# Sensory Integration of Electrotactile Stimulation as Supplementary Feedback for Human-Machine Interfaces

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# SENSORY INTEGRATION OF ELECTROTACTILE STIMULATION AS SUPPLEMENTARY FEEDBACK FOR HUMAN-MACHINE INTERFACES

BY
SHIMA GHOLINEZHAD

DISSERTATION SUBMITTED 2022

AALBORG UNIVERSITY
DENMARK

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Dissertation submitted 2022

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# CV

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Shima received the B.S degree in biomedical engineering, in 2011 from Qazvin Azad University, Iran, and the M.S degree in biomedical engineering from the University of Ulster, United Kingdom. Before she started Ph.D., she has worked as a research assistant in the department of Electrical Engineering at University College Cork, Ireland for two years (2014-2016).

Since February 2019 Shima has been a Ph.D. fellow in the department of Health, Science and Technology at Aalborg University. Shima's Ph.D. project was supervised by Associate Professor Jakob Lund Dideriksen and co-supervised by Associate Professor Strahinja Dosen. Her project focused on sensory integration of non-invasive feedback during closed-loop control of functional tasks.

# ENGLISH SUMMARY

The human central nervous system constantly receives and processes information from thousands of peripheral sensors to obtain an estimate from which future movements can be planned. State estimation can be improved by the fusion of multiple sources of sensory information. Thus, before reaching a decision, our brains combine and integrate information from different natural senses using a weighted average of the sensory estimates, where the weight assigned to each estimate reflects its reliability. Notably, the sensory integration occurs so effortlessly that we may not be aware it is happening. The lack of one natural sensory modality, however, might impair sensory integration, leading to an overreliance on residual sensory signals. For this reason, facing with an artificial system through a human-machine interface might be challenging if the interface does not provide sensory information about the state of the machine to the user. One example of this problem is the use of myoelectric prostheses, where the absence of natural sensation may constrain the functional potential of these devices. Addressing this challenge has been a highly active field of study during the last 5 decades and plenty of invasive and non-invasive approaches have been developed to allow the activity of once insensate prosthesis to be felt. According to the role of sensory integration to enhance our perceptual accuracy, one question of interest is whether supplementary feedback is integrated with other sensory information in a natural manner. In this regard, it has been already shown that the sensory feedback provided through interneural stimulation is integrated with residual natural senses in the state estimation when both natural and artificial signals were available. However, invasive approaches involve complicated hardware and specialized surgical procedures. As an alternative to invasive feedback, several noninvasive methods have been proposed by providing feedback as sensory substitution which convey information to the prosthesis user through delivering electrical or mechanical stimulation to the surface of the skin of the residual limb. Although the efficiency of sensory substitution feedback has been shown to improve control performance in some conditions, it is still unclear how such feedback is exploited by the nervous system in the state estimation process and whether multisensory integration is feasible even though the information is conveyed through a non-invasive feedback channel.

The purpose of this Ph.D. project was to develop an experimental setup to investigate whether the central nervous system processes and integrates non-invasive electrotactile feedback with natural sensory feedback. This experimental setup was then used to introduce a measure for the quality of different types of supplementary feedback, based on the degree to which the feedback is included in the central nervous system's estimation process. The central point in this experimental setup was that the subject received natural and supplementary feedback at the same time, but that the information in the supplementary feedback was manipulated. Using psychophysical tools, it was ensured that this manipulation was too small to be noticed by the subject

(study I). This framework was then validated in relation to quantifying the degree to which the central nervous system uses the supplementary feedback in the neural estimation process in a natural way (study II). Finally, this experimental setup was used to compare three different types of supplementary sensory feedback. These methods consisted in modulating the amplitude and/or frequency of the electrotactile stimulation proportional to isometric grip strength (study III). The data analysis was based on an assumption about the effectiveness of the supplementary feedback depending on its estimated weight in the estimation process.

The main results of this Ph.D. project suggest that sensory substitution does not preclude sensory integration, On the contrary, the results showed that the central nervous system attributes a very high credibility to the electrotactile stimulation (high weighting in the weighted average), and thus significantly improves the estimation of the state of a prosthesis. In addition, the results showed that this weighting could be increased when the feedback contained redundant information.

The findings of the present work improved our understanding of the role of sensory substitution feedback in the state estimation process which has important implications for the design of supplementary feedback in bidirectional human-machine interfaces.

# DANSK RESUME

Centralnervesystemet modtager og processerer kontinuerligt sensorisk information fra mange tusinde sensoriske nerver, hvorfra der dannes et estimat af kroppens tilstand. Ud fra dette estimat planlægges fremtidige bevægelser. Præcisionen af dette estimat afhænger af mængden af sensorise inputs, der er til rådighed. Derfor integrerer hjernen så vidt muligt information fra mange forskellige sensoriske modaliteter som et vægtet gennemsnit før der træffes en beslutning. I denne process afspejler vægtningen af de forskellige sensoriske input deres respektive præcision. Denne proces foregår uden at personen er bevidst om det. Hvis input fra en sensorisk modalitet mangler, kompromiteres denne proces. Estimatet afhænger for meget af de øvrige sensoriske input og præcisionen falder. Af denne årsag er det vanskeligt at interegerer med verden gennem et human-machine interface, hvis dette interface ikke giver brugeren sensorisk information omkring dets tilstand. Et eksempel på dette problem er myoelektriske hånd- og armproteser, hvor manglen på sensorisk information omkring protesents tilstand kan hæmme funktionaliteten. At løse dette problem har været et aktivt forskingsfelt igennem de sidste 50 år, hvor mange typer invasive og ikke-invasive interfaces har været udviklet til at genskabe følesans i form af supplerende feedback fra protesen. Med tanke på den sensoriske integrationsproces og dennes betydning, er det relevant at undersøge hvorvidt hjernen er i stand til at integrere sådan supplerende feedback med andre naturlige sensoriske input. Tidligere studier har indikeret at feedback givet gennem intraneural stimulation integreres med naturlig feedback på naturlig vis. Sådanne invasive systemer kræver kompliceret hardware samt specialiseret kirurgi. Som et alternativ til disse løsninger findes ikke-invasive metoder der anvender sensorisk substitution. Dette betyder at informationen fra protesen gives gennem elektrotaktil eller vibrotaktil stimulation på hudoverfladen på den resterende del af armen. Selvom ikke-invasivt feedback der er baseret på dette princip kan forbedre brugerens evne til at kontrollere en protese i nogle situationer, er det uklart hvorvidt denne type feedback rent faktisk indgår i integrationsprocessen, og i så fald i hvilken grad.

Formålet med dette Ph.D. projekt var at udvikle en forsøgsopstilling til at undersøge hvorvidt centralnervesystemet processerer og integrerer ikke-invasiv elektrotaktil feedback med naturligt sensorisk feedback. Denne forsøgsopstilling blev herefter anvendt til at introducere et mål for kvaliteten af forskellige typer supplerende feedback, med udgangspunkt i hvor høj grad feedbacken indgår i centralnervesystemets estimeringsproces. Det centrale punkt i denne forsøgsopstilling var at forsøgspersonen modtog naturlig og supplerende feedback samtidig, men at informationen i det supplerende feedback var manipuleret. Vha. psychofysiske

redskaber blev det sikret at denne manipulation var for lille til at blive bemærket af forsøgspersonen (studie 1). Herefter blev denne forsøgsopstilling valideret i forhold til kvantificering af graden hvormed centralnervesystemet anvender den supplererende feedback i den neurale estimeringsproces på naturlig vis (studie 2). Endelig blev denne forsøgsopstilling anvendt til at sammenligne tre forskellige typer supplerende sensorisk feedback. Disse metoder bestod i modulering af amplituden og/eller frekvensen af den elektrotaktile stimulation proportionelt med isometrisk grebsstyrke (studie 3). Dataanalysen tog udgangspunkt i en antagelse om den supplererende feedbacks effektivitetet afhæng af dennes estimerede vægt i estimeringsprocessen.

Det primære resultat af Ph.D. projektet viser at ikke-invasivt feedback baseret på princippet om sensorisk substitution ikke udelukker at feedbackens information integreres på naturlig vis i centralnervesystemet. Tværtimod viser resultaterne at centralnervesystemet tilskriver den elektrotaktile stimulation en meget høj troværdighed (høj vægtning i det vægtede gennemsnit), og den kan således i væsentlig grad forbedre estimeringen af en proteses tilstand. Derudover viste resultaterne at denne vægtning kunne øges når feedbacken indeholdt redundant information (modulering i både amplitude og frekvens).

Samlet set har dette projekt forbedret forståelsen af hvordan feedback baseret på sensorisk substitution indgår i centralnervesystemets estimeringsproces. Endvidere kan disse fund have en betydning for hvordan feedback i bi-direktionelle human-machine interfaces bør designes.

## ACKNOWLEDGEMENTS

*“To this lofty desire, we cannot attain*

*Unless your favor advanceth some paces”*

*Hafez*

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# CHAPTER 1. INTRODUCTION

## 1.1. OVERVIEW

Accurate control of human limbs highly depends on a dynamic interaction between motor output (feedforward) and sensory input (feedback) mechanisms. Replacing a lost hand with a prosthetic hand, however, alters the closed-loop control strategy since sensations of touch and proprioception are inherently lost.

Humans naturally seek to close the motor control loop via sensory feedback. In the unimpaired individual, the CNS constantly receives multi-modal sensory feedback (i.e. tactile, visual, and auditory) [1] and integrates information optimally from various sources to make a state estimate from which future movements can be planned [2]. This state estimate is crucial in human motor control [3], [4]. Therefore, interacting with insensate prostheses is difficult due to the absence of somatosensory feedback. Nowadays, the lack of haptic feedback can be compensated through artificial sensory feedback. According to human motor control and multisensory integration principles, one would assume that the functionality of limb prostheses would be optimal if the sensory feedback provided to the amputee would be able to integrate with the natural sensory modalities in the state estimation process.

With this Ph.D. project I aimed to understand whether and how supplementary feedback is integrated with natural sensory inputs while performing a multisensory task. This chapter provides an overview of supplementary feedback systems for closed-loop prostheses also the sensory integration principles. Furthermore, it highlights the main purpose of the study, as well as the three studies proposed to address the project's objectives.

## 1.2. BACKGROUND

The human hand is a miraculous instrument, capable of performing a variety of tasks with incredible variations in power, and precision of movements, and dexterity. In motor control system, the natural sensory information plays a vital role in controlling our limbs by shaping how we achieve everyday activities. Notably, it closes the motor control loop by enabling the real-time modifications of hand movements and responding to ambiguities during object manipulation [5].

