

Review Article

Lower-Limb Robotic Rehabilitation: Literature Review and Challenges

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This paper presents a survey of existing robotic systems for lower-limb rehabilitation. It is a general assumption that robotics will play an important role in therapy activities within rehabilitation treatment. In the last decade, the interest in the field has grown exponentially mainly due to the initial success of the early systems and the growing demand caused by increasing numbers of stroke patients and their associate rehabilitation costs. As a result, robot therapy systems have been developed worldwide for training of both the upper and lower extremities. This work reviews all current robotic systems to date for lower-limb rehabilitation, as well as main clinical tests performed with them, with the aim of showing a clear starting point in the field. It also remarks some challenges that current systems still have to meet in order to obtain a broad clinical and market acceptance.

1. Introduction

Stroke is the third most frequent cause of death worldwide and the leading cause of permanent disability in the USA and Europe [1]. Neurological impairment after stroke frequently leads to hemiparesis or partial paralysis of one side of the body that affects the patient's ability to perform activities of daily living (ADL) such as walking and eating. Physical therapy, involving rehabilitation, helps improve the lost functions [2, 3].

The goal of rehabilitation exercises is to perform specific movements that provoke motor plasticity to the patient and therefore improve motor recovery and minimize functional deficits. Movement rehabilitation is limb dependent, thus the affected limb has to be exercised [4].

This paper focuses on lower-limb rehabilitation. One-third of surviving patients from stroke do not regain independent walking ability and those ambulatory, walk in a typical asymmetric manner [1]. Rehabilitation therapies are critical to recover, and therefore many research is ongoing on the field.

The rehabilitation process toward regaining a meaningful mobility can be divided into three phases [4–6]: (1) the bedridden patient is mobilized into the chair as soon as

possible, (2) restoration of gait, and (3) improvement of gait (i.e., training of free walking if possible).

Traditional rehabilitation therapies are very labor intensive especially for gait rehabilitation, often requiring more than three therapists together to assist manually the legs and torso of the patient to perform training. This fact imposes an enormous economic burden to any country's health care system thus limiting its clinical acceptance. Furthermore, demographic change (aging), expected shortages of health care personnel, and the need for even higher quality care predict an increase in the average cost from first stroke to death in the future. All these factors stimulate innovation in the domain of rehabilitation [7] in such way it becomes more affordable and available for more patients and for a longer period of time.

Robotics for rehabilitation treatment is an emerging field which is expected to grow as a solution to automate training. Robotic rehabilitation can (i) replace the physical training effort of a therapist, allowing more intensive repetitive motions and delivering therapy at a reasonable cost, and (ii) assess quantitatively the level of motor recovery by measuring force and movement patterns.

In the recent literature many works deal with robotic lower-extremity rehabilitation. The purpose of this paper is

