Proposal

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1 Specific Aims

Split-belt treadmills have been widely used as a way to study adaptation of locomotion in humans [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20], and have also been shown to be a useful treatment for regaining gait symmetry following stroke [13, 14]. However, it has also been observed that the gait adaptation that takes place on a treadmill generalizes poorly to overground walking [4, 5], which is the true rehabilitation target behavior.
Studies on other modalities of motor adaptation such as saccadic gain adaptation, and reaching with altered visual feedback or environmental dynamics have helped develop computational descriptions of motor adaptation [21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31]. These models offer both insight into the processes that the central nervous system (CNS) relies on to control movement and testable predictions for new experimental protocols. This type of models are missing in locomotion, and here I propose to address the construction of such models on a stride-by-stride basis, in order to expand our understanding of the factors that affect it. This understanding has the potential to aid in the design of more effective rehabilitation treatments.

Aim 1: Characterize & model the dynamics of speed difference perception on a split-belt treadmill task. Mismatch between predicted and actual sensory information has been linked to recalibration of internal models used for motor control, and perceptual adaptation has been used as a proxy to assess it [32, 25]. This recalibration is believed to be the cause of the aftereffects observed following motor adaptation. We hypothesize that perception of belt-speed differences is a way to probe the recalibration of internal forward models during walking, which predict the sensory consequences of our actions. In this aim I will use a simple task to characterize the perception of belt-speed differences before, during and following split-belt treadmill adaptation. I will use this data to develop a computational description of the estimation of environmental dynamics (belt-speed difference) during walking and describe its evolution during split-belt treadmill adaptation.

Aim 2: Characterize & model motor behavior to short exposures to a split-belt treadmill environment. This aim focuses on obtaining a computational description of the input-output relation of the subjects walking on a treadmill, where the inputs are the experimenter controlled belt-speeds and outputs are gait parameters. I propose a novel approach that exposes subjects to repeated short-term perturbations lasting 1 to 20 strides. This will allow us to quantify motor behavior accurately, distinguishing between feedthrough terms, reactive or balance responses which show little or no after-effects [12], and longer-term adaptation responses which I hypothesized to be related to perceptual/motor recalibration, in opposition to the other two. Critically, I will test the effects of walking at different speeds and different perturbation sizes, factors that are often overlooked when studying split-belt treadmill adaptation.

Aim 3: Determine the interdependence of perceptual and motor aftereffects following adaptation to the split-belt treadmill environment. It is known that subjects adapt their perception of belt speeds and motor behavior following split-belt treadmill walking. Perceptual adaptation is thought to correspond to recalibration of internal forward models, while motor aftereffects correspond to inverse models. I hypothesize that the adaptation of belt-speed perception is driven by the same process that contributes to most motor aftereffects. I will test this hypothesis with an innovative adaptation protocol which dissociates the adaptation of perception and motor components. Results from this aim will help us understand the interdependence, or lack thereof, between perceptual and motor aftereffects.

Aim 4: Develop a human-in-the-loop controller of belt-speeds on a treadmill. In this aim I will test closed-loop control of treadmill speed by using subjects' motor output as feedback for the controller. This is in opposition to all of current experimental setups, in which we determine belt-speed profiles in advance and regardless of subject behavior during the task. A closed-loop controller of the treadmill will allow the development of 'error-clamp' conditions that would shed light onto how the nervous system controls walking, by for example assessing the 'natural-decay' of the different components (motor, perceptual) of the adapted state following adaptation. It is proposed to advance towards this 'error-clamp' by identifying a behavioral correlate of belt-speed perception and using that signal for closed-loop control. Belt-speed perception was chosen because it has several properties that suggests it is a prominent error signal to the CNS in the control of walking and a driver of adaptation.

2 Research Strategy

2.1 Significance and Innovation

Significance. Effective human locomotion requires adaptation of our movements in order to compensate for an ever changing environment with which we interact (e.g. icy surfaces, windy streets) or for changes in the body (e.g. growth, pregnancy). Our sensorimotor system is constantly sensing those changes and actively compensating for them, through both feedforward (predictive) and feedback (reactive) mechanisms [33].

Locomotor adaptation processes can be investigated in the laboratory with a split-belt treadmill, which has two belts that are driven at different speeds to create novel environmental conditions [12, 13, 14, 4, 5, 1, 2, 11, 15, 34, 35]. It has been demonstrated that subjects adapt and show aftereffects on their gait kinematics [12, 4, 2, 5], kinetics [8, 15], and muscle activity [36, 15] during split-belt walking to account for the experimentally imposed environmental perturbations. Diverse factors have been shown to have an effect on split-belt treadmill adaptation, such as age [11], how the perturbation is introduced [5], repeated exposures to split-belt environment [2], and neurological disorders such as cerebellar ataxia [6] or stroke [14]. However, we currently lack quantitative descriptions of the evolution of these variables upon encountering a perturbed environment, as well as how information is gathered from the environment to allow for this adaptation.

Finding computational descriptions of the dynamics that adequately explain empirical observations for split-belt experiments could lead to an opportunity to predict further results and design experiments accordingly. Other modalities of motor adaptation, such as reaching with altered visual feedback or environmental dynamics, or saccadic adaptation have already been described through computational models [21, 22, 23, 24, 37, 26, 27, 28, 29, 30, 31, 38]. Critically, these models quantify the effect of the factors that contribute to motor control and offer testable predictions about how the CNS may implement it. For split-belt treadmill adaptation, there was a single study that proposed a computational model [7]. However, this model was purely descriptive and does not offer any predictions of experimental outcomes, nor does it have any implications on how the CNS implements control of locomotion.