Losing a limb due to amputation is a dramatic event with the loss of both motor and sensory function, enormously effecting on activities of daily living and quality of life. For centuries, robotic prostheses have replaced the amputated limb, restoring partially the lost functions and providing an aesthetic appearance [6]. Upper limb prostheses have become progressively more  sophisticated over time, and myoelectric prostheses are beginning to rival intact hands especially in dexterity [7]. However, the increased sophistication of these devices uncovers the lack of sensory feedback since the reliance on open-loop control constrains their functional potential. In this regard, several studies have stated the low acceptance rate by upper limb prostheses users (rejection rate between 19-39 %) [8]–[14]. The reasons, frequently linked with abandonment of prosthesis, involved inferior durability, inadequate dexterity, and absence of sensory feedback [14], [15].

Addressing the recent issue, an immense attempt has been made to develop artificial feedback systems for use in myoelectric prostheses. However, the first systems proposed more than five decades ago [16], [17] most of them are still in the prototype stage, and their implementation in commercial devices is limited. Only recently, a few commercial myoelectric hands equipped with sensory feedback systems are beginning to emerge; Ability Hand from Psyonic Inc, LUKE arm from Mobius Bionics, and VINCENT evolution two from Vincent Systems GmbH, DE. These devices provide non-invasive somatosensory feedback through a single-channel vibrotactile feedback, indicating the magnitude of grasp force.

### 1.3. CLOSED LOOP CONTROL

As mentioned above, the motor control loop needs to be closed to ensure the prosthesis user has a complete synopsis of the environment and thus can manipulate the objects with comparable accuracy to healthy people. This might be better explained throughout an example shown in figure 1, which is an attempt to represent a comparative view of the closed loop control system of a myoelectric prosthesis versus a sound human forearm while operating a very similar functional task.

For an unimpaired limb, the muscle contraction is activated when an action potential travels along the nerves to the muscles. Simultaneously, the muscle contractions trigger various receptors connected with sensory neurons innervating skeletal muscles. This stimulation changes the discharge frequency of these nerves and consequently their feedback to the nervous system. In this way, the subject senses the information about the state of his intact arm through cutaneous receptors, proprioceptors (conveyed by muscle spindles and Golgi tendon organs) and exteroceptors (e.g., vision).

On the other side, for a prosthetic arm, feedforward control is normally accomplished using a myoelectric interface in which the user operates the system by activating remaining forearm muscles, so that the elicited electrical muscle activity is recorded and encoded into the control commands for the prosthesis. When somatosensory feedback is missing, amputees are limited to the incidental sensing modalities through

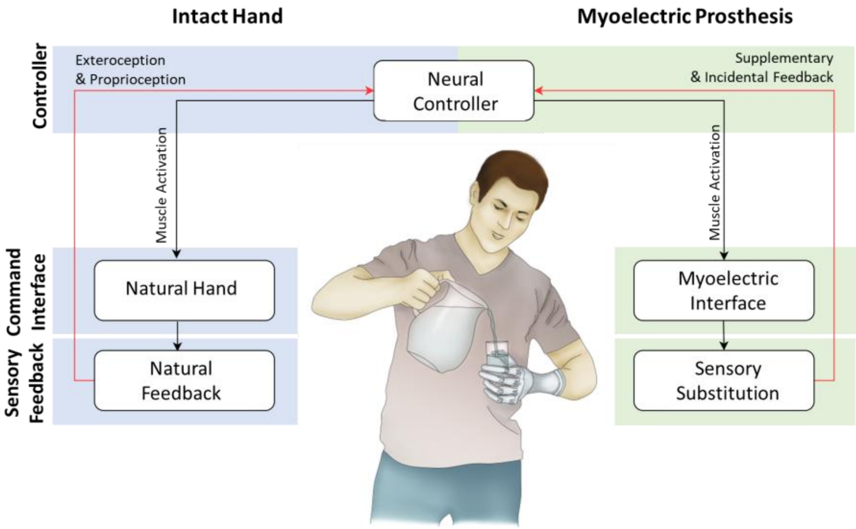



Figure 1. A simplified comparative view of the closed-loop control system of a myoelectric prosthesis (green track) versus an intact hand (blue track) while performing a similar daily task. As indicated above, the controller (CNS) is mutual to both tracks, but the control interface and sensory feedback are different.

vision, audition and vibration provided by the prosthesis and the environment [18]. In its simplest form, the users can see and hear how the limb is moving and interacting with the environment. They also receive additional information through vibration, torque and applied forces to the prosthesis. The aforementioned sensations are found as an important component of feedback for users of commercially available prosthetic limbs [19]–[21]. Despite the availability of incidental feedback, it is likely that the presence of supplementary feedback can still enhance the quality of the state estimation [8], [15], [22], [23]. To provide such feedback, the prosthesis can be equipped with sensors to record relevant data such as grasping force [24], hand posture [25], or Electromyography (EMG) signal (prosthesis command signal) [26]. This information can then be fed back (through an artificial sensory feedback system) to the amputee from the prosthesis by activating the tactile sensors which remained in the stump. In this way, such feedback allows closed-loop control of the prostheses by its user [27], [28].

## 1.4. RESTORATION OF SOMATOSENSORY FEEDBACK

There are several ways of closing the loop by restoring the somatosensory feedback, which can be divided into three categories: somatotopical feedback, modality-matched feedback, and substitution feedback [8].

Somatotopically matched methods deliver feedback applying direct neural stimulation such that an amputee senses the feedback signal as being anatomically matched in the location of their missing limb [29], [30]. Such feedback may reduce the cognitive burden placed on the user as the stimulus applied to the prosthetic sensor is perceived as occurring at a physiologically matched location in the user's missing limb.

In modality-matched methods, the information communicated to the user is matched in sensation and not necessarily in location. For example, utilizing a pressure cuff, grasp force was felt as pressure to a strategic location on the amputee's residual limb [31].

Finally, sensory substitution methods communicate the state of the prosthesis and environment to the user via sensory feedback not physiologically representative of what the missing hand or arm would experience. Usually, sensory substitution techniques are the most straightforward approaches [7,16], as they combine the advantages of noninvasiveness, low power consumption and easy implementation, therefore has a high potential for integration into practical prosthetic systems. Due to above reasons, in this research work, we have focused on perceptual integration processes with emphasis on sensory substitution feedback.

## 1.5. SENSORY SUBSTITUTION

So far, many different methods have been assessed to provide direct somatosensory feedback using closed-loop control and sensory substitution [15], [22], [23]. To this aim, the data are collected from sensors in the prosthesis, translated into stimulation patterns and delivered to the residual sensory structures still present after the amputation. The most common sensory substitution method has been to translate tactile information from the prosthesis to the amputee using vibrotactile and electrotactile stimulation. For example, adding vibrotactile feedback while performing box-and-blocks test [32] or providing EMG feedback through electrotactile sensory substitution, while holding an object [26]. Much of the research in this area has focused on this question of whether non-invasive sensory substitution systems restore sensory feedback efficiently improving users motor performance [8], [22]. In this regard, it has been found that the success of the feedback system highly depends on the user's ability to interpret the sensory information and associate it with the state of the prosthesis. Therefore, it is necessary that the tactile stimulations used in sensory feedback systems are easy to discriminate and interpret [33], [34].

In addition, the contribution of sensory substitution feedback in the state estimation process might depend on its integration with available incidental feedback, also the internal model [20]. In other words, the process of state estimation would be key to better understanding how supplementary feedback in prosthesis has worked or has failed. This would suggest that the sensory feedback might need to be assessed not only by its performance in a functional task, but also by its contribution in the state estimation process [23].

### 1.5.1. VIBROTACTILE FEEDBACK

Vibrotactile feedback, evoked by mechanical vibration of the skin, was firstly proposed by Conzelman et al. in 1953 [35]. In the field of prosthetics, vibrotactile sensory substitution is applied to communicate tactile information about the level of grasping force [36]–[40], hand aperture [40] and slippage [41] or stiffness [42] of the objects. In general, vibrotactile systems convey sensory information by manipulating vibration's main parameters of amplitude and frequency. However, spatial modulation [43], [44] also modulation of the pulse duration, shape, and duty cycle [39], [45] has been shown to be able to convey different kinds of information. The efficiency of vibrotactile sensory substitution has been reported by several studies [8], [22], [46]. For example, experiments conducted on able-bodied subjects indicated that vibrotactile feedback improved performance when visual feedback was disturbed [32]. Additionally, a study demonstrated that the embodiment of an alien hand in amputees has been possible using vibrotactile stimulation [47].

### 1.5.2. ELECTROTACTILE FEEDBACK

Electrotactile feedback elicits tactile sensations by activating cutaneous skin afferents [48] using electric currents through either single or multichannel electrodes [46], [49]. Subjects expressed electrotactile sensations qualitatively as a tingle, itch, buzz, physical touch, pinch, and burning pain [50]. However, the quality of sensation depends on the features of the stimulation (i.e. current amplitude and pulse waveform), as well as on the electrode size, skin type and site of stimulation [46].

Electrical stimulation has been widely applied as an effective sensory substitution to provide sensory feedback and thus close the loop in upper limb prosthesis [8], [22], [46]. For example, it has been shown that adding electrotactile EMG feedback improved the control and precision of prosthesis grip force [51]. Several researchers investigated ways to convey sensory information about physical property (i.e., grasping force) back to the user by modulating either one or more stimulation parameters including the amplitude of the pulses [52], [53], the frequency[54]–[56], the rate of pulse bursts [53], [57] or stimulation site[52], [54]. Generally, the perceived intensity is modulated by the pulse width and amplitude while the frequency is employed to modulate the perceived sensation (e.g., tingling) [58]–[60]. Similar to vibrotactile display, the efficacy of electrotactile feedback while execution of functional task has been investigated by number of studies [8], [22], [46].

Compared to vibrotactile systems, electrotactile devices respond faster (since there are no moving mechanical parts), also they generally consume less power. The main drawback of electrotactile feedback however might be interference the electromyographic (EMG) signals particularly when the stimulation sites are close to the EMG electrodes (i.e. stump). To overcome this issue the interference time-division multiplexing [61], frequency-division multiplexing [62] and blanking [63] techniques have been suggested.

### 1.5.3. OTHER SUBSTITUTION METHODS

Other sensory substitution principles have also been employed to provide information about the state of the prosthesis and the physical properties of the object [64], [65]. For example, auditory sensory substitution modulating the pitch, timbre, or volume enabled the identification of different textures, such as glass, metal, wood, and paper, without using vision [65].

## 1.6. SENSORY INTEGRATION AND THE PROBLEM OF CUE COMBINATION

Human lives in a multisensory world where a common source in the environment generates signals across different senses. In many situations, we seek to use of a multitude of this sensory information when estimating a property of the environment. for example, we might assume that tasting food is a pure gustatory activity, however we perceive the flavor of food through the combination of mechanical (texture), thermal, olfactory, and gustatory sensory information. Combining different senses is often essential before we make perceptual decisions. For example, while discriminating the texture of a particular material, relying on only vision may mislead us especially if they look the same. However, combining touch and vision would help us to distinguish the material.

