antagonist muscles (Kuo, 2002). The controller was based on a CPG that was simulated as acting in a pure feedforward mode (ignoring the sensory feedback), as a pure feedback mode or using an optimal combination of feedback and feedforward control, which was proven to be more robust against noise and disturbances (Kuo, 2002).

DESCENDING PATHS; SUPRASPINAL CONTROL OF GAIT

Biomimicry for biped robots may have a problem when it comes to the topic of control of the CPG (starting, stopping). The problem is that evolution works as a tinkerer and likes to work with parallel systems. Currently, robots rarely have to run from imminent danger,

however, this situation could become more common as robots are deployed in different environments. In contrast, in evolution, it is not surprising that running to escape from a danger has a high priority while such needs may not have priority for robots yet. In the section on CPGs it was seen that L-dopa injections in spinal cats was effective in activating spinal locomotor CPGs. This suggested the presence of terminals from descending pathways using either dopamine or noradrenaline (since L-dopa is a precursor of these transmitters) to innervate spinal CPGs. So far, the hypothalamic A11 region has been identified in rats, mice, cats, monkeys, zebrafish and humans to be the source of a descending dopamine (DA) path to the spinal cord (Koblinger et al., 2014). This hypothalamic region is thought to be involved in escape behavior and this may also explain its role in analgesia because suppression of pain is critical in situations where running from danger is more important than the perception of pain (Duysens, Dom, & Gybels, 1989).

In evolution, the running to escape may have been so important that it actually gave rise to a second descending system, this time originating in the amygdalae, an area involved in the detection of danger. From there a projection exist to the MLR (the mesencephalic locomotor region in the upper brainstem) which is the central station for the supraspinal control of gait. Recent studies have used optogenetics to unravel the role of the MLR. For this technique one uses a special type of proteins, called “opsines” that are light sensitive. These opsines can be made specific for given transmitters (such as glutamate) and they are then injected by means of viruses into the area of investigation. In this way some very specific populations can be selectively activated by light. This is particularly important for such areas as MLR since it contains several subpopulations of neurons that are intermingled in the 2 parts of the MLR, namely the CnF (cuneiform nucleus) and the PPN (the pedunculopontine nucleus). For example, there is a group of glutaminergic cells in one part of the MLR (in the cuneiform nucleus) that is functionally different from glutaminergic cells in another part (the PPN, the pedunculopontine nucleus). When the cells in the first subgroup are activated by light the animals run as if trying to escape from a danger (Caggiano et al., 2018). Hence this pathway seems functionally similar to the dopaminergic path from the A11 hypothalamic region. It is probably also the area that was stimulated by Shik and colleagues (Shik, Severin, & Orlovskiĭ, 1966), who were the first to discover that MLR stimulation with electric pulses could induce locomotion in cats with transected brainstem. When Caggiano and colleagues instead stimulated the glutaminergic cells in the PPN by light, the animals walked slowly in exploration of the environment (Caggiano et al., 2018). Hence the MLR functions as the meeting point for

a variety of locomotor pathways. This MLR is self under control from the input of the basal ganglia (the striatum) but different parts of the striatum affect different pathways. The emotional (ventral) locomotor system supports gait for flight or for food, according to Sinnamon (Sinnamon, 1993), while the cognitive (dorsal) locomotor system is designed for exploratory walking (Snijders et al., 2016). Both MLR systems are controlled by input from the basal ganglia. The cognitive path receives input from the neostriatum–dorsal pallidal pathway (“dorsal pathway”) while the emotional path is fed by the ventral striatum–ventral pallidal pathway (“ventral pathway”). The output of the basal ganglia occurs for the ventral part over either the lateral hypothalamus (appetitive drive) or over the medial hypothalamus (and PAG, periaqueductal grey; defensive path). For the dorsal part the output occurs over the substantia nigra (pars reticulata) which sends tonic inhibition to the MLR (Jordan, 1998; Jordan, Liu, Hedlund, Akay, & Pearson, 2008). To elicit locomotion this inhibition of the MLR has to be counteracted by inhibition of these output nuclei, which can be achieved over a so-called “direct pathway” by D1 spiny neurons of the striatum (Roseberry & Kreitzer, 2017). Inversely, to stop locomotion the D2 spiny neurons can be activated over the “indirect pathway”. These D2 neurons affect the output nuclei indirectly over the subthalamic nucleus. Instead of inhibiting they finally activate the output nuclei, thereby causing extra inhibition of the glutaminergic cells in the MLR (Ferreira-Pinto, Ruder, Capelli, & Arber, 2018). These insights were obtained with the optogenetic methods described above. The results nicely show how the striatum has all the instruments needed to start or stop locomotion. Amazingly, this sequence of MLR inhibition or disinhibition by basal ganglia has been largely preserved in evolution and dates back for over more than 500 million years when primitive swimming vertebrates such as the lamprey emerged (Grillner, Wallén, Saitoh, Kozlov, & Robertson, 2008). Thus, showing the “tinkerer” nature of evolution that recycles old structures to perform new functions.