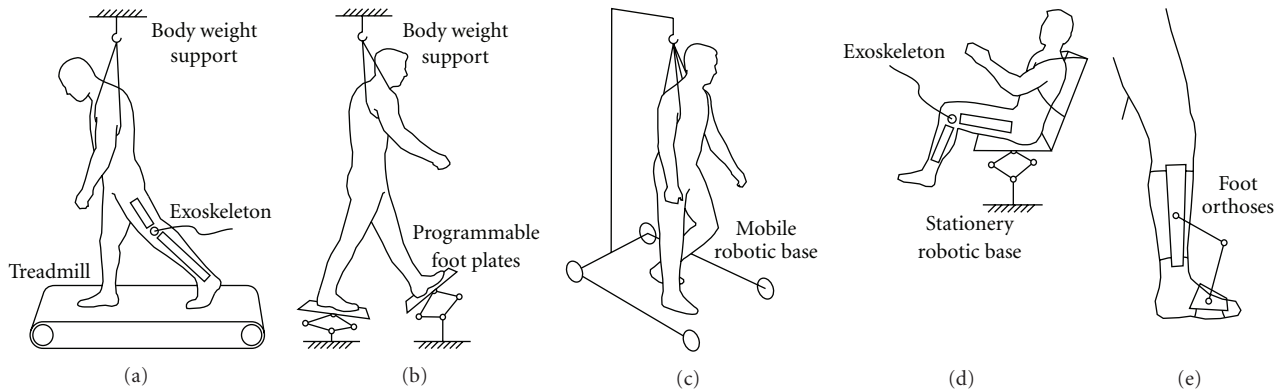


FIGURE 1: Robotic system types for lower-limb rehabilitation: (a) treadmill gait trainers, (b) foot-plate-based gait trainers, (c) overground gait trainers, (d) stationary gait and ankle trainers, and (e) active foot orthoses.

to review existing interfaces, as well as ongoing work, to show researchers current state of the art and roadmap in the field. Passive robotic rehabilitation devices, although less complex and cheaper, cannot supply energy to the affected limbs, hence are limited compared to active devices and are out of the scope of this work. Finally, current challenges in the field are also pointed out in the last section.

2. Robotic Systems for Lower-Limb Rehabilitation

Over the last decade, several lower-limb rehabilitation robots have been developed to restore mobility of the affected limbs. These systems can be grouped according to the rehabilitation principle they follow (Figure 1):

- (i) treadmill gait trainers,
 - (ii) foot-plate-based gait trainers,
 - (iii) overground gait trainers,
 - (iv) stationary gait trainers,
 - (v) ankle rehabilitation systems,
- (a) stationary systems,
 - (b) active foot orthoses.

Following subsections describe the working principle of each group and review all existing devices to date (to the best of our knowledge). Clinical tests performed with patients using such systems are also reported (test with healthy patients are excluded).

2.1. Treadmill Gait Trainers. Traditional therapies usually focus on treadmill training to improve functional mobility [8]. This rehabilitation technique is known as partial body-weight support treadmill training (PBWSTT). Three therapists assist the legs and hip of the patient walking on a treadmill while part of the patient’s body weight is supported by an overhead harness.

Many robotic systems have been developed with the aim to automate and improve this training technique as a means

TABLE 1: Robotic systems for treadmill gait training.

Robotic system	Company	Clinical tests
Lokomat [10]	Hocoma	[11–15]
LokoHelp [16]	LokoHelp Group	[16, 17]
ReoAmbulator [18]	Motorika	—
ARTHUR [19]	—	[21]
POGO and PAM [20]	—	—
ALEX [22]	—	[23]
LOPES [24]	—	[25]
ALTRACO [26]	—	—
RGR [27]	—	—
String-Man [28]	—	—

for reducing therapist labor [9]. Usually these systems are based on exoskeleton type robots in combination with a treadmill (Figure 1(a)). Table 1 summarizes the systems available in literature.

Of the 10 systems that compose the group, only three of them are on the market: the Lokomat, the LokoHelp, and the ReoAmbulator. The Lokomat (Hocoma AG) consists of a robotic gait orthosis and an advanced body weight support system, combined with a treadmill [10]. It uses computer-controlled motors (drives) which are integrated in the gait orthosis at each hip and knee joint (Figure 2). The drives are precisely synchronized with the speed of the treadmill to assure a precise match between the speed of the gait orthosis and the treadmill. Till date, it is the most clinically evaluated system [11–15] and one of the firsts of its type.

The LokoHelp (LokoHelp Group) is an electromechanical device developed for improving gait after brain injury [16]. The LokoHelp (Figure 3) is placed in the middle of the treadmill surface parallel to the walking direction and fixed to the front of the treadmill with a simple clamp. It also provides a body weight support system for the patient. Clinical trials have been conducted to analyze its feasibility and efficacy [16, 17]. The results show that the system improves the gait ability of the patient in the same way as the manual locomotor training; however, using the LokoHelp less therapeutic assistance is required and therapist



FIGURE 2: Lokomat system (picture courtesy of Hocoma).