In both abovementioned examples, sensory signals provide redundant information about the common source so that the brain exploits these properties by combining evidences across different sensory modalities (Figure 2.A). This process, called multisensory integration, brings considerable benefits for us while estimating the state of our bodies and the world. First, our sensory signals are noisy, so any state estimation, even based on the most reliable information, is subject to some uncertainty. For instance, in a winner-take-all strategy, the less reliable cues are discarded which could be used to improve the precision of the estimates. On the contrary, the redundancy of a multisensory representation offers flexibility, avoiding catastrophic failures of perception if one sense is contaminated with noise. Second, even if sensorineural noise does not lead to limitations, a single cue is usually ambiguous; therefore a strategy that does not permit the integration of all available information might fail to overcome ambiguities. Finally, the statistical advantages of having two streams of information of the same source lead to shorter reactions times also better discrimination of multisensory stimuli [66]

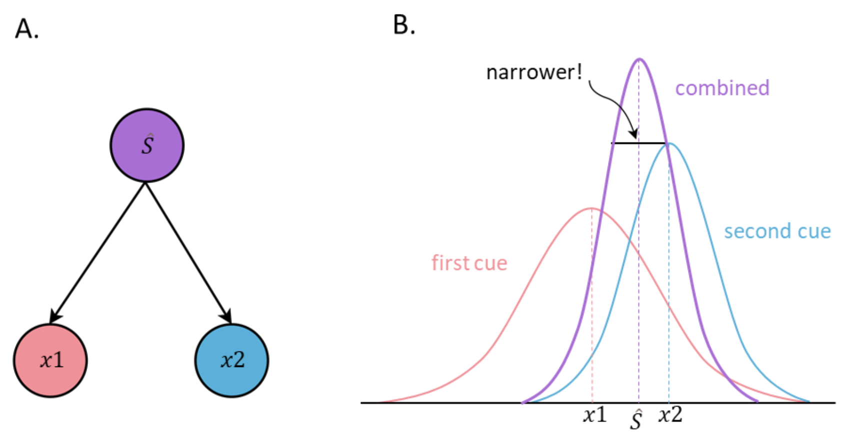



Figure 2. Graphic representation of a generative model of cue combination (Left). The two sensory cues ($x_1$and $x_2$) are from the same stimulus ($S$). By combining the two cues, the nervous system obtains a more precise estimate than each of the individual estimate in line with MLE principle. Thus, the combined variance can never be larger than either of the components (right). If the noise of the sensory information is equal, then the weights allocated to each component modality are equal as well. On the other hand, if the noise in one cue is larger, the uncertainty for that is greater and so the nervous system applies a smaller weight to its reading. Notably, the observer's estimate based on combination of the two cues shifts towards the most reliable cue (here, the second cue).

Taken together, it is clear that the key to vigorous and coherent perception is the efficient integration of multiple sources of sensory inputs [67].

## 1.7. MAXIMUM LIKELIHOOD ESTIMATION, OPTIMAL MODEL FOR SENSORY INTEGRATION

One efficient model of combining sensory information is maximum likelihood estimation (MLE), a Bayesian model that interacts with the uncertainty and noise associated with sensorineural responses to provide a statistically optimal way to integrate sensory cues. MLE achieves this through a weighted linear sum of two or more cues in which each cue is weighted inversely to its variance [68]–[72]. In this way, the final estimation is an integrated sensory estimate with minimal uncertainty, and so optimized perceptual precision (Figure 2.B).

There is considerable quantitative empirical evidence that the nervous system combines different sources of sensory information in a manner that is similar to a maximum-likelihood integrator (see [2] for seminal work; for review [73], [74]). The

MLE model in this context can be better explained by working through an example of multisensory perception. One of the best-known examples of how the nervous system deals with redundant information is the combination of visual and haptic cues while estimating the object size [2]. Receiving information simultaneously from the haptic and visual system about an object height satisfy the conditions for audiovisual fusion, but how best to integrate them?

According to MLE assumptions, the sensory signal in each modality provides an independent estimate about a specific stimulus attribute (here, estimated object size) which has a Gaussian-distributed uncertainty (Figure 2.B). The state estimate and its ambiguity are characterized by the mean and variance, respectively, of a Gaussian distribution.

As mentioned above, to improve the reliability of sensory estimates, MLE combines the information derived from the different sensory modalities. It should be noted that different sensory cues are associated with different levels of uncertainty, which is taken into account during multisensory integration [75]. This would mean if one source is less certain, the combined estimation is biased toward the information derived from the less uncertain source.

From a mathematical point of view, MLE combines the two (or more) estimates in a weighted linear sum to obtain the estimated bimodal object size [76] (Eq.1)

$$\boldsymbol{\widehat{S}_{HV} = w_H \widehat{S}_A + w_H \widehat{S}_V,} \qquad \textbf{(1.1)}$$

where $w_A$ and $w_V$ are the weights assigned to haptic and visual feedback respectively and are determined based on the relative reliability of each modality's estimate of the stimulus attribute where variance ($\boldsymbol{\sigma}^2$) and reliability are inversely related. For example, the weight assigned to haptic feedback is determined regarding MLE rule as follows:

$$\boldsymbol{W_H = \frac{\frac{1}{{\sigma_H}^2}}{\frac{1}{{\sigma_H}^2} + \frac{1}{{\sigma_V}^2}} = \frac{{\sigma_V}^2}{{\sigma_H}^2 + {\sigma_V}^2}} \qquad \textbf{(1.2)}$$

The maximum likelihood estimate of the size of the object is predicted to have the following distribution:

$$\boldsymbol{\widehat{S}_{HV} = \frac{{\sigma_V}^2}{{\sigma_H}^2 + {\sigma_V}^2} \widehat{S}_H + \frac{{\sigma_H}^2}{{\sigma_V}^2 + {\sigma_H}^2} \widehat{S}_V} \qquad \textbf{(1.3)}$$

$$\sigma_{HV}^2 = \frac{\sigma_H{}^2\sigma_V{}^2}{\sigma_H{}^2 + \sigma_V{}^2} \qquad (1.4)$$

It stands to reason that the MLE solution is optimal since it offers the final estimate with the lowest variance, given the available information, and consequently provides maximum precision (Figure2.B). This model, therefore, makes two major predictions about the mean value of the combined estimate ($\hat{S}_{HV}$) and its variance ($\sigma_{HV}{}^2$), while combining two sensory signals.

These mentioned predictions have been examined and verified in a variety of multisensory contexts [68]–[72], confirming that multisensory integration nearly approximates the MLE model. Examples include spatial localization by audiovisual cue combination [77] also physical object properties using visual-tactile stimuli [2], [78]–[80]. MLE has even been demonstrated in trimodal contexts [81] and also has been proven within a single modality between independent cues [82]. Importantly, MLE integration occurs unconsciously and does not require that attention be directed to the process [83].

## 1.8. THE ROLE OF SUPPLEMENTARY FEEDBACK IN THE STATE ESTIMATION PROCESS

As stated above, sensory integration is essential for achieving smooth and effective motor control. Since the artificial feedback is inspired by nature, the efficient supplementary feedback would be able to accomplish the same functions that our sensory system has in natural motor control. This might be achieved if the artificial feedback not only provides useful and sufficient information in the absence of natural sensory inputs but also permits cue combination with natural sensory modalities to reduce information variability when both natural and artificial feedbacks are available.

Recently, multisensory integration was studied using artificial sensory feedback using invasive technologies [84]–[87]. These studies used psychophysical methods to investigate quantitively whether the artificial feedback was integrated with the residual natural sensory information (e.g. vision) following the same principle as in the intact nervous system [2]. For example, applying vibration on the reinnervated areas to evoke an illusion of limb movement was optimally and rapidly integrated by participants and leads to clear improvements in their motor control [86]. In another study, optimal multisensory integration has been examined in non-human primates and it has been shown that the primates were able to integrate cortical stimulation with vision after long time training [87]. Finally, a recent study in one human prosthesis user indicated that sensory substitution based on intraneural feedback can be integrated with visual feedback in the state estimation process of the CNS [84].

Although the invasive methods can restore somatosensory feedback in a way that is comparable with the motor control processes of the central nervous system, they usually require specialized surgical procedures, which might be an obstacle to their wider clinical application. For instance, even in the case of prostheses, many amputees are disinclined to undergo additional surgery [88]. A simpler and more practical solution is sensory substitution feedback (see section 1.5). However, it is unknown if this substituted sensory information can be integrated in the state estimation process similar to natural sensory information.

## 1.9. AIM OF THE PROJECT

In this PhD project, first we aimed to develop a framework to probe whether and how electrotactile sensory feedback is integrated with natural sensory modalities while performing a multisensory task to elucidate the role of such feedback in the state estimation process. Next, we adopted the concept of sensory integration in the context of closed-loop prosthesis control to propose a measure of feedback dependency (estimate how much CNS rely on artificial feedback compared to natural feedback) as an evaluation criterion for comparing different types of feedback systems focusing on its neural integration rather than on how it can support prosthesis function in one specific task.

## 1.10. OVERVIEW OF THESIS

All three planned studies of the PhD project are centred around above concept and the dissertation is based on the published or submitted research publications that are listed below.

- Shima Gholinezhad, Strahinja Dosen and Jakob Dideriksen. "Continuous Transition Impairs Discrimination of Electrotactile Frequencies". Submitted in *IEEE Transaction on Haptics*, 2022. **Study I.**

- Shima Gholinezhad, Strahinja Dosen and Jakob Dideriksen. "Electrotactile feedback outweighs natural feedback in sensory integration during control of grasping force". Published in *Journal of Neural Engineering*, 2021. **Study II.**

- Shima Gholinezhad, Strahinja Dosen and Jakob Dideriksen. "Simultaneous Modulation of Frequency and Amplitude Improves Discriminability of Electrical Stimulation". Accepted in *IFESS*, 2022. **Study III.**

- Shima Gholinezhad, Strahinja Dosen, Dario Farina and Jakob Dideriksen. "Encoding Force Modulation into Two Electrotactile Feedback Parameters

Strengthen Sensory Integration According to Maximum Likelihood Estimation”, In preparation. **Study III.**

The proceeding chapters of this thesis aim to address the project’s objectives detailed in section 1.9 as follows:

- Chapter 2 – A novel framework to probe sensory integration: Describes perturbation analysis which our study design drew inspiration, the setting of the study, and psychometric assessment procedure.
- Chapter 3- Sensory integration of Electrotactile feedback (Validation): Explains how non-invasive electrotactile stimulation is included in the sate estimation process during closed-loop control of grasping force.
- Chapter 4- Quantifying the weight of feedback in the state estimation process (Exploitation): Proposes a novel evaluation criterion by quantifying the efficiency of supplementary feedback focusing on sensory integration principles.
- Chapter 5 - Future Study: Proposes a resultant future research plan for the provision of supplementary feedback (by establishing proprioceptive feedback) for transradial amputees.