THE ASYMMETRICAL CPG MODEL

Up to date, the CPG-based controllers for legged gait assume that the CPG has a symmetrical structure between flexion and extension. This is not surprising since most robotic actuators are not based on a pair of antagonistic actuators and the flexion and extension are provided by changes in the direction of rotation of motors. However, the biological CPG controller has been proven to be asymmetric (Duysens et al., 2013; Guertin, 2009). This asymmetry consists of a swing generator (or flexor burst generator) that is tightly coupled to a rhythm generating (RG) system that is common for both flexors and extensors (Pearson & Duysens, 1976).

Figure 1. A possible architecture for an asymmetric CPG model (Duysens and Forner-Cordero, 2018). It contains a rhythm generator (RG) network that is based on two mutually inhibiting half centers and two pattern formation (PF) nodes for flexion and extension. There are outputs for flexor (F) and extensor (E) muscles (FE). The Ia and Ib afferents are connected to the flexor (swing phase) and extensor (body support during stance) half centers, respectively. The RG, connected to supraspinal centers, is thought to send excitatory commands to a flexor half center that sends a parallel inhibition (via an interneuron) to the extensor half center. The extensor center is activated with the sensory input from the limb loading at the starting of the stance phase. Squared-ended lines mean excitatory connections while circle-ended ones mean inhibitory synapses. N₁ and N₂ represent groups of neurons that produce output as a non-linear function of the inputs and its own dynamics that include fatigue, such as proposed by Matsuoka (Matsuoka, 1985; Matsuoka, 2011).

The extensor generating neurons are mainly activated by sensory feedback (especially from load receptors) and by a release of inhibition from the flexor burst generator, (Duysens et al., 2000; Duysens & Forner-Cordero, 2018). In this model of CPG, the flexor circuit is more linked to the higher centers in the brain that initiate gait and control the speed of locomotion. As explained above, the support for this idea comes from the deletions of bursts in the CPG of mouse or cat preparations (Duysens, 1977; Zhong et al., 2012). This idea is further supported

by the evolutionary role of the flexor pattern generator (Machado, Pnevmatikakis, Paninski, Jessell, & Miri, 2015) and has led to new models of CPG that have not been applied yet to biped robots (Molkov, Bacak, Talpalar, & Rybak, 2015; Rybak, Dougherty, & Shevtsova, 2015; Shevtsova et al., 2015).

Another example of asymmetrical CPG that was used to control a simple neuromechanical model underscored the role of afference to control the CPG (Markin et al., 2010). This model included an external drive input directly to the extensor pattern formation (PF) part of the CPG. Although this architecture captures the strong input from load receptors that occur during limb loading, it does not consider the flexor dominance with inputs from the higher centers. Moreover, this model suggested that gait recovery without supraspinal drive would be possible after changes in the CPG weights (Markin et al., 2010). Indirect evidence from spinal cord injury patients that have no supraspinal input to the CPG seem to indicate that this model is incomplete.

In the new flexor-dominated architecture of the CPG (see figure 1) the extensor-center does not normally produce intrinsic rhythmic activity, which is either generated from a release of inhibition from the flexor center or from afferent input, more specifically from load receptors (Duysens & Forner-Cordero, 2018). Moreover, the sensory afference that dominates either flexor or extensors is different in this model. The flexors are more linked to position/velocity sensory information provided by the spindles, while the extensors are linked to the GTOs that provide force information. The overall behavior of the leg is thus a combination of force and position/velocity control, and this can be regarded as a form of impedance control. A final remark that underscores the importance of the control of the flexors from higher centers comes from a classic neurophysiological finding, namely the proprioceptive illusion induced by muscle tendon vibration that stimulate the muscle spindles (Roll & Vedel, 1982). This fact indicates that the spindle information is used in the sensory-motor areas to obtain information about joint angles (Forner-Cordero, Steyvers, Levin, Alaerts, & Swinnen, 2008) and this information can be used to track the joint angular positions and velocities during movement.

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REFERENCES

- Akay, T., Tourtellotte, W. G., Arber, S., & Jessell, T. M. (2014). Degradation of mouse locomotor pattern in the absence of proprioceptive sensory feedback. *Proceedings of the National Academy of Sciences*, *111*(47), 16877–16882. <https://doi.org/10.1073/pnas.1419045111>
- Andersson, O., Forssberg, H., Grillner, S., & Lindquist, M. (1978). Phasic gain control of the transmission in cutaneous reflex pathways to motoneurons during “fictive” locomotion. *Brain Research*, *149*(2), 503–507.
- Andersson, O., & Grillner, S. (1981). Peripheral control of the cat’s step cycle I. Phase dependent effects of ramp-movements of the hip during “fictive locomotion.” *Acta Physiologica Scandinavica*, *113*(1), 89–101. <https://doi.org/10.1111/j.1748-1716.1981.tb06867.x>
- Andersson, O., & Grillner, S. (1983). Peripheral control of the cat’s step cycle: II. Entrainment of the central pattern generators for locomotion by sinusoidal hip movements during “fictive locomotion.” *Acta Physiologica Scandinavica*, *118*(3), 229–239. <https://doi.org/10.1111/j.1748-1716.1983.tb07267.x>
- Aoi, S., Ogihara, N., Funato, T., Sugimoto, Y., & Tsuchiya, K. (2010). Evaluating functional roles of phase resetting in generation of adaptive human bipedal walking with a physiologically based model of the spinal pattern generator. *Biological Cybernetics*, *102*(5), 373–387. <https://doi.org/10.1007/s00422-010-0373-y>
- Caggiano, V., Leiras, R., Goñi-Erro, H., Masini, D., Bellardita, C., Bouvier, J., ... Kiehn, O. (2018). Midbrain circuits that set locomotor speed and gait selection. *Nature*, *553*(7689), 455–460. <https://doi.org/10.1038/nature25448>
- Conway, B. A., Hultborn, H., & Kiehn, O. (1987). Proprioceptive input resets central locomotor rhythm in the spinal cat. *Experimental Brain Research*, *68*(3), 643–656. <https://doi.org/10.1007/BF00249807>
- Danner, S. M., Hofstoetter, U. S., Freundl, B., Binder, H., Mayr, W., Rattay, F., & Minassian,