FIGURE 3: LokoHelp gait trainer “Pedago” (picture courtesy of LokoHelp Group).

discomfort is reduced. This fact is a general conclusion for almost all robotic systems to date.

ReoAmbulator (Motorika Ltd., marketed in the USA as the “AutoAmbulator”) is another body-weight-supported treadmill robotic system [18]. Robotic arms are strapped to the patient’s legs at the thigh and ankle, driving them through a stepping pattern (Figure 4). A single-blind, randomized clinical trial to assess its effectiveness in stroke patients is currently underway. ReoAmbulator was developed in cooperation with the HealthSouth network of rehabilitation hospitals.

Other robotic systems are at a research state or under development, but have been already used to conduct some clinical testing. For example, the Biomechanics Lab at the University of California has developed several robotic devices for locomotor training after spinal cord injury: the Ambulation-assisting Robotic Tool for Human Rehabilitation (ARTHuR), a device designed to measure and manipulate human stepping on a treadmill [19]; the Pneumatically



FIGURE 4: ReoAmbulator robotic system (picture courtesy of Motorika Ltd.).

Operated Gait Orthosis (POGO), an improved leg-robot design; the Pelvic Assist Manipulator (PAM), a device that can accommodate and control naturalistic pelvic motion [20]. The former, ARTHuR, has been tested in a clinical trial [21] showing its reliability to perform subject-specific assisted stepping, thus reducing the effort required by the trainer during manual assistance.

The Active Leg Exoskeleton (ALEX) is a powered leg orthosis with linear actuators at the hip and knee joints, and with a force-field controller developed to provide assistance to the patient by using the assist-as-needed approach [22]. It has been tested with two chronic stroke survivors, whose gait patterns were substantially improved after the training [23]. Improvement was measured as an increase in the size of the patients’ gait pattern and in their walking speeds on the treadmill.

The gait rehabilitation robot LOPES (LOWER-extremity Powered ExoSkeleton) can move in parallel with the legs of a person walking on a treadmill, at pelvis height flexibly connected to the fixed world [24]. A first clinical trial is already completed that tests the efficacy of LOPES in improving the walking ability and quality of chronic stroke survivors [25].

Finally, there are three robotic systems under research: ALTRACO, RGR, and String-Man. The Automated Locomotion Training using an Actuated Compliant Robotic Orthosis (ALTACRO) project aims to develop a novel step rehabilitation robot using a lightweight, compliant, pneumatic actuator [26]. The device consists of a unilateral exoskeleton and a supportive arm to passively gravity-balance the device.

The Robotic Gait Rehabilitation (RGR) Trainer was built to target secondary gait deviations in patients after stroke. While patients ambulate on a treadmill, force fields are applied to the pelvis, that generate corrective forces as

TABLE 2: Foot-plate-based robotic systems.

Robotic system	Company	Clinical tests
Gangtrainer GT I [29]	Reha-Stim	[29–32]
HapticWalker [33]	—	[34]
GM5 [35]	—	[35]
LLRR [36]	—	—
Univ. Gyeongsang [37]	—	[37]

a response to deviations from normal pelvic motion [27]. The device is coupled to the patient via an orthopedic brace.

The String-Man [28], developed at Fraunhofer IPK, Berlin, is a robotic system for supporting the gait rehabilitation and restoration of motor functions. It has a particular kinematic structure with 7 wires attached to the trunk of the patient.

2.2. Foot-Plate-Based Gait Trainers. Some rehabilitation machines are based on programmable foot plates. That is, the feet of the patient are positioned on separate foot plates, whose movements are controlled by the robotic system to simulate different gait patterns (Figure 1(b)). Table 2 shows the review of such systems. It can be seen that only one system is on the market, although many others have done some clinical testing.