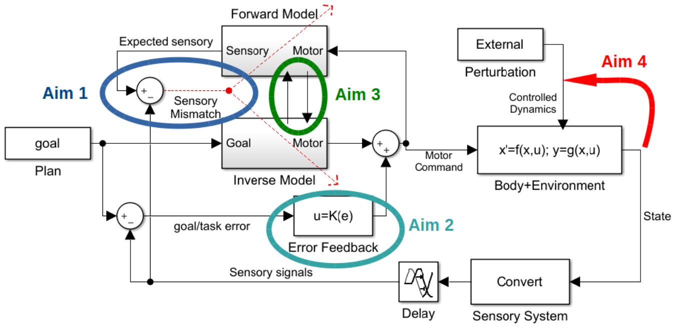

Figure 1: Summary of aims. Schematic of motor control architecture adapted from [31] and [39].

Characterization of the adaptation dynamics of subjects in a split-belt environment would help us understand the relation between the different processes that contribute to locomotor adaptation responses in the intact nervous system. For example, it has been suggested that temporal and spatial parameters are adapted independently through processes that have different timescales [12], and it is well established that some features of gait change rapidly in a reactive manner and show no adaptation or aftereffects, while some others are only slowly adapted requiring longer exposure periods [2]. A recent study we conducted (unpublished) on a chronic stroke population suggests that it is possibly the reactive behavior, and not the adaptive one, which is most impaired in this population. However it is difficult to model the different components of subjects' responses and their relation, when the dynamics of the responses have not been properly characterized and we don't understand how they depend on simple factors like walking speeds or belt-speed differences.

Understanding the role of internal model recalibration in locomotor adaptation can positively impact the design of rehabilitation treatments for hemiparetic gait. Perceptual recalibration following motor adaptation is a well-established fact, and has recently been shown for locomotor adaptation too [9]. Sensory information plays two key roles in motor control. First, it is used to guide feedback control which allows subjects to rapidly respond to perturbation (e.g. to avoid falling). Second, it is used to construct internal models of how the environment and the body function, which are used for planning of actions and prediction of the sensory consequences [**?**, 31]. Recalibration of these models during motor adaptation is one of the possible causes of aftereffects [40]. Aftereffects that originate in perceptual recalibration, as opposed to those that originate on the learned dynamics of a new environment possibly generalize more to different or 'real-world' contexts such as overground walking [22]. Understanding how to maximize generalization is essential to the development of effective rehabilitation treatments where subjects learn on a given context (e.g. treadmill on a clinical environment) but are expected to carry the learned behavior to everyday tasks that occur outside the clinical setting.

Innovation. This proposal aims at developing computational models of motor and sensory adaptation on a split-belt treadmill in a systematic way. These models will offer a summarizing description of previously acquired knowledge, and will give us further understanding and interpretation of how locomotion is controlled by the CNS. For example, they may help understand which variables play important roles in the healthy motor system but are impaired following injury. Importantly, these models will also enable the prediction of behavior, which so far has not been achieved for locomotion.

It is also proposed to address the role of perceptual recalibration in locomotion not just as a by-product of motor adaptation, but as a proxy for the changes in internal models that happen during this adaptation. Because sensory mismatch is hypothesized to be a signal that drives motor adaptation, understanding this recalibration offers a first approach to identifying the driving signals of locomotor adaptation, which are currently unknown.

Finally, a novel way to conduct split-belt experiments is proposed, moving away from predefined experimental schedules towards an environment controlled through the real-time feedback of subject behavior into belt speeds. This closed-loop control can be useful for the design of novel experimental paradigms to test motor control, but is potentially useful in gait rehabilitation too, allowing for the reinforcement of specific desired behaviors (or minimizing undesired ones) in patients undergoing treatment on a split-belt treadmill.

2.2 Approach

Aim 1: Characterize and model the dynamics of speed difference perception on a split-belt treadmill task

Introduction

This aim looks to answer two questions about belt-speed perception on a split-belt treadmill. First, can we computationally characterize how healthy subjects perceive a speed difference between the two belts in a split-belt treadmill and drive it to zero when given control over the speeds?. Second, what are the dynamics of perceptual adaptation during split-belt treadmill exposure? It is proposed to explore both questions through a modified version of the perceptual task used on [9], which showed that speed perception is adapted following split-belt treadmill walking. Subjects will be perturbed by having one belt be faster than the other, and then will be given control of the belt speeds and asked them to return them to what they feel is symmetrical (i.e. no belt-speed difference). A task which assesses subjects' perception of belt speeds and can be completed in a short period of time is useful for probing perceptual adaptation during motor adaptation protocols [32, 25]. The usefulness of the probe depends on understanding the characteristics of the response such as accuracy (i.e. how close are the responses to actual belt speeds), settling-time (i.e. how long it takes to reach the final response), and the dependence on the initial condition (i.e. whether perception is affected by belt-speed history). Additionally, understanding and modeling how subjects gather information from the environment to form an estimate of belt-speed difference may offer insight on the split-belt treadmill adaptation process. Study 1 will look to answer the first question by characterizing the response of a group of individuals to a belt-speed difference when their perception is not altered. Study 2 will address the second question by using the same task as a 'perceptual catch' during a motor adaptation protocol. Understanding and modeling this dynamics may also enable the prediction of its evolution, allowing for the simulation of virtual experiments which can aid in the selection and design of further experiments.

Justification & Feasibility

Sensory velocity mismatch is the difference between the predicted and actual sensation of belt speeds. It is hypothesized that sensory velocity mismatch is one of the signals used for recalibration of the internal models used for control of walking. This sensory mismatch will be probed through a perception task, as has been done before for reaching [32, 25]. Understanding the dynamics of this signal will offer a window into the dynamics of internal model recalibration. Study 1 has two objectives, a methodological one and a basic science one. Methodologically, I will test and validate a task for assessing perception of belt-speed difference on a split-belt treadmill, and characterize subject responses (in particular response times and repeatability). This will enable us to use the task for the assessment of perceptual adaptation through 'perceptual catch' trials within an arbitrary split-belt treadmill adaptation protocol, as is done in study 2. From the basic science point of view, I will obtain information about the limits (accuracy) of belt-speed difference perception in humans, understand how short-term perceptual adaptation may affect the responses, characterize inter-subject differences, and model how subjects make decisions on a dynamic perception task. It is well established that split-belt treadmills induce motor adaptation and aftereffects in both treadmill and overground walking and its evolution during adaptation has been described [12, 4, 5, 2, 11]. It has been shown that belt speed perception is also adapted upon split-belt treadmill exposure [9]. However, the dynamics of perceptual adaptation have not been properly studied. While it has been reported that introducing a perturbation gradually instead of abruptly leads to larger belt-speed perceptual adaptation [10], other questions remain regarding specificity of perceptual adaptation, learning, forgetting and re-learning rates, its dependence on perturbation size, and possible computational models that can be used to describe it (e.g. linear time-invariant systems, which have been shown to be insufficient to describe all characteristics of motor adaptation [24, 7]). Understanding these things can shed light on the relation of perceptual to motor adaptation. Study 2 looks to characterize this perceptual adaptation dynamics.