- K. (2015). Human spinal locomotor control is based on flexibly organized burst generators. *Brain: A Journal of Neurology*, 138(Pt 3), 577–588. <https://doi.org/10.1093/brain/awu372>
- Deliagina, T. G., Orlovsky, G. N., & Pavlova, G. A. (1983). The capacity for generation of rhythmic oscillations is distributed in the lumbosacral spinal cord of the cat. *Experimental Brain Research*, 53(1), 81–90. <https://doi.org/10.1007/BF00239400>
- Dietz, V. (2003). Spinal cord pattern generators for locomotion. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, 114(8), 1379–1389.
- Dietz, V. (2004). Locomotor activity in spinal cord-injured persons. *Journal of Applied Physiology*, 96(5), 1954–1960. <https://doi.org/10.1152/japplphysiol.00942.2003>
- Dietz, V. (2008). Body weight supported gait training: from laboratory to clinical setting. *Brain Research Bulletin*, 76(5), 459–463. <https://doi.org/10.1016/j.brainresbull.2008.02.034>
- Dietz, V., Colombo, G., & Jensen, L. (1994). Locomotor activity in spinal man. *Lancet (London, England)*, 344(8932), 1260–1263.
- Dietz, V., & Duysens, J. (2000). Significance of load receptor input during locomotion: A review. *Gait and Posture*, 11(2), 102–110. [https://doi.org/10.1016/S0966-6362\(99\)00052-1](https://doi.org/10.1016/S0966-6362(99)00052-1)
- Dietz, V., Müller, R., & Colombo, G. (2002). Locomotor activity in spinal man: significance of afferent input from joint and load receptors. *Brain: A Journal of Neurology*, 125(Pt 12), 2626–2634.
- Dietz, V., Wirz, M., Curt, A., & Colombo, G. (1998). Locomotor pattern in paraplegic patients: training effects and recovery of spinal cord function. *Spinal Cord*, 36(6), 380–390.
- Dimitrijevic, M. R., Gerasimenko, Y., & Pinter, M. M. (1998). Evidence for a spinal central pattern generator in humans. *Annals of the New York Academy of Sciences*, 860, 360–376.
- Dobkin, B. H., Harkema, S., Requejo, P., & Edgerton, V. R. (1995). Modulation of locomotor-like EMG activity in subjects with complete and incomplete spinal cord injury. *Journal of Neurologic Rehabilitation*, 9(4), 183–190.
- Dominici, N., Ivanenko, Y. P., Cappellini, G., D'Avella, A., Mondì, V., Cicchese, M., ... Lacquaniti, F. (2011). Locomotor Primitives in Newborn Babies and Their Development.

Science, 334(6058), 997–999. <https://doi.org/10.1126/science.1210617>

- Duysens, J. (1977). Reflex control of locomotion as revealed by stimulation of cutaneous afferents in spontaneously walking premammillary cats. *Journal of Neurophysiology*, 40(4), 737–751.
- Duysens, J. (2006). How deletions in a model could help explain deletions in the laboratory. *Journal of Neurophysiology*, 95(1), 562-3; author reply 563-5. <https://doi.org/10.1152/jn.00888.2005>
- Duysens, J., Clarac, F., & Cruse, H. (2000). Load-regulating mechanisms in gait and posture: comparative aspects. *Physiological Reviews*, 80(1), 83–133. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10617766>
- Duysens, J., De Groote, F., & Jonkers, I. (2013). The flexion synergy, mother of all synergies and father of new models of gait. *Frontiers in Computational Neuroscience*, 7, 14. <https://doi.org/10.3389/fncom.2013.00014>
- Duysens, J., Dom, R., & Gybels, J. (1989). Suppression of the hindlimb flexor reflex by stimulation of the medial hypothalamus and thalamus in the rat. *Brain Research*, 499(1), 131–140.
- Duysens, J., & Forner-Cordero, A. (2018). Walking with perturbations: a guide for biped humans and robots. *Bioinspiration & Biomimetics*, 13(6), 061001. <https://doi.org/10.1088/1748-3190/aada54>
- Duysens, J., & Loeb, G. E. (1980). Modulation of ipsi- and contralateral reflex responses in unrestrained walking cats. *Journal of Neurophysiology*, 44(5), 1024–1037.
- Duysens, J., & Pearson, K. G. (1976). The role of cutaneous afferents from the distal hindlimb in the regulation of the step cycle of thalamic cats. *Experimental Brain Research*, 24(3), 245–255. <https://doi.org/10.1007/BF00235013>
- Duysens, J., & Pearson, K. G. (1980). Inhibition of flexor burst generation by loading ankle extensor muscles in walking cats. *Brain Research*, 187(2), 321–332. [https://doi.org/10.1016/0006-8993\(80\)90206-1](https://doi.org/10.1016/0006-8993(80)90206-1)
- Duysens, J., & Pearson, K. G. (1998). From cat to man: Basic aspects of locomotion relevant to motor rehabilitation of SCI. *NeuroRehabilitation*, 10(2), 107–118. [https://doi.org/10.1016/S1053-8135\(97\)00050-4](https://doi.org/10.1016/S1053-8135(97)00050-4)