# CHAPTER 2. A NOVEL FRAMEWORK TO PROBE SENSORY INTEGRATION

## 2.1. OVERVIEW

As stated in the previous chapter, the principles of sensory integration have been extensively investigated for natural sensory feedback systems [2], [77], [89], [90]. All these studies have used the classic perturbation analysis method to explore how the nervous system integrates sensory signals.

The specific outcome of the chapter is a novel setup that allowed us to investigate sensory integration of electrotactile feedback by the nervous system during isometric grasp force tasks.

## 2.2. PERTURBATION ANALYSIS

To test theories of sensory integration, many researchers have used different experimental procedures inspired by variants of perturbation analysis techniques, first introduced by Young and colleagues [91]. In such experiments, a common trick is to introduce a small unnoticeable mismatch (bias) between the two sensory information about a specific environmental property, in order to examine the sensory integration by observing the subject's behavior in response to induced conflict. For example, consider the seminal study [2] in which the visual and tactile cues were combined while estimating an object size. In this study, the human subjects were asked to make judgements about an object height while receiving visual, haptic or haptic-visual stimuli. In subset of trials the size indicated by visual cues slightly perturbed (outside of the subject's awareness) from that depicted by haptic cue. Such a conflict can be used in different ways to estimate the way in which different sensory signals are combined. To assess whether the observed combined variance is in accordance with the MLE-predicted variance (Eq.1.4; *see section 1.7*), the researchers compared the empirically measured variance of the combined stimulus with the variance computed from the unisensory haptic and visual variances. Specifically, they assessed the reliability of each sensory modality individually by measuring the subject's Just Noticeable Difference (JND) and then compared subject's performance obtained in the bimodal conditions with the prediction derived from the performance in unimodal conditions.

Moreover, the biased trials, allowed the investigators to measure the relative weight assigned to each sensory modality. In fact, the degree to which the induced mismatch affected the state estimation indicated how much the decision on object size depended on the each of two modalities. In this example the empirical weight allocated to each sensory modality could be measured through the following equation:

$$\boldsymbol{W_{V,emp} = \frac{S_{\Delta HV} - S_H}{S_V - S_H} \text{ with } W_V = 1 - W_H} \qquad \textbf{(2.1)}$$

In which the $S_{\Delta HV}$ is the Point of Subjective Equality (the object diameter that was perceived as larger than the standard in 50% of the trials) of the bimodal psychometric function in the biased condition, $S_V$ is the true visual stimulus and $S_H$ is the true haptic stimulus (i.e., assume there is a conflict between haptic and visual stimuli).

The empirical sensory weights can then be statistically compared with the MLE-predicted weights (Eq.1.2; *see section 1.7*) Notably, in case there was a mismatch between the two sensory information in the bimodal condition, the perceived object size for the combined stimulus (HV) should be biased toward the true information carried by the visual feedback, if the visual reliability is greater than the haptic reliability, and vice versa for greater haptic reliability, in accordance with MLE-based integrator.

Similar to abovementioned framework, in the present study, we designed an experiment in which the subjects were asked to perform a force matching task while they were able to feel the force through natural sensors also through electrotactile feedback. Unknown to the subjects, a small (unnoticeable) mismatch between the information about grasping force (conveyed by the two sensory modalities) was induced in some trials. By systematically exploring the impact of this bias in the artificial feedback, the degree to which the mismatch affected the state estimation process would indicate how much the decision on grasping force depended on each of the two modalities.

## 2.3. IMPERCEPTIBLE PERTURBATION

The key point in sensory integration experiments is to note that the induced bias is adjusted at a level below the subject's conscious perception. Of course, the observer will only believe the sensory inputs convey information about a common source if the discrepancies between the two sensory modalities are small enough. Otherwise, the observer will notice the conflict. In many relevant studies [2], [90], subjects are typically questioned if they have noticed the conflict between the investigated sensory inputs at the end of experiment to ensure the subjects are not aware about the bias.

Similarly, here we needed to ensure that subjects will not notice the mismatch between the two sensory modalities while performing the task. To do this, we systemically measured the subject’s discriminability by psychophysical tools particularly Just noticeable Difference (JND) before the experiment starts.

## 2.4. JUST NOTICEABLE DIFFERENCE

The (JND) is a psychophysical tool to measure perceptual acuity defined as the minimum difference between two physical stimuli that can be perceived by a human subject. In sensory feedback application, the JND has also been often used to measure the sensitivity of a feedback channel [46].

### 2.4.1.THE MEASUREMENT OF JND

Different methods can be used to estimate JND [92]: In the method of limits the stimulus is gradually increased in fixed steps until the subject reports that he/she felt a change [93]. In the method of constant stimuli, a set of test stimulus is always compared against a standard stimulus, which provides a fixed reference. In such non-adaptive method a constant set of test stimuli are chosen before the testing begins [94]. The adaptive staircase procedure is often favored as compared with the method of constant stimuli [95], [96], in which test stimulus set values are selected on the basis of the observer’s previous trial-by-trial performance [97]. Different adaptive methods have been developed: the up/down method [98], transformed up/down method [99] and weighted up/down method [100].

Generally, in all staircase procedure, a pair of physical stimuli (test and standard) with different magnitude (i.e., intensity or frequency) is delivered to the subject in random order. The observer is then asked to indicate which stimulus is perceived as being stronger [101]. If he/she responds incorrectly, the difference between the two stimuli intensity is increased on the next trial, whereas if the observer responds correctly on a trial (or trials), the difference between the stimuli intensity is decreased on the next trial. With decreasing difference in the stimulation parameters, the subject will eventually become unable to correctly identify the stimulus with the higher parameter value. Over the course of a sufficient number of trials, the stimulus intensity will tend towards a particular proportion correct and oscillate around it. Once it occurs, the JND will be adopted as a difference between the oscillation point and the reference stimulus.

Throughout this project, we used the adaptive weighted up–down procedure. In this approach a 1 up/1 down rule is used, but the steps up are not equal in size to the steps down. For example, for a target performance of 75 % correct, in a descending approach the sizes of the steps up (when the subject's response is not correct) is three times larger than the steps down (and vice versa for ascending approach).

### 2.4.2. TIMING OF STIMULUS PRESENTATION

As mentioned above, the perturbation analysis can only be done if the perturbation is unnoticed. To ensure the subject would not notice the bias, in this study the subject's discriminability decided to be measured prior to experiment. However, the key question was whether the estimated JND can be used to determine the magnitude of the perturbation which the subject does not notice during the experiment. One of the critical factors we should consider here is the timing of stimulus presentations, which its variation might affect the JND estimation [102] .

Conventionally, the two stimuli are delivered sequentially separated by a brief interval without stimulation, so-called inter-stimulus interval (ISI). There is no hard-and-fast rule to set inter-stimulus interval (ISI), and markedly different ranges have been used in literature e., 0.5-1 s [102]–[106], 1 s [107]–[112] or 2-4 s [113], [114]. Notably, in all above-mentioned studies, the two stimuli are presented discretely, however this mode of presentation of stimuli, is quite different from how tactile stimulation is modulated in our setup (*see section 2.6*) in which the grasping force were translated into electrical stimuli continuously.

With study I in this Ph.D. project we intended to investigate whether JND estimated through classical approach with two time-separated stimuli is appropriate to predict the subject's sensitivity to discriminate the same change in stimulation parameters if the stimuli are continuously during the experiment. In other words, we aimed to understand if the JND estimated through time-separated paradigm is equal or lower than subject's actual JND when the transition between the stimuli is continuous.

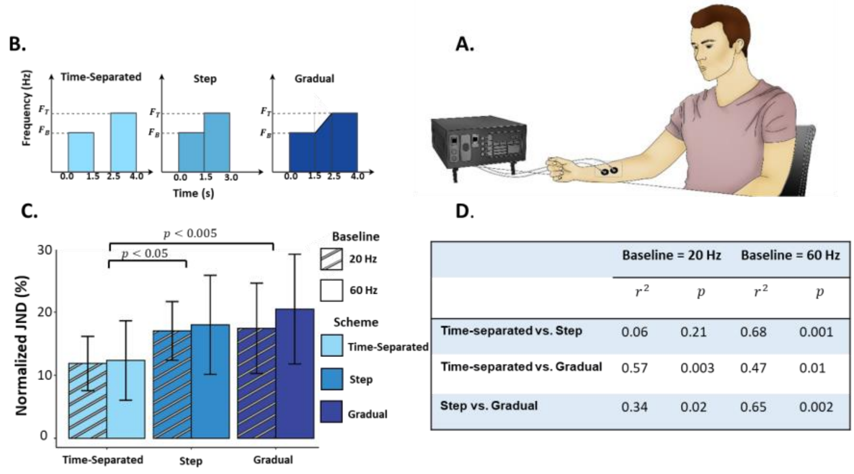
To this end, we recruited 12 able-bodied volunteers and we estimated the JND using weighted up-down staircase procedure with separate or continuous transitions between stimuli with regards to two different baseline frequencies (20 and 60 Hz) of electrical stimulation. Specifically, three different transition schemes were used to deliver the two pulse trains, as indicated in Figure 3.B. In all the schemes, the two pulse trains were 1.5 s in duration. In the *time-separated* approach, the two pulse trains were separated by a 1-s pause. During the *step* scheme, the second pulse train was presented right after the first (no ISI). Finally, in the continuous *gradual* scheme, the two pulse trains were connected by a gradual linear transition between the two stimuli lasting for 1 s (Figure 3.B).

## 2.5. ACCURATE DISCRIMINATION OF ELECTROTACTILE FREQUENCIES REQUIRES STIMULI SEPARATED IN TIME

As indicated by Figure 3.C, we found that the temporal pattern would affect human's ability to discriminate the difference between the frequency of tactile stimuli (Paper I). Specifically, the average JND was 12.3 ± 4.8 % (20 Hz baseline) and 13.9 ± 7.3 % (60 Hz baseline) in *time-separated* scheme, 18.5 ± 5.8 % (20 Hz baseline) and 19.6 ± 9.0 % (60 Hz baseline) in *step* scheme and 18.7 ± 7.9 % (20 Hz baseline) and 22.9 ± 9.1% (60 Hz baseline) in *gradual* scheme. Statistical analysis revealed that JND varied across the three schemes ($p < 0.001$) and not across the baseline frequencies ($p = 0.186$). This difference was mainly due to better discrimination ability in *time-separated* scheme than in the two other schemes ($p < 0.05$ and $p <0.005$ for the *step* and the *gradual* scheme, respectively).