Methods

Methods common to both studies: In both studies the same perceptual task will be used, shown in Figure 2. Subjects will be walking on a split-belt treadmill with belt speeds determined by the experimenters. At given times (signaled by an audio cue) subjects will be asked to change the belt speeds to what they perceive to be equal speeds in both legs (response phase). Subjects will respond by using a keypad with two buttons. One button increases the speed in one belt while reducing it by an equal amount in the other; the other button has the opposite effect. The mean speed of the belts remains fixed during the task. Subjects will be allowed to familiarize themselves with the control system prior to any data being recorded. During the task, subjects will be deprived of environmental auditory cues through the use of noise-cancelling headphones, and of visual cues by blocking their ability to see their feet or the treadmill.
Study 1: The perceptual task will be applied repeatedly to a group (N=10) of healthy subjects. Each repetition of the perceptual task will be inserted within a 'trial' that consists of four phases: baseline, perturbation, response and return. During baseline (8 strides), subjects will be walking with both belts moving at the same speed (1m/s). The perturbation phase (2 strides) is characterized by a sudden change in belt-speed difference determined by the experimenters. At this point the subjects will hear the audio cue that marks the start of the perceptual task (response phase), which lasts for 15 strides until subjects hear the auditory cue that marks the end of this phase. During these 15 strides, subjects have control of belt-speed difference through the provided keypad. The last phase is the return (5 strides), in which belt speeds are gradually returned from their current state to baseline speeds (tied belts). All perturbations will be such that the mean belt speed always stays at 1m/s (e.g. one perturbation has one belt going at 1.1m/s while the other moves at 0.9m/s). The perturbation sizes to be used (difference in belt speeds) will be 6: 0m/s (null trial), .05m/s, 0.1m/s, 0.2m/s and 0.3m/s, presented with either belt going faster for a total of 12 different perturbations. The perturbation schedule will be organized in 10 identical blocks that are presented successively. Each block will have 12 trials, with each trial using a different perturbation presented in pseudo-random order. Subjects will be allowed to take a break of up to 10 minutes following the 5th block. The full protocol is expected to take between 60 and 90 minutes to complete for each subject.
Study 2: Five groups of subjects (N=10 each) will complete a split-belt treadmil adaptation and washout protocols. At fixed intervals during the protocol subjects will have to complete the perceptual task described above.

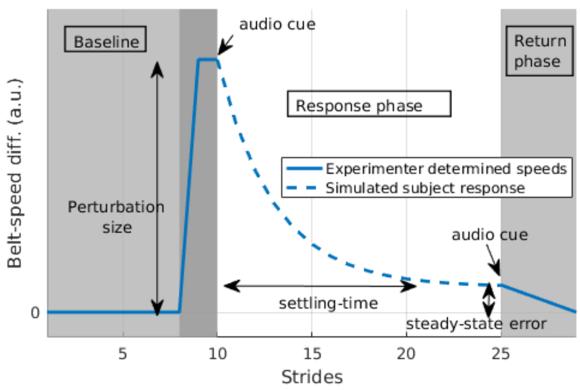

Figure 2: Study 1 perceptual task. Belt speeds will be perturbed, subjects will respond and then belt-speeds will be driven gradually to baseline.

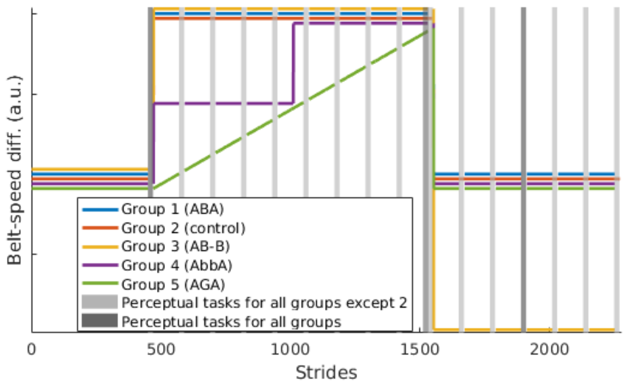

Figure 3: Study 2 proposed protocol. Different from study 1, perceptual tasks in this protocol will start with the belt-speed difference that subjects were walking at, and return to it.

In this case the initial belt-speeds in the response phase will be the same that the subjects were previously walking at (belts are not stopped). After the response phase is over (15 strides), subjects will be gradually returned to the same speeds they were previously walking at (10 strides) and continue with the adaptation protocol. Group 1 will follow an abrupt adaptation and washout paradigm (ABA), and will be used as a baseline for comparison to other groups. Group 3 will be adapted abruptly (same as group 1), but will follow an augmented washout protocol (AB-B) [41] in which the belt speeds will be inverted (the belt that was previously the fastest will become the slowest and viceversa). This group, when compared to group 1, will allow us to understand how the washout dynamics are affected by the washout condition. Groups 4 and 5 will be introduced to a perturbation of the same size as 1, but introduced differently to test for the effect of error sizes during introduction, and specifically for non-linearities in perception dynamics. Group 4 (AbbA) will be introduced to it through two abrupt changes of equal size, while group 5 (AGA) will be introduced to it gradually. Group 2 will serve as a control for the effect of having multiple perceptual tasks. It will follow the same paradigm as group 1, but will only complete the perceptual tasks at the end of baseline, end of adaptation and halfway into washout. This will enable us to assess if performing the perceptual task alters in any way the perceptual or motor adaptation dynamics.