- Duysens, J., Tax, A. A., Trippel, M., & Dietz, V. (1993). Increased amplitude of cutaneous reflexes during human running as compared to standing. *Brain Research*, 613(2), 230–238. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/8186969>
- Duysens, J., Trippel, M., Horstmann, G. A., & Dietz, V. (1990). Gating and reversal of reflexes in ankle muscles during human walking. *Experimental Brain Research*, 82(2), 351–358. <https://doi.org/10.1007/BF00231254>
- Duysens, J., & Van De Crommert, H. W. A. A. (1998). Neural control of locomotion; Part 1: The central pattern generator from cats to humans. *Gait and Posture*, 7(2), 131–141. [https://doi.org/10.1016/S0966-6362\(97\)00042-8](https://doi.org/10.1016/S0966-6362(97)00042-8)
- Duysens, J., van Wezel, B. M., van de Crommert, H. W., Faist, M., & Kooloos, J. G. (1998). The role of afferent feedback in the control of hamstrings activity during human gait. *European Journal of Morphology*, 36(4–5), 293–299.
- Dzeladini, F., van den Kieboom, J., & Ijspeert, A. (2014). The contribution of a central pattern generator in a reflex-based neuromuscular model. *Frontiers in Human Neuroscience*, 8, 371. <https://doi.org/10.3389/fnhum.2014.00371>
- Edamura, M., Yang, J. F., & Stein, R. B. (1991). Factors that determine the magnitude and time course of human H-reflexes in locomotion. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 11(2), 420–427.
- Faist, M., Hoefer, C., Hodapp, M., Dietz, V., Berger, W., & Duysens, J. (2006). In humans Ib facilitation depends on locomotion while suppression of Ib inhibition requires loading. *Brain Research*, 1076(1), 87–92. <https://doi.org/10.1016/j.brainres.2005.12.069>
- Ferreira-Pinto, M. J., Ruder, L., Capelli, P., & Arber, S. (2018). Connecting Circuits for Supraspinal Control of Locomotion. *Neuron*, 100(2), 361–374. <https://doi.org/10.1016/j.neuron.2018.09.015>
- Fleshman, J. W., Lev-Tov, A., & Burke, R. E. (1984). Peripheral and central control of flexor digitorum longus and flexor hallucis longus motoneurons: the synaptic basis of functional diversity. *Experimental Brain Research*, 54(1), 133–149. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/6321220>
- Formento E, Minassian K, Wagner F, Mignardot JB, Le Goff-Mignardot CG, Rowald A, Bloch J, Micera S, Capogrosso M, Courtine G. (2018) Electrical spinal cord stimulation must preserve proprioception to enable locomotion in humans with spinal cord injury. *Nature*

Neuroscience, 21(12):1728-1741. doi:10.1038/s41593-018-0262-

- Forner-Cordero, A., Steyvers, M., Levin, O., Alaerts, K., & Swinnen, S. P. (2008). Changes in corticomotor excitability following prolonged muscle tendon vibration. *Behavioural Brain Research*, 190(1), 41–49. <https://doi.org/10.1016/j.bbr.2008.02.019>
- Forssberg, H. (1979). Stumbling corrective reaction: a phase-dependent compensatory reaction during locomotion. *Journal of Neurophysiology*, 42(4), 936–953. <https://doi.org/10.1152/jn.1979.42.4.936>
- Forssberg, H., Grillner, S., & Rossignol, S. (1975). Phase dependent reflex reversal during walking in chronic spinal cats. *Brain Research*, 85(1), 103–107. [https://doi.org/10.1016/0006-8993\(75\)91013-6](https://doi.org/10.1016/0006-8993(75)91013-6)
- Geyer, H., & Herr, H. (2010). A Muscle-reflex model that encodes principles of legged mechanics produces human walking dynamics and muscle activities. *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, 18(3), 263–273. <https://doi.org/10.1109/TNSRE.2010.2047592>
- Gosgnach, S., Quevedo, J., Fedirchuk, B., & McCrea, D. A. (2000). Depression of group Ia monosynaptic EPSPs in cat hindlimb motoneurons during fictive locomotion. *The Journal of Physiology*, 526 Pt 3, 639–652.
- Gossard, J. P., Brownstone, R. M., Barajon, I., & Hultborn, H. (1994). Transmission in a locomotor-related group Ib pathway from hindlimb extensor muscles in the cat. *Experimental Brain Research*, 98(2), 213–228. <https://doi.org/10.1007/BF00228410>
- Gossard, J. P., Cabelguen, J. M., & Rossignol, S. (1991). An intracellular study of muscle primary afferents during fictive locomotion in the cat. *Journal of Neurophysiology*, 65(4), 914–926. <https://doi.org/10.1152/jn.1991.65.4.914>
- Goulding, M. (2009, July 1). Circuits controlling vertebrate locomotion: Moving in a new direction. *Nature Reviews Neuroscience*. <https://doi.org/10.1038/nrn2608>
- Grey, M. J., Nielsen, J. B., Mazzaro, N., & Sinkjær, T. (2007). Positive force feedback in human walking. *Journal of Physiology*, 581(1), 99–105. <https://doi.org/10.1113/jphysiol.2007.130088>
- Grillner, S. (2011, November 18). Human locomotor circuits conform. *Science*. <https://doi.org/10.1126/science.1214778>