The Gangtrainer GT I (Figure 5), commercialized by Reha-Stim, can assist the patient in the recovery of his freedom of movement by relieving the body of its own weight and adapting speed from the individual ability of the patient [29]. Harness-secured patients are positioned on two foot plates, whose movements simulate stance and swing, and ropes attached to the patient can control the vertical and lateral movements of the center of mass. Many clinical studies have been conducted worldwide with this device [30–32], and it is considered as one of the pioneering robotic systems for rehabilitation. Similarly as for treadmill gait trainers, the Gangtrainer GT I is at least as effective as the manual treadmill therapy but requiring less input from the therapist.

The HapticWalker is a haptic locomotion interface able to simulate not only slow and smooth trajectories (like walking on an even floor and up/down staircases), but also foot motions like walking on rough ground or even stumbling or sliding, which require high-order system dynamics [33]. It is a major redesign of GT I with foot plate trajectories fully programmable, and it is currently being clinically evaluated in several trials with stroke patients and spinal cord injury patients [34].

The GaitMaster5 (GM5) is a recently developed gait rehabilitation system at the University of Tsukuba [35]. The patient straps his/her feet into pads that are lined with sensors (Figure 6). These pads are connected to motion platforms that can move the user’s foot forward (simulating walking) or up and down (like climbing).

The Lower-Limb Rehabilitation Robot (LLRR) can assist patients in simulating normal people’s footsteps and



FIGURE 5: The Gangtrainer GT I (picture courtesy of Reha-Stim).

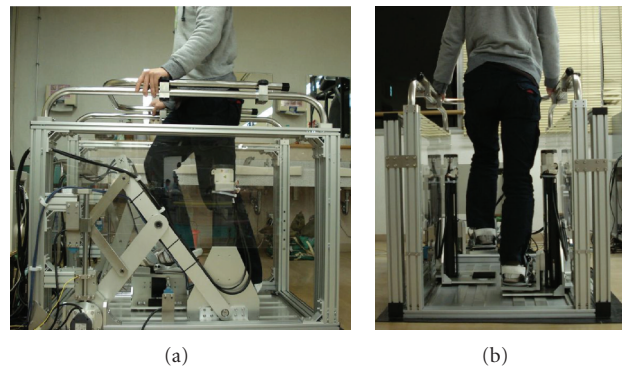


FIGURE 6: The GaitMaster5 gait rehabilitation system (picture courtesy of Dr. Hiroaki Yano).

exercising leg muscles [36]. It is comprised with steps posture controlling system and weight alleviation controlling mechanism.

A 6-degree-of-freedom (DOF) gait rehabilitation robot has been developed at the Gyeongsang National University with upper and lower limb connections that allow walking velocity updates on various terrains. It is composed of an upper limb device, a sliding device, two footpad devices, and a body support system. A pilot clinical test has been conducted with a hemiplegic patient [37].

2.3. Overground Gait Trainers. Systems reported in Table 3 consist of robots that servo-follow the patient’s walking motions overground. They allow patients move under their own control rather than moving them through predetermined movement patterns (Figure 1(c)). It is very noticeable that almost all systems reviewed have been commercialized.

The KineAssist is a robotic device (Figure 7), commercialized by Kinea Design, LLC, for gait and balance training [38]. It consists of a custom designed torso and pelvis harness attached to a mobile robotic base. The robot is controlled

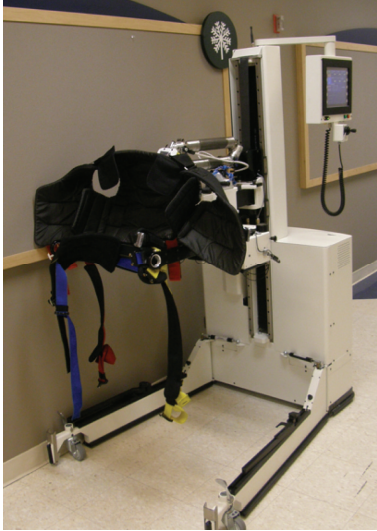


FIGURE 7: KineAssist robotic device (picture courtesy of Kinea Design, LLC).