Data Analysis

Study 1: The quantity of relevance during the experiment is belt-speed difference. Since the mean belt speed is maintained throughout the experiment, belt speed difference fully characterizes the environment in which the subjects are walking. I will test whether the belt speed difference at the end of the response phase, for each perturbation value, is significantly different from 0 (i.e. whether subjects can return to symmetry from that initial condition). The statistical test will be a 1-way ANOVA (initial perturbation will be the independent factor) with corresponding Tukey-Kramer post-hoc if any significant differences are found. I will also compare the final differences to the value at the beginning of the response phase (i.e. whether subjects are able to perceive the perturbation). The responses for each subject will be averaged over repetitions of each perturbation (e.g. all the blocks in which the belt speed difference was initially 200 mm/s will be averaged), and these will be used to inform the development of a computational model for subject responses in the task. In particular, to answer the question of whether there is or not a perceptual threshold, or just reduced sensitivity to small errors. Initially it will be attempted to model responses through the system represented by equations 1 and 2. The model has three variables that need to be fitted: the variances of the stochastic signal w_k (assumed to have zero mean), the gain a, and the functional form of f. The functional form f is the only one that is expected to be common to all subjects, while the other three will be allowed to have different values for each subject.

Study 2: Results for group 1 and 2 will be compared at the time points in which both groups performed the perceptual task (two-sample t-test), to test for differences introduced by multiple perceptual testing. All groups will be compared (one-way ANOVA with GROUP as factor) in their perception results at the end of adaptation, and perception at the first task during adaptation and post-adaptation. One- and two-state LTI systems will be fitted to the data of all groups, to assess which model better describes the observed dynamics of speed perception during adaptation and washout phases. Akaike's Information Criteria (AIC) [42] will be used to assess the goodness-of-fit of the models, since they may have a different number of parameters. Results from group 3 we will determine the number of strides required in the augmented washout phase to return subjects to their baseline perception levels, and compared to the strides required for group 1. This information is relevant for the design of Aim 3.

Expected results

Study 1: Two prior studies indicate that subjects are unable to perceive belt-speed differences smaller than 0.1m/s [35, 34], while another study concluded that subjects are able to perceive differences as small as 0.02m/s [43]. Our expectation is that subjects will be unable to respond to perturbations much smaller than 0.1m/s (i.e. the final speed difference will not be significantly different from the initial speed difference), but will be able to do so for larger perturbations, up to this threshold (i.e. will be unable to correct further). It is also expected that there will be a perturbation effect size. Specifically that large perturbations will be corrected with less precision than small ones, because of an adaptation effect that happens during the task itself.
Study 2: The expectation here is that the dynamics of perceptual adaptation will be simpler than those of motor adaptation, as it is hypothesized to be a sub-process of it. A single LTI system (such as the one proposed in [21]) may be sufficient to describe the data from all groups, but it is unlikely given that LTI systems have been shown to be insufficient to explain motor adaptation in the past [7, 24]. Non-linear model alternatives to be tested are a bayesian estimation and integration approach [22], and self-tuning control architectures. Learning and decay rates are expected to be consistent with previously reported rates for abrupt motor adaptation in split-belt treadmills, in particular with the slow-rate of the two-state models fitted in [7]. Dynamics are expected not to have discontinuities following belt speed changes, as perceptual changes are hypothesized to happen slowly.

Preliminary Studies

The proposed protocol for study 1 was tested on a few expert subjects and one naive subject, and all were able to complete the task with varying degrees of accuracy. This shows that there are no impediments to collect the data and perform the desired analysis. Sample results are presented in Figure 4.

Correction dynamics model (study 1):

$$\Delta v_{k+1} = \Delta v_k + u_k \tag{1}$$

$$u_k = -a.f(\hat{\Delta v_k}) + w_k \tag{2}$$

Where Δv_k is the belt-speed difference in step k, $\hat{\Delta v_k}$ is the perceived difference, u_k is the action taken to modify the speeds, w_k is the action noise or exploratory behavior, f is the perception function that maps actual belt-speed difference to perception (e.g. a linear or quadratic mapping), and a is an action gain ($a > 0$). A simple *memory-less* estimation model would have $\hat{\Delta v_k} = \Delta v_k + z_k$, where z_k is a sensory noise term. A more sophisticated model could incorporate dynamics of state-estimation in the form $\hat{\Delta v_k} = A\hat{\Delta v_{k-1}} + B\Delta v_k + z_k$, in a Kalman-like [44] framing of the problem.

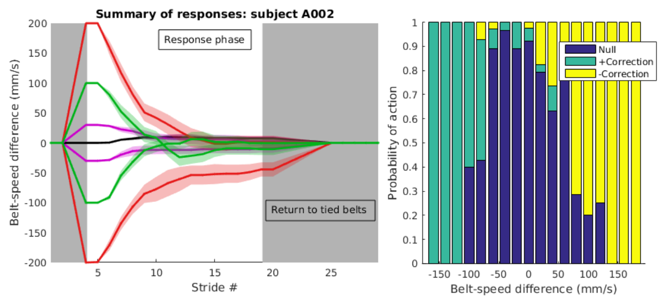

Figure 4: Results from pilot of study 1. First panel shows average subject responses for several different initial belt-speed differences. Second panel shows the probabilities of action (increasing, decreasing or not changing belt speeds) as a function of belt-speed difference for all strides in the experiment.

Potential Problems and Alternative Approaches

Study 1: It may be that there is no threshold and subjects are able to correct (on average), above chance levels for all perturbations we can present (consistent with [43]). Fitting the function f is the main challenge. Initial

guesses in the will be linear or quadratic functions ($f(x) = x$ or $f(x) = sg(x).x^2$), but these may not be able to describe the data if there exists a threshold or subject-specific biases. In that case, we will try with functions that are biased (e.g. $f(x) = x + b$) or thresholded (e.g. $f(x) = sg(x).(|x| - t)$, if $|x| > t$, and 0 otherwise). It is possible that no set of parameters is able to adequately reproduce the data. In that case I plan to inform the design of an alternative model through the analysis of the relation between errors and actions taken on a step-by-step basis (as shown on Figure 4, right panel), as well as analysis on the distribution of final errors (regardless of initial perturbation size).
Study 2: Although unlikely, it could be that the dynamics of perceptual adaptation are too fast to be captured properly with this protocol. If that is the case, the inter-task intervals will be reduced.