- Grillner, S., Robertson, B., & Stephenson-Jones, M. (2013). The evolutionary origin of the vertebrate basal ganglia and its role in action selection. *The Journal of Physiology*, 591(22), 5425–5431. <https://doi.org/10.1113/jphysiol.2012.246660>
- Grillner, S., & Rossignol, S. (1978). On the initiation of the swing phase of locomotion in chronic spinal cats. *Brain Research*, 146(2), 269–277. [https://doi.org/10.1016/0006-8993\(78\)90973-3](https://doi.org/10.1016/0006-8993(78)90973-3)
- Grillner, S., Wallén, P., Saitoh, K., Kozlov, A., & Robertson, B. (2008). Neural bases of goal-directed locomotion in vertebrates-An overview. *Brain Research Reviews*, 57(1), 2–12. <https://doi.org/10.1016/j.brainresrev.2007.06.027>
- Grillner, S., & Zangger, P. (1975). How detailed is the central pattern generation for locomotion? *Brain Research*, 88(2), 367–371. [https://doi.org/10.1016/0006-8993\(75\)90401-1](https://doi.org/10.1016/0006-8993(75)90401-1)
- Grillner, S., & Zangger, P. (1984). The effect of dorsal root transection on the efferent motor pattern in the cat's hindlimb during locomotion. *Acta Physiologica Scandinavica*, 120(3), 393–405. <https://doi.org/10.1111/j.1748-1716.1984.tb07400.x>
- Guertin, P. A. (2009). The mammalian central pattern generator for locomotion. *Brain Research Reviews*, 62(1), 45–56. <https://doi.org/10.1016/j.brainresrev.2009.08.002>
- Guertin PA, Ung R-V, Rouleau P. (2010). Oral administration of a tritherapy for central pattern generator activation in paraplegic mice: proof-of-concept of efficacy. *Biotechnology Journal* 2010; 5: 421-6.
- Guertin, P., Angel, M. J., Perreault, M. C., & McCrea, D. A. (1995). Ankle extensor group I afferents excite extensors throughout the hindlimb during fictive locomotion in the cat. *The Journal of Physiology*, 487 197–209. <https://doi.org/10.1113/jphysiol.1995.sp02087>
- Haeufle, D. F. B., Schmorte, B., Geyer, H., Müller, R., & Schmitt, S. (2018). The Benefit of Combining Neuronal Feedback and Feed-Forward Control for Robustness in Step Down Perturbations of Simulated Human Walking Depends on the Muscle Function. *Frontiers in Computational Neuroscience*, 12, 80. <https://doi.org/10.3389/fncom.2018.00080>
- Harkema, S. J., Hurley, S. L., Patel, U. K., Requejo, P. S., Dobkin, B. H., & Edgerton, V. R. (1997). Human lumbosacral spinal cord interprets loading during stepping. *Journal of Neurophysiology*, 77(2), 797–811. <https://doi.org/10.1152/jn.1997.77.2.797>
- Hiebert, G. W., & Pearson, K. G. (1999). Contribution of sensory feedback to the generation of

- extensor activity during walking in the decerebrate Cat. *Journal of Neurophysiology*, 81(2), 758–770. <https://doi.org/10.1152/jn.1999.81.2.758>
- Hiebert, G., Whelan, P., Prochazka, A., & Pearson, K. (1996). Contribution of hind limb flexor muscle afferents to the timing of phase transitions in the cat step cycle. *Journal of Neurophysiology*, 75(3), 1126–1137.
- Hofstoetter, U. S., Knikou, M., Guertin, P. A., & Minassian, K. (2017). Probing the Human Spinal Locomotor Circuits by Phasic Step-Induced Feedback and by Tonic Electrical and Pharmacological Neuromodulation. *Current Pharmaceutical Design*, 23(12), 1805–1820. <https://doi.org/10.2174/1381612822666161214144655>
- Houk, J. C., Keifer, J., & Barto, A. G. (1993). Distributed motor commands in the limb premotor network. *Trends in Neurosciences*, 16(1), 27–33. [https://doi.org/10.1016/0166-2236\(93\)90049-R](https://doi.org/10.1016/0166-2236(93)90049-R)
- Jankowska, E., Jukes, M. G. M., Lund, S., & Lundberg, A. (1967). The Effect of DOPA on the Spinal Cord 6. Half-centre organization of interneurons transmitting effects from the flexor reflex afferents. *Acta Physiologica Scandinavica*, 70(3–4), 389–402. <https://doi.org/10.1111/j.1748-1716.1967.tb03637.x>
- Jordan, L. M. (1998). Initiation of locomotion in mammals. *Annals of the New York Academy of Sciences*, 860, 83–93. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/9928303>
- Jordan, L. M., Liu, J., Hedlund, P. B., Akay, T., & Pearson, K. G. (2008). Descending command systems for the initiation of locomotion in mammals. *Brain Research Reviews*, 57(1), 183–191. <https://doi.org/10.1016/j.brainresrev.2007.07.019>
- Katz, R., Meunier, S., & Pierrot-Deseilligny, E. (1988). Changes in presynaptic inhibition of Ia fibres in man while standing. *Brain : A Journal of Neurology*, 111 (Pt 2), 417–437.
- Kiehn, O. (2006). Locomotor circuits in the mammalian spinal cord. *Annual Review of Neuroscience*, 29, 279–306. <https://doi.org/10.1146/annurev.neuro.29.051605.112910>
- Kiehn, O. (2011). Development and functional organization of spinal locomotor circuits. *Current Opinion in Neurobiology*, 21(1), 100–109. <https://doi.org/10.1016/j.conb.2010.09.004>
- Kistemaker, D. A., Van Soest, A. J. K., Wong, J. D., Kurtzer, I., & Gribble, P. L. (2013). Control of position and movement is simplified by combined muscle spindle and Golgi tendon organ feedback. *Journal of Neurophysiology*, 109(4), 1126–1139.