FIGURE 8: ReWalk wearable system (picture courtesy of ARGO Medical Technologies Ltd.).

TABLE 3: Overground gait trainers.

Robotic System	Company	Clinical Tests
KineAssist [38]	Kinea Design LLC	[39]
WalkTrainer [40]	Swortec SA	[41]
ReWalk [42]	ARGO Medical	—
HAL [43]	CYBERDYNE Inc.	[44, 45]
WHERE I-II [46]	—	[46]

according to the forces detected from the subject by the load cells located in the pelvic harness. A recent clinical trial has been conducted [39] in order to evaluate overground walking speed changes when using the KineAssist system.

The WalkTrainer (Swortec SA) is a robotic rehabilitation system composed by a deambulator, a pelvis orthosis, a body weight support, two leg orthoses, and a real-time controlled electrostimulator [40]. It is an overground walking reeducation deambulator with the association of pelvic and leg orthoses. First clinical trials have been carried out with the system [41].

ReWalk is a wearable, motorized quasi-robotic suit from ARGO Medical Technologies Ltd., (Figure 8) that can be used for therapeutic activities [42]. ReWalk comprises light wearable brace support suit, which integrates DC motors at the joints, rechargeable batteries, an array of sensors, and a computer-based control system. Upper-body movements of the user are detected and used to initiate and maintain walking processes. The device is undergoing clinical trial testing at the Moss Rehabilitation Hospital in Philadelphia.

Hybrid Assistive Limb (HAL) is a wearable robot designed for a wide range of applications, from rehabilitation to heavy works support, and built in several versions (full body version and two-leg version) [43]. Current version 5 has been used to conduct clinical tests [44]. A single-leg version of HAL has also been developed to support the walking of persons with hemiplegia (Figure 9). The walking support was

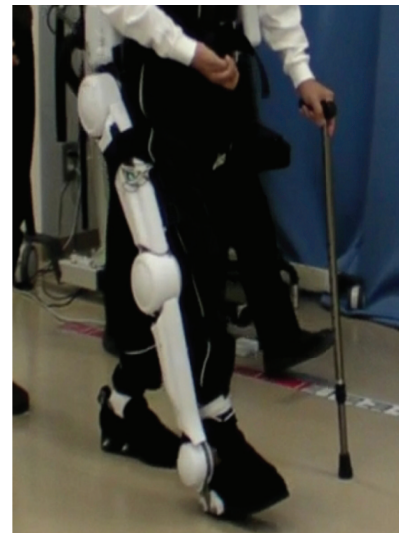


FIGURE 9: Single-leg version of HAL robot (picture courtesy of Professor Sankai, CYBERDYNE Inc./Univeristy of Tsukuba).

assessed with one hemiplegic subject who was not able to bend his right knee [45].

WHERE I and II are two mobile gait rehabilitation systems that enable overground gait training. Pilot clinical trials have been carried out to demonstrate the effectiveness of both systems (patients were in the stage of gait rehabilitation after suffering minor leg injuries) [46].

2.4. Stationary Gait Trainers. Table 4 presents robotic systems that are focused on guided movements of limbs in order to have an optimal effect from a therapeutic and functional perspective (Figure 1(d)). The objective of these systems is to obtain efficient strengthening of the muscles and the development of endurance, as well as joint mobility and movement coordination.

TABLE 4: Stationary robotic gait trainers.

Robotic system	Company	Clinical tests
MotionMaker [47]	Swortec SA	[40, 47]
Lambda [48]	—	—
AIST Tsukuba [49]	—	—



FIGURE 10: The MotionMaker rehabilitation system (Picture courtesy of Swortec SA).

The MotionMaker (Swortec SA) is a stationary training system which allows to carry out fitness exercises with active participation of the paralyzed limbs [47]. The limbs are only attached to the orthoses at the foot level to simulate natural ground reaction forces (Figure 10). The advantage of the MotionMaker is its real-time sensor-controlled exercises, combined with the controlled electrostimulation, adapted to the patients efforts. First clinical trials have been carried out with the system [40], showing an improvement of the patient's ability to develop a higher voluntary force during a leg-press movement.