Aim 2: Characterize and model motor output in short exposures to a split-belt treadmill environment.

Introduction

Computational models of motor adaptation have been developed for reaching and saccadic adaptation [45, 21, 24, 46, 38, 23, 22]. Having those models offers insight about how the nervous system controls movement and allows for the prediction of experimental outcomes and therefore aids in the design of experiments. The objective of this aim is to characterize split-belt treadmill adaptation in a way that is sufficient to compare the validity of different models in this context. In particular, we are interested in having a model that affords prediction of the kinematic and kinetic consequences of belt speed changes. Several studies have described aspects of the dynamics of locomotor adaptation in split-belt treadmills [47, 2, 12, 5] but computational models are still lacking. Because walking task is dynamic in nature (i.e. it cannot be separated into discrete movements such as saccades or reaching toward targets), it is not possible to acquire data for a single stride (i.e. trial) at a time. Further, some of the main output variables used for the description of this task (e.g. step-length asymmetry, step-time asymmetry) are discontinuous following belt speeds changes (i.e. they are significantly different between the stride before perturbation introduction and the first few strides after [12, 2]). This discontinuity may be due to the fact that belt speeds directly affect the variables being measured (a 'feedthrough' term in the input-output relation) or that subjects have a very rapid balance response in order to avoid falling. Properly understanding the effect of the perturbation on measured variables will allow us to quantify after-effects accurately, distinguishing between feedthrough terms, reactive (or balance) responses, and longer-term adaptation responses, which I hypothesize are more likely related to perceptual/motor recalibration. Good characterization of these responses will offer predictive power on the consequences that any belt speed change will induce on the measured variables.

Justification & Feasibility

There has only been one study that has tried to model locomotor learning in a split-belt treadmill [7]. It showed that fixed-parameters linear time-invariant (LTI) models are insufficient to describe all characteristics of motor learning, in particular savings. They also showed that variable-parameters (piece-wise) LTI models, where the coefficients of the system are different during adaptation, washout and re-adaptation, perform better. However, this model is only descriptive of the data and does not allow for any prediction. Further, they used a single perturbation size to fit their models although it has been shown that error-size affects aftereffects both on the treadmill and when walking overground [5]. Understanding how system responses differ for large and small perturbations, and for different walking speeds, is a necessary previous step to understanding generalization across speeds (i.e. how much learning at one speed transfers to other speeds). In turn, this understanding is critical to the study of generalization of treadmill walking to overground, where speeds are self-selected by the subjects and are usually different from training speeds.

Methods

Five groups of subjects will be exposed repeatedly (without stopping walking) to several short-term (< 20 strides) split-belt perturbations followed by washout periods of random duration, but at least as long as twice the exposure time, resembling a square-wave of variable period. The short-term perturbations will be used as a way to observe motor changes that correspond to reactive or balance responses, which have been under-characterized in previous studies. Having multiple exposures allows for averaging across repetitions and reducing some of the variability present in the responses, isolating the more permanent features. At each perturbation appearance duration will be one of 1,2,3,4,10 or 20 strides, and all subjects in each group will experience each duration ten times (total walking of 1800 strides, about 45 minutes). Having several different perturbation lengths allows for quantification of responses as a function of perturbation duration. Presentation order will be pseudo-random to keep subjects from anticipating perturbation removal. The very short perturbations (1,2,3 and 4 strides) are meant to achieve a good description of the dynamics of the responses that occur immediately after belt-speed changes. The other perturbations (10 and 20 strides) are meant to characterize the beginning of adaptive responses. Before any perturbation is presented (baseline) and after the final one (post-exposure), subjects will walk for 150 strides with both belts moving at the same speed.

There will be 5 main groups, three of them experiencing perturbations of different sizes (.1ms/, .35m/s, .7m/s) and consistent sign (the same leg is always the fastest) with the same mean speed (1.05 m/s), and a control group (group 4) in which perturbation signs will be varied pseudo-randomly to avoid subjects overlearning to respond to a specific perturbation. Perturbation sizes were chosen to span most of the range of perturbations used in other studies [12, 14, 9, 2, 4, 5]. The smallest perturbation size was chosen to be below to the perceptual threshold that was reported in other studies [35, 16]. Group 5 will be used to assess the effect of mean belt speed, with the subjects walking at a mean speed of 0.525 m/s while still using a .35m/s difference between the belts (which corresponds to a 2:1 belt-speed ratio).

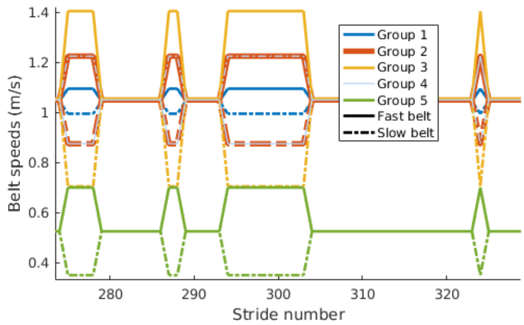

Figure 5: Proposed protocol for Aim 2. Group 2 and group 4 have the same mean walking speed and perturbation size, but group 4 has randomly alternating perturbation signs (i.e. the leg which walks at the fast speed varies).