<https://doi.org/10.1152/jn.00751.2012>

- Koblinger, K., Füzesi, T., Ejdrygiewicz, J., Krajacic, A., Bains, J. S., & Whelan, P. J. (2014). Characterization of A11 neurons projecting to the spinal cord of mice. *PloS One*, 9(10), e109636. <https://doi.org/10.1371/journal.pone.0109636>
- Kuo, A. D. (2002). The Relative Roles of Feedforward and Feedback in the Control of Rhythmic Movements. *Motor Control*, 6(2), 129–145. <https://doi.org/10.1123/mcj.6.2.129>
- Loeb, G. E., & Duysens, J. (1979). Activity patterns in individual hindlimb primary and secondary muscle spindle afferents during normal movements in unrestrained cats. *Journal of Neurophysiology*, 42(2), 420–440. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/154557>
- Machado, T. A., Pnevmatikakis, E., Paninski, L., Jessell, T. M., & Miri, A. (2015). Primacy of Flexor Locomotor Pattern Revealed by Ancestral Reversion of Motor Neuron Identity. *Cell*, 162(2), 338–350. <https://doi.org/10.1016/j.cell.2015.06.036>
- MacKay-Lyons, M. (2002). Central pattern generation of locomotion: a review of the evidence. *Physical Therapy*, 82(1), 69–83.
- Markin, S. N., Klishko, A. N., Shevtsova, N. A., Lemay, M. A., Prilutsky, B. I., & Rybak, I. A. (2010). Afferent control of locomotor CPG: Insights from a simple neuromechanical model. *Annals of the New York Academy of Sciences*, 1198(1), 21–34. <https://doi.org/10.1111/j.1749-6632.2010.05435.x>
- Markin, S. N., Lemay, M. A., Prilutsky, B. I., & Rybak, I. A. (2012). Motoneuronal and muscle synergies involved in cat hindlimb control during fictive and real locomotion: a comparison study. *Journal of Neurophysiology*, 107(8), 2057–2071. <https://doi.org/10.1152/jn.00865.2011>
- Matsuoka K (1985) Sustained oscillations generated by mutually inhibiting neurons with adaptation. *Biological Cybernetics* 52: 367–376.
- Matsuoka K. (2011). Analysis of a neural oscillator. *Biological Cybernetics*, 104(4-5):297-304. doi: 10.1007/s00422-011-0432-z
- Mayer, W. P., Murray, A. J., Brenner-Morton, S., Jessell, T. M., Tourtellotte, W. G., & Akay, T. (2018). Role of muscle spindle feedback in regulating muscle activity strength during walking at different speed in mice. *Journal of Neurophysiology*, 120(5), 2484–2497. <https://doi.org/10.1152/jn.00250.2018>