Two other robotic systems that have been developed with a similar working principle: the Lambda, a rehabilitation and fitness robot used for mobilization of lower extremities [48] that provides the movement of the lower extremities in the sagittal plane, including an additional rotation for the ankle mobilization; and a wire-driven leg rehabilitation system [49] developed by the National Institute of Advanced Industrial Science and Technology (AIST) of Tsukuba.

2.5. Ankle and Knee Rehabilitation Systems. Neurological impairment after stroke can lead to reduced or no muscle activity around the ankle and knee causing the inability of an individual to lift their foot (drop foot). Ankle motion is very complicated due to its complex bone structures [50]. The overall motions of the ankle can be arranged as dorsiflexion/plantarflexion, inversion/eversion, abduction/adduction, and pronation/supination.

Many systems have been developed to enforce or restore these ankle and knee motions specifically. These systems can be grouped into stationary or active foot orthoses.

2.5.1. Stationery Systems. Stationary systems (Table 5) are those robotic mechanism designed to exercise the human

TABLE 5: Stationery robotic systems for ankle rehabilitation.

Robotic System	Company	Clinical Tests
Rutgers Ankle [51]	—	[52–54]
IIT-HPARR [56]	—	—
AKROD [57]	—	—
Leg-Robot [58]	—	—
GIST [59]	—	—
NUVABAT [60]	—	—
Univ. London [61]	—	—
Univ. Auckland [62]	—	—
Univ. Cheng Kung [63]	—	—
Univ. Fuzhou [50]	—	—
AIST Tsukuba [64]	—	—

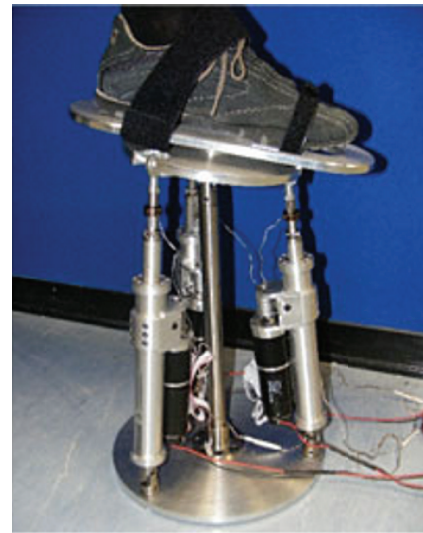


FIGURE 11: High Performance Ankle Rehabilitation Robot developed at the Istituto Italiano di Tecnologia.

ankle and knee motions without walking. The patient is positioned always in the same place, and only the target limb is exercised (Figure 1(d)).

The Rutgers Ankle was the first of this kind. It is a Stewart platform-type haptic interface that supplies 6 DOF resistive forces on the patient's foot, in response to virtual reality-based exercises [51]. Many clinical trials have been conducted with this system [52–54], showing the improvement of the patient on clinical measures of strength and endurance. In [55], the system was extended to a dual Stewart platform configuration to be used for gait simulation and rehabilitation.

The Istituto Italiano di Tecnologia (IIT) has developed a High Performance Ankle Rehabilitation Robot [56]. The proposed device allows plantar/dorsiflexion and inversion/eversion using an improved performance parallel mechanism that makes use of actuation redundancy to eliminate singularity and greatly enhance the workspace dexterity (Figure 11).

A more recent system, the Active Knee Rehabilitation Orthotic Devices (AKROD), provides variable damping at the knee joint, controlled in ways that can facilitate motor recovery in poststroke and other neurological disease patients and to accelerate recovery in knee injury patients [57]. Although it has been grouped as a stationary system, future work is focused on an actuated AKROD during walking.