Data Analysis

The output signals that will be analyzed are step-length symmetry, and the three components that contribute to it: velocity asymmetry, step-time asymmetry, and foot-placement (spatial) asymmetry [18]. For all these variables, I will average across repetitions of the step perturbations to characterize the response and fit LTI models with different numbers of states. Model selection will be performed by using Akaike's Information Criterion [42], which quantifies goodness-of-fit and also takes into account the number of free parameters in the model.Initially it will be assumed that the step-response is not adapted because of repeated exposure (time-invariant) and that the washout periods between perturbations are sufficient to return the system to the initial (null) state. I will test for differences in the step-response across exposures (paired t-test comparing the final value of the response between the first and last 20-stride exposure), in order to test for it being adapted through repetition. Finally, I will compare the values of the variables in the baseline period (before any exposure) to the post-adaptation period (100 strides after the last exposure) to test for aftereffects that may be induced by the environment. Special attention will be paid to differentiating feed-through responses (defined as those that occur on the same stride in which the perturbation is introduced), reactive responses (those that occur within the first three or four strides after perturbation onset) and adaptive responses (longer-term changes that appear slowly). All the previously described quantities will also be compared between groups (1-way ANOVA with GROUP as a factor or two-sample t-test), as follows:

- Groups 1,2,3 to test for the effect of perturbation size. The response of each group will be divided by the perturbation size to explicitly test for linearity of responses.
- Group 2 to group 4, to test for the effect of perturbations that are variable in sign.
- Group 2 to group 5, to test for the effect of mean belt speed with fixed perturbation size.

Expected results

Dynamics: Given our preliminary studies, we expect the dynamics to be characterized by a combination of feedthrough terms (responses that appear immediately after perturbation onset), fast reactive responses (settling in less than 5 strides) that may be described through LTI systems, and longer-term adaptation responses that appear more slowly (e.g. step-length symmetry is expected to change at a rate in the order of 1 mm per stride during the first ≈ 100 strides, based on results from other studies [47, 18]). **Effect of perturbation size:** It is anticipated that behavior for small perturbations will be qualitatively different from larger ones (i.e. not scaling linearly), possibly relying less on balance responses (smaller contribution of the step-time asymmetry relative to the overall perturbation). Aftereffects are also not expected to scale linearly with perturbation size. This is consistent with other findings [10, 5, 38]. **Effect of mean speed:** We expect all these variables to be affected by mean walking speed, with responses being smaller and more variable for slower mean walking speeds.

Preliminary Studies

Our preliminary data (Figure 6) shows that step-length asymmetry is effectively altered immediately after perturbation onset (feed-through component), but that the stance-time symmetry response starts a full stride cycle after it, suggesting that it is part of a balance/reactive response. Further, it takes another cycle for the response to stabilize (compensating for about 50% of the perturbation). This is consistent with reports by other groups regarding the existence of immediate (1 stride), reactive (2-10 strides) and adaptive (>50 strides) changes [2, 12].

Potential Problems and Alternative Approaches

The largest potential problem with this approach is that the step-responses from the subjects are found to change across repetitions or induce aftereffects that are not washed out properly between repetitions, falsifying the assumptions that justify the averaging. If either is true, it may be useful to describe this 'meta-adaptation', and construct a model that could explain those results. In particular, the second case (insufficient washout) would suggest that sustained exposure to a perturbed environment is not necessary to induce lasting motor aftereffects, a very interesting result in itself. Group 4 was included to test for the possibility that a perturbation consistent in size, but not in sign, would lead to reduced adaptation of step-responses and show less aftereffects than the other groups. If this hypothesis is correct, all the experimental groups could be changed to a protocol in which perturbation sign is varied randomly.

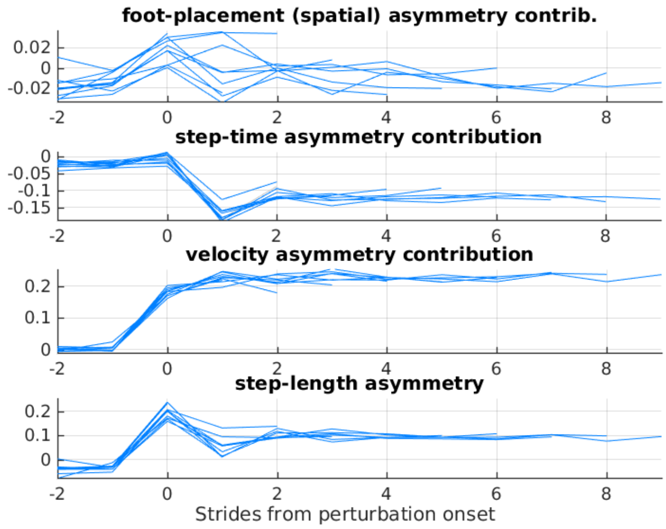

Figure 6: Average step-responses (sample subject), for perturbations of same size and speed but of different durations (data shown only while the perturbation is present). Y-axis quantities are relative to the sum of step-lengths (dimensionless) [5].

Aim 3: Determine the interdependence of perceptual and motor aftereffects following adaptation to the split-belt treadmill environment

Introduction

Internal models are thought to be used by the CNS to both predict the sensory consequences of actions (forward models) and to compute the necessary actions in order to achieve certain goals in task-space (inverse models). Motor adaptation is suggested to occur, at least partially, because of the CNS' recalibration of these internal models in order to conciliate actions and their observed consequences [27, 48, 23, 29, 31, 40]. Perceptual aftereffects are often observed, along with motor aftereffects, following motor adaptation. Recalibration of forward models has been proposed as the cause for these perceptual aftereffects [32, 25]. Given that both motor and perceptual aftereffects occur as a consequence of motor adaptation, it is interesting to understand what is the relation between the two. On one extreme it is possible that all motor aftereffects are related to altered perception. On the other, it could be that the two are independent but are driven by the same perceptual mismatch signals, which is why they are often observed together. Here we will consider perceptual aftereffects as a proxy for forward model (perceptual) recalibration. I hypothesize that perceptual recalibration is the main driving factor behind the motor aftereffects that are observed in split-belt treadmill adaptation. Any treatment that reduces or eliminates perceptual aftereffects will result in a significant reduction of motor aftereffects and possibly eliminate them completely (sufficient condition). This aim looks to explore the relation between these two types of aftereffects following split-belt treadmill adaptation.