- Mayr W, Krenn M, Dimitrijevic MR. Epidural and transcutaneous spinal electrical stimulation for restoration of movement after incomplete and complete spinal cord injury. *Curr Opin Neurol*. 2016 Dec;29(6):721-726.
- Mazurek, K. A., Holinski, B. J., Everaert, D. G., Stein, R. B., Etienne-Cummings, R., & Mushahwar, V. K. (2012). Feed forward and feedback control for over-ground locomotion in anaesthetized cats. *Journal of Neural Engineering*, 9(2), 026003. <https://doi.org/10.1088/1741-2560/9/2/026003>
- McCrea, D. A., & Rybak, I. A. (2007). Modeling the mammalian locomotor CPG: insights from mistakes and perturbations. *Progress in Brain Research*, 165, 235–253. [https://doi.org/10.1016/S0079-6123\(06\)65015-2](https://doi.org/10.1016/S0079-6123(06)65015-2)
- McCrea, D. A., & Rybak, I. A. (2008). Organization of mammalian locomotor rhythm and pattern generation. *Brain Research Reviews*, 57(1), 134–146. <https://doi.org/10.1016/j.brainresrev.2007.08.006>
- Ménard, A., Leblond, H., & Gossard, J.-P. (2002). Sensory Integration in Presynaptic Inhibitory Pathways During Fictive Locomotion in the Cat. *Journal of Neurophysiology*, 88(1), 163–171. <https://doi.org/10.1152/jn.2002.88.1.163>
- Meyns, P., Van De Crommert, H. W. A. A., Rijken, H., Van Kuppevelt, D. H. J. M., & Duysens, J. (2014). Locomotor training with body weight support in SCI: EMG improvement is more optimally expressed at a low testing speed. *Spinal Cord*, 52(12), 887–893. <https://doi.org/10.1038/sc.2014.172>
- Molkov, Y. I., Bacak, B. J., Talpalar, A. E., & Rybak, I. A. (2015). Mechanisms of Left-Right Coordination in Mammalian Locomotor Pattern Generation Circuits: A Mathematical Modeling View. *PLoS Computational Biology*, 11(5), e1004270. <https://doi.org/10.1371/journal.pcbi.1004270>
- Nichols, T. R., & Houk, J. C. (1976). Improvement in linearity and regulation of stiffness that results from actions of stretch reflex. *Journal of Neurophysiology*, 39(1), 119–142. <https://doi.org/10.1152/jn.1976.39.1.119>
- Ogihara, N., & Yamazaki, N. (2001). Generation of human bipedal locomotion by a bio-mimetic neuro-musculo-skeletal model. *Biological Cybernetics*, 84(1), 1–11. <https://doi.org/10.1007/PL00007977>
- Paul, C., Bellotti, M., Jezernik, S., & Curt, A. (2005). Development of a human neuro-musculo-

- skeletal model for investigation of spinal cord injury. *Biological Cybernetics*, 93(3), 153–170. <https://doi.org/10.1007/s00422-005-0559-x>
- Pearson, K. G. (2004). Generating the walking gait: role of sensory feedback. *Progress in Brain Research*, 143, 123–129. [https://doi.org/10.1016/S0079-6123\(03\)43012-4](https://doi.org/10.1016/S0079-6123(03)43012-4)
- Pearson, K. G., & Duysens, J. (1976). Function of Segmental Reflexes in the Control of Stepping in Cockroaches and Cats (pp. 519–537). Springer, Boston, MA. https://doi.org/10.1007/978-1-4757-0964-3_21
- Philippson, M. (1905). L'autonomie et la centralisation dans le système nerveux des animaux: étude de physiologie expérimentale et comparée.
- Prilutsky, B. I., Herzog, W., & Allinger, T. L. (1994). Force-sharing between cat soleus and gastrocnemius muscles during walking: Explanations based on electrical activity, properties, and kinematics. *Journal of Biomechanics*, 27(10), 1223–1235. [https://doi.org/10.1016/0021-9290\(94\)90276-3](https://doi.org/10.1016/0021-9290(94)90276-3)
- Prochazka, A., Gillard, D., & Bennett, D. J. (1997). Implications of positive feedback in the control of movement. *Journal of Neurophysiology*, 77(6), 3237–3251.
- Roll, J. P., & Vedel, J. P. (1982). Kinaesthetic role of muscle afferents in man, studied by tendon vibration and microneurography. *Experimental Brain Research*, 47(2), 177–190.
- Roseberry, T. K., & Kreitzer, A. (2017). Neural circuitry for behavioural arrest. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, 372(1718), 20160197. <https://doi.org/10.1098/rstb.2016.0197>
- Rossignol, S. (2006). Dynamic Sensorimotor Interactions in Locomotion. *Physiological Reviews*, 86(1), 89–154. <https://doi.org/10.1152/physrev.00028.2005>
- Rybak, I. A., Dougherty, K. J., & Shevtsova, N. A. (2015). Organization of the Mammalian Locomotor CPG: Review of Computational Model and Circuit Architectures Based on Genetically Identified Spinal Interneurons. *ENeuro*, 2(5), ENEURO.0069-15.2015. <https://doi.org/10.1523/ENEURO.0069-15.2015>
- Rybak, I. A., Shevtsova, N. A., Lafreniere-Roula, M., & McCrea, D. A. (2006). Modelling spinal circuitry involved in locomotor pattern generation: Insights from deletions during fictive locomotion. *Journal of Physiology*, 577(2), 617–639. <https://doi.org/10.1113/jphysiol.2006.118703>