Our findings in this study indicate that, the classical method of JND estimation might lead to overestimation of the sensitivity of perception in case the tactile stimuli are presented continuously. And if the conventional method is used to determine JND, the subject might fail to perceive changes in the feedback levels of this magnitude, while the feedback modulates continuously. Nevertheless, we found linear correlations between the estimated JND values, across most stimulation transitions (Figure 3.D). This means that the higher sensitivity (lower JND), as revealed by *time-separated* method, still leads to lower JND when using continuous transitions between the stimulations and vice versa. Therefore, while the conventional method might not be suitable for feedback calibration, it can be validly used to choose optimal stimulation strategy for closed-loop human-machine interface, i.e., the one that is characterized with the best sensitivity (lowest JND) [115], [116].

The findings of the present study, on a general level, is consistent with a previous study [102], in which the spatial discriminability of stimulation improved when the ISI was increased from 20 to 120 ms [102]. This might indicate that the processing of the first stimulus occurs over an interval of time, and that the receiving of next stimuli within this interval might disrupt this process. The importance of stimulus processing interval was also demonstrated where the ability to distinguish two vibration intensities was decreased when a disturbing stimulus was delivered to the contralateral somatosensory cortex within 600 ms after the first stimulus [117]. However, the discriminability remained unaffected when this disturbance was arrived after 900 ms or more. On the other hand, it has been shown that JND increases with intervals ≥5 s




| | Baseline = 20 Hz | | Baseline = 60 Hz | |
|---|---|---|---|---|
| | $r^2$ | $p$ | $r^2$ | $p$ |
| Time-separated vs. Step | 0.06 | 0.21 | 0.68 | 0.001 |
| Time-separated vs. Gradual | 0.57 | 0.003 | 0.47 | 0.01 |
| Step vs. Gradual | 0.34 | 0.02 | 0.65 | 0.002 |

Figure 3. Summary of Study 1. A) Schematic of Discrimination Task. A pair of tactile stimuli (the baseline frequency ($F_B$) and test frequency ($F_T$)) is delivered to subject's skin with different frequencies, and the subject is asked to choose the stimulus with higher frequency. B) Illustrations of the three paradigms for the transition between the two stimuli; *time-separated*, in which the two stimuli were separated by an ISI of 1 s; *step*, in which the ISI was eliminated and *gradual*, with a 1-s linear transition between $F_B$ and $F_T$. for all the three schemes, both baseline and test stimuli were 1.5 s in duration. In these figure $F_B$ is always presented first, but the order of stimuli was randomized across the trials. C) Average normalized JND across three stimulation schemes for the baseline frequency of 20 Hz and 60 Hz. The results indicated that the transition mode of the stimulus pair affected the obtained JNDs, and the discrimination ability was better if there is an ISI between stimuli without stimulation (*time-separated* scheme) compared to when the two stimuli were delivered without the break.

between stimuli [106]. Taken together, this implies that an accurate perception of the first stimulus, once formed (after approximately 600 ms) is preserved only for a few seconds.

The primary motivation behind study I was to estimate subject's discriminability of frequency modulation codes for electrical stimulation in order to determine the magnitude of unnoticeable perturbation (*see section 2.2 & 2.3*). As a result of study 1, the most we can conclude is that the higher sensitivity (lower JND) was achieved when the stimuli were separated in time as compared if the stimuli are delivered continuously. Therefore, the perturbation (*see section 2.2*) that is estimated through *time-separated* transition mode (conventional procedure) would be unlikely noticed by the subjects.

## 2.6. GENERAL EXPERIMENTAL SETUP

The setup consisted of the closed-loop system shown in Figure 4.B The system included a standard PC, a grip force dynamometer, an electrical stimulator connected to a pair of stimulation electrodes, and a data acquisition board to sample the force and also transfer analog input (command signal) to the stimulator. The model was implemented in Matlab (MathWorks, USA), Simulink, using a toolbox for human manual control [118]. In each session, the subjects sat comfortably in front of a desk. A pair of stimulation electrodes were placed on the radial side of the forearm in the abled bodied subjects and lateral posterior region of stump for amputee subject. During the experiment, the subjects were asked to hold and squeeze a grip force dynamometer with their dominant hand (the amputee subject used her intact hand). The signal was sampled and processed on a PC, where it was encoded in a stimulation pattern according to the selected encoding strategy. The stimulation was then delivered to the skin of the arm in real-time by electrodes. Furthermore, in some trials the system added a mismatch (bias) in the relation between the recorded force signal and the encoding pattern regarding to the perturbation analysis (*see section 2.2*).
Finally, a computer monitor was used to display force data through a floating vertical bar, indicating the magnitude of the generated force. In this way, the instantaneous grasp force was fed back to the subject through the three following channels (Figure 4.A): natural feedback (hand grasping the gripper), electrotactile feedback (the sensation of the electrotactile stimulation) and visual feedback (visual representation on the screen; only appeared during target task).

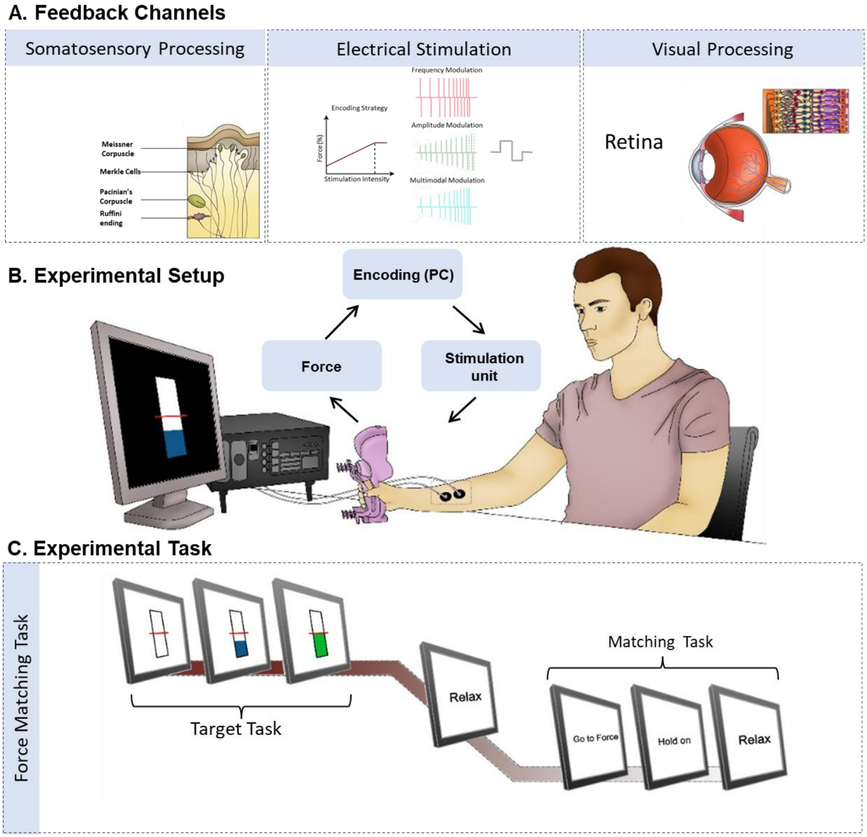



Figure 4. The experimental setup included a force dynamometer, a standard PC, an electrical stimulator connected to a pair of stimulation electrodes located on the lower arm of the subject. The recorded force signal was sampled and processed on a PC, where it was linearly encoded to stimulation parameters (i.e., pulse frequency or pulse amplitude) generated by the stimulator. In addition, during the target task a visual representation of the grasping force was shown on the computer screen by a floating bar. In this way, the subjects received information regarding the generated grip force from up to three different channels: through vision, natural force feedback (i.e., cutaneous receptor and Golgi tendons) and electrotactile stimulation (top panel). In the primary experimental task (bottom panel), each trial consisted of two contractions. First, the subject was asked to generate the specific force by reaching the target force and hold it over a few seconds (target task), relax and recreate the same force but without visual feedback and to hold it for few seconds (matching task). In a subset of trials in the matching task, the relation between the electrotactile feedback and grasp force was perturbed, to induce a conflict between the information carried by the natural and electrotactile feedback (biased conditions).

## 2.7. EXPERIMENTAL PROCEDURE

### 2.7.1. FORCE NORMALIZATION AND PSYCHOMETRIC ASSESSMENT

In the first phase of the experiment, the maximum voluntary contraction (MVC) force was measured by asking the subject to maximally grasp the hand dynamometer for 5 seconds. The measurement was repeated three times and the MVC was defined as the mean value of the plateau force across three repetitions. Next, the stimulation amplitude required for sensation (ST) and discomfort (DT) were determined using the method of limits [93]. This was achieved by increasing the stimulation intensity for a fixed increment. For ST, the subject was asked to report when he/she first felt the sensation and for DT, the subject reported when the sensation became uncomfortable. While measuring ST and DT, the pulse frequency was set at baseline frequency. The subject's JND was then measured using adaptive methods (*time-separated* scheme; regarding to the results of study 1) to identify the subject's sensitivity in order to determine the magnitude of the applied bias. This used procedure in our studies implied that the estimated JND corresponded to the difference in frequency that the subject was able to recognize with a success rate of 75% [101].

### 2.7.2. TRAINING PROTOCOL

Next, the participants underwent two training sessions lasting approximately 5 minutes in total to generate an intuitive understanding of the relation between natural feedback (proprioception, cutaneous and visual input) and the generated force. First, the subject was asked to generate a specific force level indicated by a horizontal line on the screen. The second training task was similar to the first, but the visual feedback of the instantaneous force was disappeared for the first few seconds, leaving the subject to rely only on natural input to generate the desired force. The bar reappeared during the last three seconds of the trial, so that the subject was able to correct it if necessary.

### 2.7.3. PRIMARY EXPERIMENTAL TASK

Throughout the task (Figure 4.C), the subjects were asked to generate specific force, while receiving visual feedback, natural sensation through hand, also the artificial feedback (target task). After relaxing for few seconds, the subject was asked to generate the same force without visual feedback and hold it for 5 s (matching task). In subset of trails a small (unnoticeable) systematic error is added to the artificial feedback. The magnitude of bias in the stimulation frequency was set equal to 80% of subject's JND, which implied that all four feedback mappings should be consciously perceived as identical by the subject. Importantly, the subjects were not informed about the fact that the mapping would be biased in some trials and presumably assumed that it was identical across all trials. At the end of experiment the subjects were questioned if they had noticed any difference in the force–frequency mapping across trials. The degree to which the resulting aperture is biased by the mismatch reveals if CNS attempts to primarily match the natural or the artificial feedback received in the target task.