The Osaka University has developed a leg-shaped robot (Leg-Robot) with a compact magnetorheological fluid clutch to demonstrate several kinds of haptic control of abnormal movements of brain-injured patients [58]. This system can be used in the practical training for students of physical therapy.

The Gwangju Institute of Science and Technology (GIST) has developed a reconfigurable ankle/foot rehabilitation robot to cover various rehabilitation exercise modes [59]. The robot can allow desired ankle and foot motions, including toe and heel raising as well as traditional ankle rotations. The system was designed to perform strengthening and balance exercises.

The so-called Northeastern University Virtual Ankle and Balance Trainer (NUVABAT) rehabilitation system is a low-cost, compact, mechatronic rehabilitation device for training of ankle range of motion (ROM) exercise in sitting and standing positions and also weight shifting and balance training in standing position [60].

The Department of Mechanical Engineering at the King's College has proposed an ankle rehabilitation robot based on a parallel mechanism with a central strut [61]. The University of Auckland has also developed a parallel robot to perform ankle rehabilitation exercises [62]. In this last system, the human ankle is secured to the end effector in such a way that it forms part of the kinematic constraint of the robot.

The Man-Machine Systems Laboratory (MML) at the National Cheng Kung University (NCKU) has developed a robot for assisting rehabilitation of patients with ankle dysfunction [63], and the School of Mechanical Engineering and Automation at the University of Fuzhou has performed an in-depth motion analysis of the ankle and has proposed two different kinds of rehabilitation robots [50]. The AIST of Tsukuba has developed a robotic device for ankle dorsiflexion/plantarflexion that can be applied to patients with complicated ankle joint deformity [64].

2.5.2. Active Foot Orthoses. On the contrary to stationary systems, active foot orthoses (Table 6) are actuated exoskeletons that the user wears while walking overground or in a treadmill (Figure 1(e)). They are intended to control position and motion of the ankle, compensate for weakness, or correct deformities. They are an evolution of traditional passive lower limb orthoses, with additional capabilities to promote appropriate gait dynamics for rehabilitation [65].

Two early attempts to develop such systems were the Powered Gait Orthosis (PGO) [66] and the Pneumatic Active Gait Orthosis (PAGO) [67]. Both devices underwent testing on human participants, but they were not commercialized.

TABLE 6: Active foot orthoses.

Robotic system	Company	Clinical tests
PGO [66]	—	[66]
PAGO [67]	—	[67]
Anklebot [68]	Interactive Motion	[69, 70]
MIT-AAFO [71]	—	[71]
AFOUD [72]	—	—
KAFO [73]	—	[81]
RGT [75]	—	[76]
Yonsei-AAFO [77]	—	[78]
SUKorpion AR [79]	—	—

Currently, the only commercialized system for rehabilitation is the Anklebot (Interactive Motion Technologies, Inc.), an ankle robot developed at the Massachusetts Institute of Technology (MIT) to rehabilitate the ankle after stroke [68]. It allows normal range of motion in all 3 DOF of the foot relative to the shank while walking overground or on a treadmill. Pilot controlled trials with such device were presented in [69, 70], showing a carry over to characteristics of gait with a general improvement in the walking distance covered and time.

The MIT also developed an Active Ankle-Foot Orthosis (AAFO) where the impedance of the orthotic joint is modulated throughout the walking cycle to treat drop-foot gait [71].

Another system is the Ankle Foot Orthosis at the University of Delaware (AFOUD) with 2 DOF. The two motions incorporated are dorsiflexion/plantarflexion and inversion/eversion motion [72].

Knee-Ankle-Foot-Orthosis (KAFO) is an orthosis powered by artificial pneumatic muscles during human walking [73]. The authors had previously built a powered Ankle-Foot-Orthosis (AFO) and used it effectively in studies on human motor adaptation and gait rehabilitation [74].