- Rybak, I. A., Stecina, K., Shevtsova, N. A., & McCrea, D. A. (2006). Modelling spinal circuitry involved in locomotor pattern generation: Insights from the effects of afferent stimulation. *Journal of Physiology*, 577(2), 641–658. <https://doi.org/10.1113/jphysiol.2006.118711>
- Schomburg, E. D., & Behrends, H. B. (1978). Phasic control of the transmission in the excitatory and inhibitory reflex pathways from cutaneous afferents to α -motoneurons during fictive locomotion in cats. *Neuroscience Letters*, 8(4), 277–282. [https://doi.org/10.1016/0304-3940\(78\)90136-2](https://doi.org/10.1016/0304-3940(78)90136-2)
- Sherrington, C. S. (1910). Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping and standing. *The Journal of Physiology*, 40(1–2), 28–121. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/16993027>
- Shevtsova, N. A., Talpalar, A. E., Markin, S. N., Harris-Warrick, R. M., Kiehn, O., & Rybak, I. A. (2015). Organization of left-right coordination of neuronal activity in the mammalian spinal cord: Insights from computational modelling. *Journal of Physiology*, 593(11), 2403–2426. <https://doi.org/10.1113/JP270121>
- Shik, M. L., Severin, F. V., & Orlovskii, G. N. (1966). [Control of walking and running by means of electric stimulation of the midbrain]. *Biofizika*, 11(4), 659–666.
- Sinnamon, H. M. (1993). Preoptic and hypothalamic neurons and the initiation of locomotion in the anesthetized rat. *Progress in Neurobiology*, 41(3), 323–344.
- Snijders, A. H., Takakusaki, K., Debu, B., Lozano, A. M., Krishna, V., Fasano, A., ... Hallett, M. (2016). Physiology of freezing of gait. *Annals of Neurology*, 80(5), 644–659. <https://doi.org/10.1002/ana.24778>
- Song, S., & Geyer, H. (2015). A neural circuitry that emphasizes spinal feedback generates diverse behaviours of human locomotion. *The Journal of Physiology*, 593(16), 3493–3511. <https://doi.org/10.1113/JP270228>
- Stein, R. B. (1995). Presynaptic inhibition in humans. *Progress in Neurobiology*, 47(6), 533–544.
- Stephens, M. J., & Yang, J. F. (1996). Short-latency, non-reciprocal group I inhibition is reduced during the stance phase of walking in humans. *Brain Research*, 743(1–2), 24–31. [https://doi.org/10.1016/S0006-8993\(96\)00977-8](https://doi.org/10.1016/S0006-8993(96)00977-8)
- Thorsen, D. H., Cassidy, J. J., & Hale, M. E. (2004). Swimming of larval zebrafish: fin-axis coordination and implications for function and neural control. *The Journal of*

Experimental Biology, 207(Pt 24), 4175–4183. <https://doi.org/10.1242/jeb.01285>

- Tourtellotte, W. G., & Milbrandt, J. (1998). Sensory ataxia and muscle spindle agenesis in mice lacking the transcription factor Egr3. *Nature Genetics*, 20(1), 87–91. <https://doi.org/10.1038/1757>
- Van der Noot, N., Ijspeert, A. J., & Ronsse, R. (2018a). Neuromuscular model achieving speed control and steering with a 3D bipedal walker. *Autonomous Robots*. <https://doi.org/10.1007/s10514-018-9814-6>
- Van der Noot, N., Ijspeert, A. J., & Ronsse, R. (2018b). Bio-inspired controller achieving forward speed modulation with a 3D bipedal walker. *The International Journal of Robotics Research*, 37(1), 168–196. <https://doi.org/10.1177/0278364917743320>
- Wernig, A., & Dobkin, B. H. (2006). Weight-supported treadmill vs over-ground training for walking after acute incomplete SCI. *Neurology*, 67(10), 1900–1900. <https://doi.org/10.1212/01.wnl.0000249079.73112.38>
- Yang, J. F., & Stein, R. B. (1990). Phase-dependent reflex reversal in human leg muscles during walking. *Journal of Neurophysiology*, 63(5), 1109–1117. <https://doi.org/10.1007/S00221-007-0990-4>
- Yang, J. F., Stein, R. B., & James, K. B. (1991). Contribution of peripheral afferents to the activation of the soleus muscle during walking in humans. *Experimental Brain Research*, 87(3), 679–687. <https://doi.org/10.1007/BF00227094>
- Yang, J. F., Stephens, M. J., & Vishram, R. (1998). Infant stepping: a method to study the sensory control of human walking. *Journal of Physiology*, 507(3), 927–937. <https://doi.org/10.1111/j.1469-7793.1998.927bs.x>
- Zehr, E. P., Balter, J. E., Ferris, D. P., Hundza, S. R., Loadman, P. M., & Stoloff, R. H. (2007). Neural regulation of rhythmic arm and leg movement is conserved across human locomotor tasks. *The Journal of Physiology*, 582(Pt 1), 209–227. <https://doi.org/10.1113/jphysiol.2007.133843>
- Zhong, G., Shevtsova, N. A., Rybak, I. A., & Harris-Warrick, R. M. (2012). Neuronal activity in the isolated mouse spinal cord during spontaneous deletions in fictive locomotion: insights into locomotor central pattern generator organization. *The Journal of Physiology*, 590(19), 4735–4759. <https://doi.org/10.1113/jphysiol.2012.240895>

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Conflict of Interest Statement

To whom it may concern:

The authors, Jacques Duysens and Arturo Forner-Cordero, declare no conflict of interest or competing financial interests with regard to the manuscript: **“A controller perspective on biological gait control: Reflexes and Central Pattern Generators”** by **J. Duysens and A. Forner-Cordero** for consideration for publication in Annual Reviews in Control.

We certify that we have no affiliation with or financial involvement in any organization or entity with a direct financial interest in the subject matter or materials discussed in the manuscript.

It is an original contribution, has not been previously published, is not under consideration for publication elsewhere, and, if accepted, it will not be published elsewhere in similar form, in any language.

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