## 2.8. ENCODING SCHEMES

As shown in Figure 4.A, throughout the next studies, the instantaneous force signal (*f*) was encoded in either stimulation pulse amplitude, stimulation pulse frequency or combination of them (multimodal modulation). In amplitude modulation, the carrier frequency was set to baseline frequency in a range between 5-65 Hz. The amplitude of the stimulation pulses (*A*) was proportional to grasping force according to the following linear relationship:

$$\boldsymbol{A(t) = 0.8 \cdot (PT - ST) \cdot f(t) + ST} \qquad \textbf{(2.2)}$$

where ST and DT indicates the sensation and discomfort thresholds respectively.

In frequency modulation, the stimulation amplitude was set to halfway between ST and DT to ensure a clear, comfortable sensation. The stimulation frequency range was determined to be between 5-65 Hz, since within this range it is feasible to distinguish between frequencies. Moreover, it has been demonstrated that the discharge rate of cutaneous afferents is below 65 Hz [119]. Therefore, the frequency of the stimulation pulses (*F*) was proportional to grasping force as indicated by equation 2.3:

$$\boldsymbol{F(t) = 60 \cdot f(t) + 5} \qquad \textbf{(2.3)}$$

And finally, the multimodal modulation condition was obtained based on modulating frequency and amplitude simultaneously regarding equations 2.2 and 2.3.

# CHAPTER 3. SENSORY INTEGRATION OF ELECTROTACTILE FEEDBACK

## 3.1. STUDY OVERVIEW

As stated in chapter 1, our nervous system relies on multisensory integration across different senses to register an event. In this chapter, we aimed to probe neural integration of somatosensory feedback during closed-loop control of grasping force while the feedback is provided through sensory substitution feedback (study II).

To do this, in study II, we used the framework described in previous chapter. Specifically, 14 able-bodied volunteers performed a grasp force-matching tasks (*see section 2.7.3*) with natural force feedback as well as electrotactile feedback with a frequency representing the generated force (*see section 2.7*; Figure 4). In a subset of the repetitions of the matching task, an unnoticeable bias was introduced (study I, *see section 2.3-2.5*) in the electrotactile feedback, which implied that it was not possible to perfectly match the natural sensation of force and the electrotactile frequency from the target task. The baseline condition, three different biased conditions as well as a control condition without electrotactile feedback (*natural feedback only*) was repeated 30 times each. The biased conditions involved stimulation frequencies biased towards lower or higher values than in the target task ($bias^-$ and $bias^+$ conditions, respectively). Furthermore, the $bias^+$ condition was repeated with a 125 ms delay in the electrotactile feedback ($bias^{+d}$) to emulate a realistic time lag between activation and movement of a prosthesis [120]. In order for the subject to enable adjustments to the appropriate target level, the state of the task (i.e. instantaneous grasp force) had to be estimated. In this way, in the biased conditions, the subject had to subconsciously generate a weighted average of the two sources of information. Therefore, a non-zero weight assigned to electrotactile feedback would imply that human observers adopt the information from supplementary feedback and integrates it naturally.

## 3.2. THE MATCHING FORCE SHIFTED TOWARD ELECTROTACTILE FEEDBACK AS MORE RELIABLE SENSORY MODALITY

The primary outcome measure in this study was the plateau force (the mean force) in the matching task ($f_{mt}$) which was expressed as a percentage of the target task (the target force shown by red line on screen in Figure 4.B). Figure 5 depicts the corresponding profiles of instantaneous force generated by one subject during the *baseline*, and $bias^+$ conditions (two trials each). In the target task the force generated accurately in all trials of course due to the presence of visual feedback. In the *baseline* condition, electrotactile and natural force feedback were consistent, so both artificial and natural cues indicated the same force. Consequently, in the matching task of the *baseline* condition, the target force was reproduced with a quite high accuracy (top panel). On the other hand, in *bias*$^+$ condition the two sensory modalities were inconsistent in which the natural feedback depicted one magnitude of force $f_N$ while the electrotactile stimulus indicated a different magnitude of force ($f_E$). In this case, the plateau forces were systematically shifted, meaning that in this condition the subject subconsciously produced the force by making a compromise between matching the perceived natural sensation (natural feedback) versus repeating the perceived stimulation frequency that they were received in the target task (bottom panel).

Figure 6.B illustrates the average plateau force under different conditions across all subjects. The target force was accurately regenerated in the *baseline* condition (average $f_{mt}$: 99.3 ± 7.5 %), while it was higher (average $f_{mt}$: 109.8 ± 11.6 %) and lower (average $f_{mt}$: 88.6 ± 7.4%) in the *bias*$^-$ and *bias*$^+$ conditions, respectively. Statistical analysis revealed that the bias significantly affects the matching plateau force ($p < 0.001$). This suggests that the subjects on average failed to match the target force in the biased condition, due to a trade-off between matching the two sources of information regarding the force, and such integration is exactly what we would expect to observe if the sensory inputs are integrated based on MLE-framework. Our findings also indicated that adding 125 ms delay in the feedback did not affect the results (average $f_{mt}$ in *bias*$^{+d}$: 90.0 ± 7.9%).

In case of a discrepancy between multiple sensory cues, humans tend to be biased toward the senses that are more reliable and have higher acuity [121]. For instance, visual stimuli will often dominate auditory stimuli as observed in the McGurck effect [122] or ventriloquist illusion [123]. In our study, reproduced plateau force was more biased toward the force that is generated by the observer to evoke the same stimulation frequency as in the target task. This might reflect that subject's uncertainty for the natural feedback was greater and so they applied a smaller weight to its reading which entailed shifting the final estimate closer to electrotactile estimation.

## 3.3. ELECTROTACTILE FEEDBACK OUTWEIGHS NATURAL FEEDBACK IN SENSORY INTEGRATION

In previous section, we found that the information transmitted by the electrotactile feedback was exploited in the sensory integration process with a substantial weight (*see section* 3.3). In next step, we aimed to quantify this weight allocated to electrotactile signal. Specifically, the empirical weights were estimated from whether the force in the final estimation was closer to the natural estimate or the electrotactile estimate. This can be obtained from the conflict conditions data by the following equation:

$$\boldsymbol{W_E = \frac{f_{mt}\{bias^*\}-100}{f_E\{bias^*\}-100}} \qquad \textbf{(3.1)}$$

where $f_{mt}\{bias^*\}$ is the average matching task plateau force, $f_E\{bias^*\}$ refers to the force that should be created in the matching task in order to produce the target frequency, and * indicates the type of condition (+, -, +d).

Across subjects, we found that the average relative weight of electrotactile feedback was 0.69 ± 0.29, implying that the weight of natural force feedback was 0.31 ± 0.29 (Eq.2.1). This result suggests that in multisensory integration process the electrotactile feedback outweighed the natural feedback for most subjects. In other words, when faced with inconsistent information, the nervous system tended to mostly rely on electrotactile feedback relative to natural feedback. This is a notable finding since the grasping with a certain accuracy is a common element in many every-day tasks, and one could have assumed that the nervous system would not substantially alter the degree to which it relies on the natural grasp force feedback. In an unimpaired individual, the grasp force estimate is obtained naturally from many sources including cutaneous receptors through the mechanical deformation of the tissue and Golgi tendon organs sensing forces generated by muscle [124], [125]. Each of these two groups of feedback consist of thousands of receptors, whose individual activity may vary considerably across repetitions. For example, even a small shift in the position of the force gripper would cause a redistribution of the force across the palm and fingers, thereby activating the receptors in a different way. Moreover, the redundancy of the forearm muscles imply that one specific grasp force magnitude can be generated by different combinations of muscle activation patterns. This is not just a theoretical option, but it is due to the fact that the nervous system actively exploits different solutions while repeating the same motor tasks [126], [127] which entails that the activation of individual Golgi tendon organs would differ across repetitions, even in the simple task of isometric force tasks [128]. Therefore, the nervous system has to estimate the information on the grasping force, by such an inherently variable activation of a network of receptors. On contrary, electrotactile feedback provided a

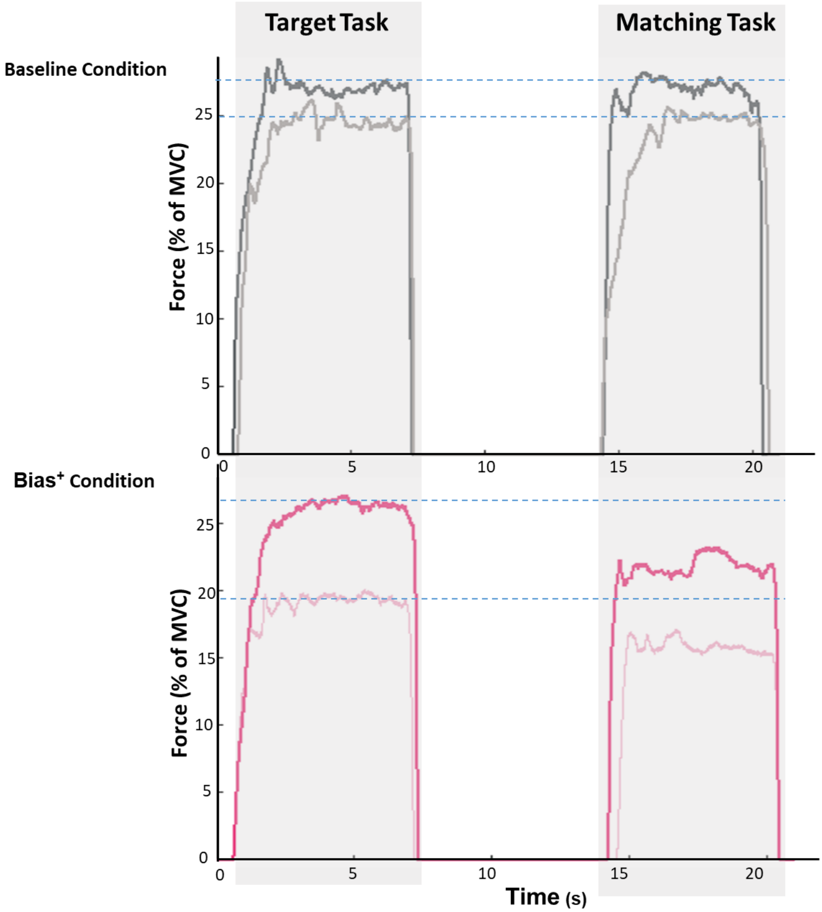



Figure 5. Force profiles generated by a subject under two different conditions of baseline and *bias*$^{+}$ (two repetitions each). In the top panel the subject reproduced the force with high accuracy in the baseline condition, in which the natural and electrotactile feedback were congruent. In the *bias*$^{+}$, the mapping between force and frequency was slightly manipulated. The subject was not aware of this conflict and assumed that the mapping was the same. However, the force reproduced in the matching task were suppressed, suggesting that the subject subconsciously compromised between the sensory inputs from the natural sensation of force and the sensation of frequency modulated electrotactile feedback to determine the appropriate force commands.

less ambiguous source of information (though tingling sensation on the forearm) while estimating the force state. In fact, electrotactile feedback provides a simpler and more stable representation of the grasp force, since the task relevant information is transmitted directly, encoded in the stimulation frequency, through the same group of nerves activated in a synchronous manner.