The Robotic Gait Trainer (RGT) developed in the Human Machine Integration Laboratory at the Arizona State University is a walking device (Figure 12) meant to be used on a treadmill [75]. It is naturally compliant due to the spring in muscle actuators and has the ability to achieve a more natural gait by allowing the patient's ankle joint to move in eversion, inversion, plantarflexion, and dorsiflexion. A case study conducted with a female was reported to examine the performance of the system [76]. The patient suffered no disadvantage as a result of the RGT incorporated therapy, where performance indicators either improved or stayed the same.

The Yonsei University has developed an active ankle-foot orthosis (Yonsei-AAFO) that can control dorsiflexion/plantarflexion of the ankle joint to prevent foot drop and toe drag during walking [77]. Gait analyses were performed on a hemiplegic patient, and the results indicated that the developed AAFO might have more clinical benefits to treat foot drop and toe drag in hemiplegic patients, comparing with conventional AFOs [78].

In a recent work, The Sabanci University Kinetostatically Optimized Reconfigurable Parallel Interface on Ankle Rehabilitation (named SUKorpion AR) has been presented,

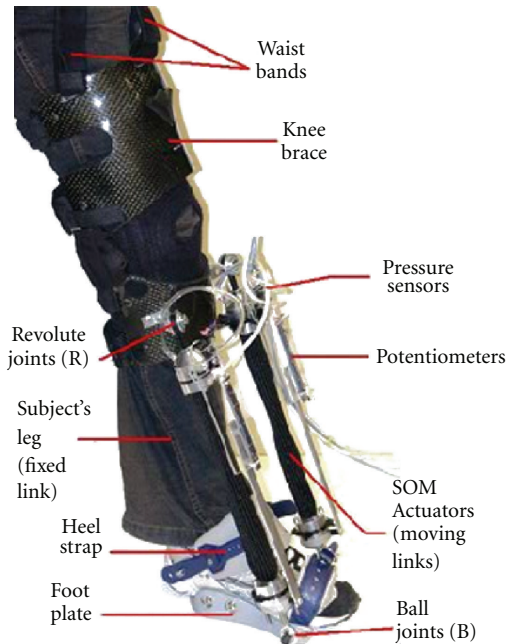


FIGURE 12: The Robotic Gait Trainer developed in the Human Machine Integration Laboratory at the Arizona State University.

which can be either employed as a balance/proprioception trainer or configured to accommodate range of motion and strengthening exercises [79].

3. Challenges

Robotic systems are believed to be used as standard rehabilitation tools in the near future. Furthermore, worldwide efforts are being made to automate locomotor training to reduce health care costs. The capacity of robots to deliver training with high intensity and repeatability make them very valuable assistant tools to provide high quality treatment at a lower cost and effort. These systems should also be used at home to allow patients to perform therapies independently, not replacing the therapist but supporting the therapy program.

This work has reviewed 43 robotic systems for lower-limb rehabilitation, of which more than half have not yet been marketed. Moreover, those systems available at the market are not developed as yet for application at home. Main reasons are elevated costs, lack of high clinical improvement evidence, and the need for a therapy protocol and assessment criteria. In addition, current systems are somewhat bulky and the mobile systems still lack long duration power supply solutions.

The usage of robotic systems allows precise measurement of movement kinematics and dynamics, which should be used for assessing patient recovery ability and progress. However, there is a need to develop standard protocols and procedures to obtain reliable assessment data. Currently, patient recovery of walking ability is usually quantified by employing clinical measures such as the Barthel index [80]. Regarding robotic systems, gait velocity and walking distance, ROM,

and many other dynamic measures have been used for assessment. However, there is not an standardized and widely (and clinically) accepted method. Therefore, large clinical trials are needed to determine clinical criteria for its use.

Finally, clinical studies conducted still show little evidence for a superior effectiveness of the robotic therapy, although a clear benefit is shown in reduced therapist effort, time, and costs. It has been shown that robotic rehabilitation can be as effective as manually assisted training for recovery of locomotor capacity, but a higher benefit should be desirable to spread its use in clinics worldwide.

Conflict of Interests

The authors have declared that no conflict of interests exists.

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