Justification & Feasibility

It has been reported that there exist aftereffects in the perception of belt-speed difference after split-belt treadmill adaptation, but not in the perception of force or foot position[9]. The same group also observed that cerebellar patients have reduced perceptual recalibration. Previously it was shown that cerebellar patients have reduced motor aftereffects[6]. Other studies have shown that adapting subjects through a gradual protocol induces larger motor aftereffects than subjects adapted abruptly[5], and the same thing was reported for perceptual aftereffects[10]. However the latter study failed to reproduce the results regarding motor aftereffects of [5].

Methods

Subjects will follow an adaptation protocol that follows a perturbation with a counter-perturbation. Critically, dosage of the counter-perturbation will be such that at the end of the counter-perturbation period subjects will have no remaining perceptual after-effects. Dosage will be designed in accordance to results from Aim 1, study 2 (see Figure 7). At this point subjects will either walk on a tied-belt condition (group 1) or perform the perceptual task used in Aim 1, followed by tied-belt walking (group 2).

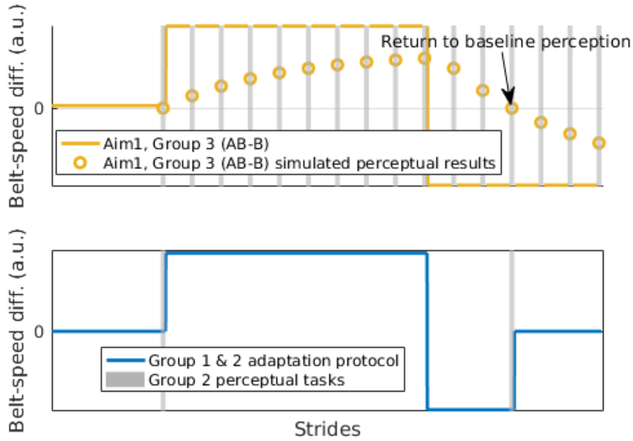

Figure 7: Top panel shows adaptation protocol and simulated results for Group 3 (AB-B) in Aim 1, study 2, which will be used to compute the dosage for the protocol for this study. Bottom panel shows the adaptation protocol to be followed by both groups in the study, as well as the perceptual tasks to be completed by group 2.

Data Analysis

Group 1 will be tested for motor aftereffects by comparing post-washout motor output with baseline motor output (paired t-test). Group 2 will be tested for perceptual aftereffects by comparing results from the two perceptual tasks administered (paired t-test), and for motor aftereffects in the same way as group 1.

Expected results

Group 2 is expected to show perceptual aftereffects that are not significantly different from 0, following the results from Aim 1. Group 1 is expected to show no motor aftereffects. This follows from the hypothesis that perceptual adaptation is the driving force of motor adaptation. Should any motor aftereffects be found, it would mean that there are other factors/processes that play a role in motor aftereffects.

Preliminary Studies

N/A

Potential Problems and Alternative Approaches

If the hypothesis is incorrect, motor aftereffects will be present even when perceptual aftereffects are not. The alternative is that perceptual aftereffects are only one of the factors that describe the adaptation of the system, but that there are others. For example, motor adaptation is sometimes described by a two-state LTI system [21]. An alternative hypothesis is that perceptual adaptation shares a neural process with, and its dynamics evolve with the just one of these components but not the other. Assuming that the processes that are involved in inducing motor aftereffects evolve on different timescales from those of perceptual adaptation, this hypothesis could be tested by an experimental design in which dosage of the adaptation phase is varied across groups. This would mean that the different groups have different relative contributions of each process, and thus we could characterize which timescales correspond to the perceptual adaptation-related processes. Another alternative hypothesis is that some specific motor aftereffects are related to perceptual adaptation (e.g. foot-placement) but not others (e.g. step-time asymmetry). This could be further tested by providing feedback to subjects during adaptation, in order to constrain their foot-placement response and assessing how this affects the adaptation of their perception.

Aim 4: Develop a human-in-the-loop controller of belt-speeds on a treadmill.

Introduction

When trying to reverse-engineer a plant, in order to understand how it operates, characterizing the input-output relation by probing the plant with different input signals is often the first step. Closed-loop or feedback control can offer even more insight, by tailoring the input according to what is happening with the output. On a split-belt treadmill, the input is the belt speeds, and the output can be any quantity that is measurable in real-time, be it kinematic, kinetic, muscular or neural. Through this type of feedback we may achieve:

1. Controlling of confounding variables in studies, e.g. cadence.
2. Targeting of specific subject behaviors in order to amplify or suppress them (e.g. stance time asymmetry, or a specific muscle's activation)
3. Generation of a more natural walking environment (i.e. that more closely resembles walking in day to day activities) in which walking speed is determined by the subject's behavior (e.g. taking stride length as a proxy for desired walking speed).

In order to achieve any of these on a split-belt treadmill we need to consider that the actual output does not depend only on the implemented feedback law, but also on the subject's response. This is where the difficulty lies: we need to understand how subjects react to our manipulations in order to design the feedback accordingly. An extra level of difficulty is added if we desire to target signals that are not directly measurable. In that case we also have to estimate the target signals from available information, and the performance of the loop depends on the accuracy of our estimation. Properly understanding all of these factors is a task that exceeds the scope of this proposal. This aim looks to take the first steps in performing treadmill control with a human-in-the-loop, hoping to move towards the future implementation of an error-clamp environment for split-belt treadmill motor adaptation.

Justification & Feasibility

The term 'error-clamp' refers to an environment whose dynamics prevent subjects from making mistakes on a task. Such environments have been used to assess motor learning, and have been shown to be a useful tool for identifying feedforward mechanisms of control by limiting error-driven feedback responses [21, **?**, 38, 49]. Implementation of error-clamps are often achieved through a closed-loop controller, in which external perturbations are adjusted to subject behavior so that they result in the elimination of the relevant error signal.