## 3.4. ELECTROTACTILE FEEDBACK INTEGRATES IN THE STATE ESTIMATION PROCESS ACCORDING TO MLE

As stated in chapter 1, optimal mechanism of sensory integration is to make a minimum-variance estimate, so that the variance of combined estimate is less than of that either of estimates, fed into the averaging process. Therefore, the final estimation (Figure 6.A) arising from multisensory integration shows greater reliability and less effects of noise (less variance). Based on MLE-framework precision of the final estimate based on the available streams of information can be predicted through the variance of involved feedback sources (i.e., [2]). Thus, if the weight allocated to artificial feedback is high,  one would expect that the precision of the final state estimate improves when electrotactile feedback is added into state estimation process (and vice versa for low $W_E$).

To explore whether providing electrotactile feedback led to improvement in the precision of the final estimate (variance reduction occurred), we compared the change in variance as the ratio between the variance of average estimated plateau force in the conditions with and without electrotactile feedback (i.e. *natural feedback only*/*baseline*). In this way, a low value of ratio suggests a better precision, while the values at or higher than 1.0 indicate the same or lower precision with the presence of the electrical stimulation.

Our results indicated that the empirical weights of electrotactile feedback (Eq.3.1) was significantly correlated with the improvement in the precision of the matching task plateau force with the addition of electrotactile feedback ($r^2 = 0.75, p < 0.001$; Figure 6.C). This is indeed in line with MLE-framework which indicates that a precise source of information would be assigned a high weight.  In addition, we observed that for those subjects with high variance ratio, the distributions of plateau force in biased conditions (*bias*$^+$, *baseline*, and *bias*$^-$ conditions) were largely overlapping (the bias did not affect), reflecting the fact that subject might not include electrotactile feedback in the sensory integration process while performing matching force task. On the other hand, smaller variance ratio (precision improvement), led to a clear shift in the estimate value of the fitted distributions to the *bias*$^+$, *baseline*, and *bias*$^-$ conditions, indicating that the electrotactile feedback was added as an input to the process of multisensory integration.

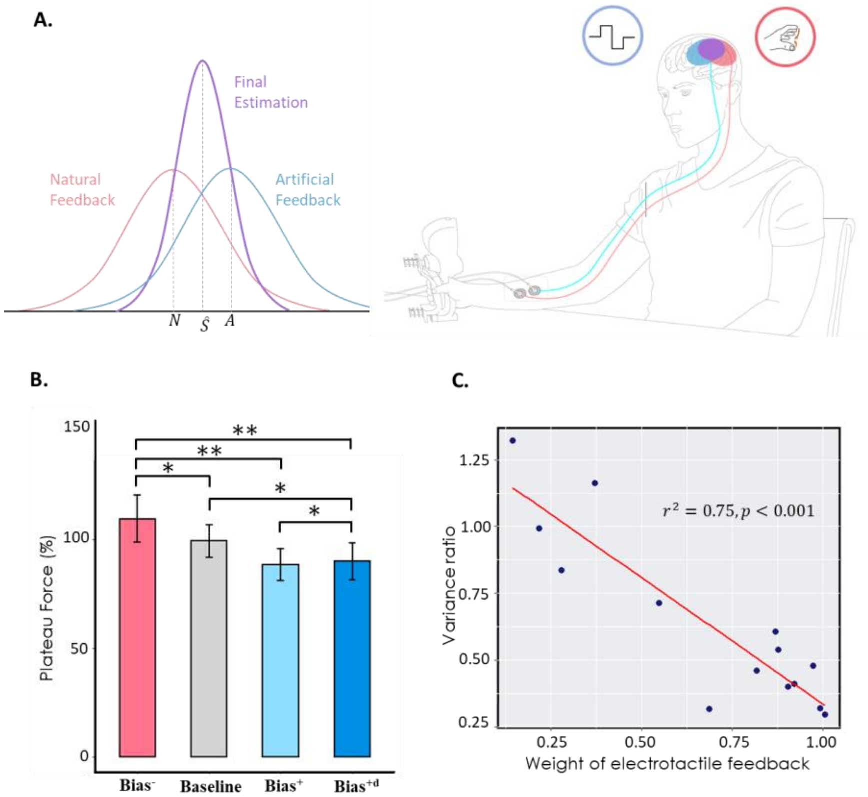



Figure 6. Summary of Study II. Abled-bodied participants performed a force matching task (*see section* 2.7) while receiving electrical stimulation with a pulse train frequency proportional to the generated force as well as natural sensation through their hand. Information from these two cues, prompting the observer to estimate the true force as the weighted average between the two streams of information (A). The average plateau force was altered across different conditions (B). Specifically, in trials where no bias was imposed (baseline), the force was accurately reproduced (100%). However, in trials where force-frequency mapping was biased, the plateau forces were systematically shifted toward the somatosensory modality, even though the subjects did not notice the bias. Indeed, the overall perception experienced by the subjects was a compromise between the sensory modalities, which was then applied to estimate the matching force based on weighted average. To infer these weights, the difference between the target force and the matching force under biased conditions were analyzed (Eq.3.1). Adding electrotactile feedback in baseline condition leads to variance reduction of sensory estimate (C). This suggests that electrotactile feedback was integrated in the neural process of estimating the generated grasp force in a way similar to natural sensory modalities (C).

In the literature regarding sensory substitution feedback, it is typically assumed that sensory substitution feedback is processed consciously as against natural feedback which is mainly processed subconsciously [23]. Moreover, exploiting this stream is assumed to imply a considerable cognitive load since the sensation of tingling has to be explicitly re-interpreted as the modality that is encoded in the feedback (in this case grasp force) [15]. The findings of this study, however, showed that the information from electrotactile feedback is also processed subconsciously and that the resolution of this stream might not be limited by JND. This is similar to the processing of natural feedback, as the nervous system continuously receives and processes information, yet it does this process so effortlessly that we might not be aware it is happening. Nevertheless, this information can be exploited, as shown previously in the studies from which our study design drew inspiration (tactile and proprioceptive sensory feedback) [2], [90], and other studies (visual feedback) [129].

In conclusion, in study II we showed that electrotactile feedback with a frequency modulation proportion to the generated grasp force is perceived and processed subconsciously according to the principles of MLE and that the integration is not limited by JND. Furthermore, the weight assigned to the electrotactile feedback, and thus its contribution in the state estimation, outweighs its natural counterpart.

# CHAPTER 4. QUANTIFYING THE ROLE OF FEEDBACK IN THE STATE ESTIMATION PROCESS

## 4.1. STUDY OVERVIEW

Nowadays, there is a considerable evidence that supplementary feedback is capable to enhance task performance in individuals with upper limb prosthesis [33], [36], [130]–[134]. These studies employed different technological devices and approaches, aimed to further improve the sensory input available to the user. One interesting question to explore in this regard is the way different system performance are evaluated.

Recent research efforts have been directed towards designing approaches for the assessment of upper limb prostheses equipped with artificial somatosensory feedback. These approaches have included evaluation of subjective experience [135]–[137] or analytical assessments of the amount of information that could effectively be conveyed to the subject through supplementary feedback [138], [139]. However, such evaluation often lacks functional correlates, which obscures interpretation of potential benefits [140] . Therefore, most studies have focused on evaluation using functional tasks; In this way, once the system is implemented, the subject is asked to perform a functional task under different conditions; often with and without feedback ( reviewed in [23]). Across different studies, the functional task may be very simple (e.g., generating a specific force level), or more representative of actual daily tasks such as box-and-blocks test [141], the Clothespin Relocation task [142], a block-foraging stiffness discrimination task [143], and the virtual egg test [132]. The performance in such tasks, however, depends on multiple parameters including task constraints, user experience [144], and the degree to which other task-relevant sources of feedback is available [23]. To compensate for this, recent studies have suggested a battery of tests with varying requirements for task speed and accuracy, as well as for user attention [130], [140] . However, in such assessment, the same sensory feedback may not be equally efficient across different tasks. This indicates a need for simpler, more objective and time-efficient evaluation criteria.

In previous chapter we quantified the quality of supplementary feedback from a sensory integration point of view. Specifically, in study II we showed that electrotactile feedback integrates with natural sensory inputs in the state estimation process during control of grasp force (paper II). In this integration process, the relative weight to be attributed to each sensory signal was determined based on the perceived reliability of the corresponding signal in accordance with MLE. Accordingly, we hypothesized that the optimal design for supplementary feedback would be characterized by a high weight in this sensory integration process, therefore, the relative weight of the electrotactile feedback can be a relevant measure of its reliability as perceived by the central nervous system (paper II; [145]).

Available single channel sensory feedback system, typically conveys feedback information through either amplitude or frequency modulation [23]. Simultaneous encoding of the feedback signal in amplitude and frequency was recently proposed through direct peripheral nerve stimulation. While George et al. compared such multimodal stimulation to binary encoding (stimulation either off or on at a constant intensity) [146], Valle et al. stimulated peripheral nerves evoking a localized sensation of vibration to encode prosthesis grasp force in stimulation amplitude, frequency, or both (so-called hyprid) [113]. In the later study simultaneous modulation of pulse amplitude and frequency found to be superior to single feature modulation with regards to performance and naturalism of the sensory encoding algorithms [113]. Resembling the characteristics of natural sensory feedback was probably the underlying the reason of proposing multimodal modulation in the previous researches [113], [146], assuming that it is easier for the brain to recognize the feedback evoked by multimodal stimulation as a meaningful sensory signal therefore leads to more natural perception.

Although the evoked sensation through invasive approaches and the present study are different in somatotopy, but we believe the evoked sensation is comparable in quality. Inspired by abovementioned studies, here we aimed to use sensory integration principle to assess three different configurations for sensory substitution feedback systems. A method based on this principle can be used as an objective figure of merit, compared to previous assessment methods. Specifically, we recruited 14 able-bodied subjects who participated in the three-session experiment performed in three consecutive days. We used the framework described in chapter 2, to compare the efficiency of three different encoding strategies, by modulating amplitude or frequency individually, or both parameters simultaneously (multimodal encoding*; see section 2.8*) proportion to instantaneous grasp force.