While there has been interest in identifying an error signal for split-belt treadmill walking [50], no studies have directly tested for them. Study 1 is a proof-of-concept that aims to show the feasibility of closed-loop control while targeting some variable that is both easy to measure in real-time and that has a simple relation to belt-speeds. This study looks to implement a closed-loop controller in which subject cadence is maintained at a fixed value throughout the experiment by variation of the mean belt speed on a stride-by-stride basis. The experimenter is still allowed to set the belt-speed ratio (i.e. the quotient between the two belt speeds). An environment in which cadence is controlled, will allow for experiments that look to dissociate the confounding role that variable cadence may have on locomotor adaptation. For example, it could be used to understand the role cadence plays in learning and unlearning rates during adaptation. Study 2 looks to move towards an error-clamp environment on a split-belt treadmill. I hypothesize that a relevant error signal for split-belt treadmill walking is the perceived belt speed difference. An error-clamp-like environment will be attempted by having the belt speeds always at values that feel symmetrical to the subject (no perceptual mismatch).

Methods

Study 1: Cadence control will be obtained by a simple feedback rule. Upon each heel-strike, the time will be compared with that of the previous ipsi-lateral heel-strike to compute the stride time (T_i). This time will be subtracted from the desired cadence (T_d), obtaining an error signal e_T. This signal will go through a proportional-integral (PI) controller to update the mean belt speed. The proportionality and integration constants of the system will be tuned so that the controller achieves an acceptable response. A first approach for achieving the PI tuning is to use the Ziegler-Nichols heuristic.
Study 2: The hypothesized error signal depends on two factors: the actual belt speed difference (d), and the difference that would cause the subject to perceive that the belts move at the same speed ($\bar{d}$). It will be assumed that the error signal is $e = d - \bar{d}$. From the results of Aim 1 (characterization of perceptual dynamics during motor adaptation), train a regressor to predict the necessary belt-speed difference for ($\bar{d}$) from all available kinematic and kinetic data. This is, from a set of measurable variables (y), estimate a function (f) such that $\bar{d} \approx f(y)$ on each stride. The simplest approach is to assume that the function is linear, so that $\bar{d} \approx w^T y$, and only the weights w need to be estimated. In that case, finding the optimal weights (in the sense that they minimize the difference between the estimated value of $\bar{d}$ and the actual value measured in Aim 1) reduces to solving a simple optimization problem.

Data Analysis

Study 1: The control loop will be tested by having subjects repeat the paradigm of Aim 2 (multiple short perturbations). The magnitude of interest will be the difference between the desired and actual cadences e_t. It will be tested for a steady-state value different from 0 (one-sample t-test). The convergence time of the signal will be characterized as a function of perturbation size.
Study 2: The estimator will be validated in two ways. First, by computing RMS error between estimated and measured signals on a subject-by-subject basis, to assess how well the estimator performs on different subjects. N-fold cross-validation will be used to quantify the ability of the estimator to generalize to subjects not used for training. Once we are satisfied with the performance of the estimator as quantified above, we will conduct an experiment in which we will assess the natural-decay responses with two groups of subjects that are adapted equally and are washed-out in two different perceptually-clamped environments: Group 1 will be washed-out while allowing them to self-select the belt-speed ratio throughout [10], while group 2 will be washed-out while the belt-speeds are determined through closed-loop control, in a way that $e \approx 0$. These two groups will be compared in their initial belt-speed difference during washout, decay-rates and belt-speed differences after 600 strides of washout (all comparisons through two-sample t-tests).

Expected results

Study 1: Response will be fast enough so that cadence is not different from the desired value (< 5%) for more than 3 stride cycles following a step perturbation, will have no asymptotic error and is stable.
Study 2: An estimator of $\bar{d}$ will be obtained. This estimator will provide a way to track subjects' perception of belt-speeds without explicitly probing them through specific tasks, such as the one described in Aim 1. Once

the estimator described before is designed and validated, we can use this regression to compute the difference between actual belt-speed difference and predicted belt-speed difference. This signal will be used to control the belt speed difference so that this d is always equal to the estimated $\bar{d}$ and therefore the proposed error signal is 0.

Preliminary Studies

A sandbox environment which ties belt-speed updates to measured subject behavior has been implemented. This proves it is technically feasible to do a real-time closed-loop controller with our current laboratory setup.

Potential Problems and Alternative Approaches

Study 1: Potential problems are that no PI controller can achieve the desired response of the system. Adding a derivative term to have a full proportional-integral-derivative (PID) control may help with some settling time and stability issues.
Study 2: It is possible that no simple linear regression is sufficient to compute $\bar{d}$. In that case a non-linear regression may be used by generating non-linear mappings of the available regressors and then doing a linear regression. It is also possible that any estimate is too noisy and variable for it to be useful in real-time control of the treadmill. In that case, we could incorporate knowledge about the dynamics of $\bar{d}$ (characterized in Aim 1) and implement the estimation as a Kalman filter[44], or in general through bayesian integration, in which new estimations of $\bar{d}$ (computed as previously described) are incorporated gradually depending on the noise in the estimation and our confidence in prior beliefs. Another potential problem is that inter-subject variability is too large, not allowing for a single estimator of perception from kinematics across subjects. Such a problem would be diagnosed when assessing the goodness-of-fit of any given estimator across the population. Here it would be necessary to identify some predictor of inter-subject differences that can be used to design estimators that work for each particular individual. An extreme version of the previous problems is that belt-speed perception cannot be estimated from any directly measurable variables even for individual subjects. This is considered unlikely, since some kinematic correlates of belt-speed difference perception have already been identified in another work by (unpublished results from Vazquez et al.). If it were the case, a plausible alternative is not to try to estimate $\bar{d}$ directly, but just the sign of $d - \bar{d}$. The sign of that difference cannot be used to infer $\bar{d}$, and is less powerful in that sense, but it can still be used to implement a feedback controller in which we aim to achieve $d \approx \bar{d}$ (through a simple negative feedback rule). If this approach were also to fail, we can move to implement a closed-loop controller for a directly measurable variable such as foot placement asymmetry. While more limited in its applications, this would still be useful to understand how we can constrain locomotor adaptation, and be used to test for the effects of this constrained adaptation on perceptual and other motor aftereffects.

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