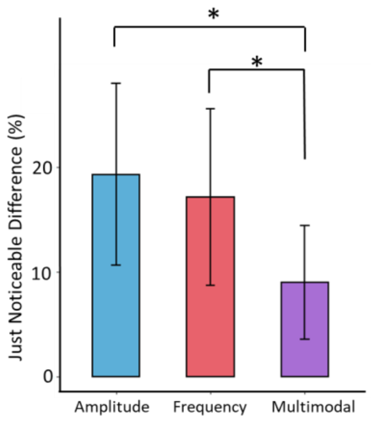



Figure 7. Average normalized JND across three stimulation modulations (paper III). In this study, we found that discriminability was higher when both amplitude and frequency increased or decreased simultaneously than when changed in isolation. Consequently, multimodal modulation resulted in the best feedback resolution (lowest mean JND) as compared with the two other conditions.

## 4.2. SIMULTANEOUS MODULATION OF FREQUENCY AND AMPLITUDE IMPROVES DISCRIMINABILITY OF ELECTRICAL STIMULATION

To determine the magnitude of induced bias for the three mentioned modulations, the subject's JND was determined using adaptive weighted staircase procedure [100] using *time-separated* paradigm (*see section 2.5*) in three different sessions. These experiments yielded psychometric functions relating discrimination performance to differences in stimulation intensity (amplitude, frequency and multimodal).

In all three sessions, the amplitude and frequency of the standard stimulus were set at the baseline amplitude (halfway between sensation and discomfort threshold) and baseline frequency equal to 42.5 Hz, respectively. For amplitude discrimination, the first comparison stimulus was set at an amplitude 30% higher than the baseline and its frequency was constant across trials. The frequency parameters were determined as a function of the amplitude of the stimulus (based on a linear relationship assumed between amplitude and frequency). Specifically, the amplitude of the standard and comparison stimuli were adjusted depending on the subject's sensation and discomfort threshold, while their frequency, as well as the step size, was determined as a function of amplitude. Finally, in the multimodal condition, the standard and first comparison stimuli values for frequency and amplitude discrimination sessions were adopted, and the comparison stimulus varied in both amplitude and frequency across trials according to the step sizes used in amplitude and frequency modulation sessions, respectively.

Figure 7 shows how the subjects discriminate the perceived intensity of pairs of stimulation pulse trains that varied in amplitude, frequency, or both (multimodal).

Specifically, the subject's discriminability was higher when both amplitude and frequency were modulated concurrently ($JND_{multi}$: 8.98 ± 5.41 %%) compared to changing the stimulation features individually ($JND_A$: 19.29 ± 8.64 %)., $JND_F$: 17.11 ± 8.39 %). Statistical analysis revealed that JND varied across the three stimulation conditions ($p < 0.01$), and post hoc analysis indicated lower JND in multimodal condition than in the two other conditions ($p < 0.05$ for both amplitude and frequency modulation).

The results are partly in line with the findings of a recent study using intraneural stimulation, that showed that amplitude and combined modulation in the encoding scheme led to better discrimination ability [113]. However, in the present study, no significant difference was found comparing the JND values between amplitude and frequency conditions. Such variations can be explained by the fact that the sensitivity to tactile discrimination also depends on the sensation evoked by a different types of stimulation [114].

### 4.3. MULTIMODAL ENCODING STRATEGY INCREASES THE WEIGHT OF ELECTROTACTILE FEEDBACK IN THE STATE ESTIMATION PROCESS

In next step, we quantified the empirical weights applied to the electrotactile signal for the three encoding conditions (amplitude, frequency, multimodal), through the framework described in chapter 2. Here, we particularly assumed that the higher weight allocated to feedback in the state estimation process by the nervous system, the more efficient the feedback.

The results of study III (manuscript IV) showed that the empirical relative weight (*see section 3.3*) was significantly higher in multimodal condition 0.86 ± 0.02 compared to amplitude only ($0.67 \pm 0.061\,;\, p < 0.05$) and frequency only modulations ($0.65 \pm 0.034\,;\, p < 0.005$) as shown by Figure 8. This would mean that the highest weight was obtained when the frequency as well as amplitude of the stimulation were modulated simultaneously (multimodal condition). In this case, the relative weight was > 0.9 in half of the subjects, indicating an almost complete reliance on electrotactile feedback. The results also indicates that the nervous system relies more on electrotactile feedback ($W_E$> 0.5) than on the natural force feedback while estimating the magnitude of force generated by the hand, regardless of how electrical stimulation is modulated. As discussed in detail in section 3.3, this confirms the remarkable ability of the nervous system to adopt the sensation of tingling on the arm as the primary source of information regarding grasp force magnitude after just a brief training.

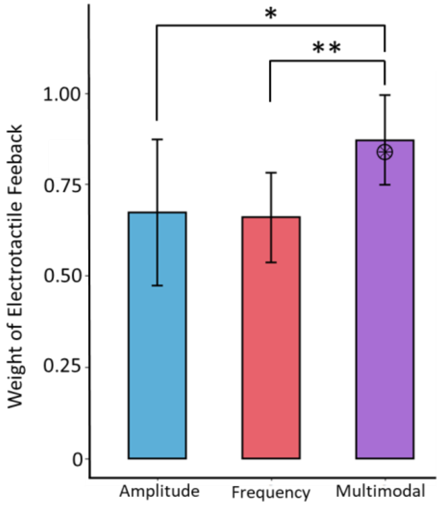



Figure 8. The relative weight assigned to electrotactile feedback with three encoding schemes. In this study, we found that the weight assigned to electrotactile feedback was significantly higher for multimodal condition.

Comparing the three modulation conditions, across all subjects the plateau forces in multimodal modulation were produced with less variability and error reflecting higher accuracy and precision, respectively. Statistical analysis revealed significant differences across the three encoding schemes for error ($p < 0.05$) as well as for the variance ($p < 0.005$). This was mainly due to higher accuracy in multimodal condition (less error) compared to amplitude modulation ($p < 0.05$) and higher precision in multimodal condition compared to both amplitude and frequency modulation (multimodal vs. amplitude: $p < 0.05$ multimodal vs. frequency: $p < 0.005$). Moreover, the comparison between the amplitude and frequency modulations revealed significant difference between the two groups in error ($p < 0.05$) , but not in variance.

This is partly in agreement with [113], which reported that multimodal modulation improve sensation naturalness, tactile sensitivity, manual dexterity, and prosthesis embodiment. Similarly, the participants in our study tended to prefer multimodal modulation (regarding the questionnaire results). With regards to performance, however, amplitude was as efficient as multimodal modulation enabling similar performance in functional tasks in [113], whereas we found that multimodal modulation was superior with respect to contribution in the state estimation process (see section 4.3), tactile sensitivity (*see section 4.2*), also the accuracy.

## 4.4.THE MODULATION IN AMPLITUDE AND FREQUENCY INTEGRATED AS TWO INDEPENDENT FEEDBACK SOURCES

So far, we have found that multimodal modulation weights heavily the contribution of the electrotactile feedback to the final estimate as compared with unimodal modulations. It has been well established that the state estimation based on multiple streams of information is always more reliable than each of the individual sensory estimates in line with MLE [147], [148]. In the present study, we hypothesized that the multimodal encoding paradigm enhances the electrotactile feedback by providing two independent feedback signals within a single-channel stimulation pattern. This would mean that in the multimodal condition the two sensory cues (conveyed through amplitude and frequency modulation) are integrated by the nervous system as effectively two independent sensory inputs. To test this hypothesis, we investigated if the variance of $f_{mt}$ and relative weight of the electrotactile feedback in the multimodal condition could be predicted from the variance and weights measured in the amplitude only and frequency only modulation conditions.

So far, it was explained in detail how two signals from multiple sensory modalities can be combined in MLE-framework (*see section 1.7*). In such multisensory task, the MLE combines the three estimates in a weighted linear sum to obtain the estimated trimodal grasping force:

$$\boldsymbol{S_{final}[multi] = W_E[AM]S_E[AM] + W_E[FM]S_E[FM] + W_N S_N} \qquad \textbf{(4.1)}$$

where S indicates the state estimates (i.e., the grasp force) from the two individual sensory sources (electro (E) and natural (N)) and the final estimate ($\boldsymbol{S_{final}}$) determines the force in multimodal condition. Notably, estimating the force under multimodal condition is based on the integration of the states estimated by amplitude (AM) and frequency (FM) (assumed as two separate inputs), as well as of natural input (N). Thereby this condition three sensory inputs are fed into the multisensory integration process.

According to MLE, the weights (W) were associated with the reliability (inverse variance) of the input. so the weight assigned to electrotactile and natural feedback in unimodal conditions are measured by Eq. 4.2 & 4.3 respectively:

$$\boldsymbol{W_E = \frac{\sigma_N^2}{\sigma_N^2 + \sigma_E^2}} \qquad \textbf{(4.2)}$$

and

$$\boldsymbol{W_N = \frac{\sigma_E^2}{\sigma_N^2 + \sigma_E^2}} \quad \textbf{(4.3)}$$

As to remined, in Eq. 4.2 & 4.3 the empirical weights assigned to electrotactile and natural feedback are known from the observed data through Eq.3.1 *(see section 3.3)*.

Figure 9 illustrates how we predicted the variance of final estimate in multimodal condition. In step 1, we used above information to compute the variance of each individual feedback source (i.e. $\sigma_N^2$ and $\sigma_E^2$) from the data collected in the experimental sessions with amplitude and frequency modulation conditions as follows:

$$\boldsymbol{\sigma_E^2[*] = \frac{\sigma_{EN}^2}{W_E}} \quad \textbf{(4.4)}$$

$$\boldsymbol{\sigma_N^2[*] = \frac{\sigma_{EN}^2}{W_N}} \quad \textbf{(4.5)}$$

where * indicates the type of modulation (either frequency or amplitude). In step 2, the estimated values of $\sigma_E^2$ and $\sigma_N^2$ was used to predict the variance of $f_{mt}$ with multimodal modulation ($predicted\ variance$; $\overline{\sigma_E^2[multi]}$) through Eq.4.6.

$$\boldsymbol{\overline{\sigma_E^2[multi]} = \frac{1}{\frac{1}{\sigma_N^2} + \frac{1}{\sigma_E^2[AM]} + \frac{1}{\sigma_E^2[FM]}}} \quad \textbf{(4.6)}$$

In above equation, the average value of the two values of $\sigma_N^2$ obtained from the amplitude and frequency sessions, was used. In step 3, This predicted value could then be compared to experimentally measured variance ($\boldsymbol{\sigma_E^2}[multi]$) from each subject in the multimodal condition.

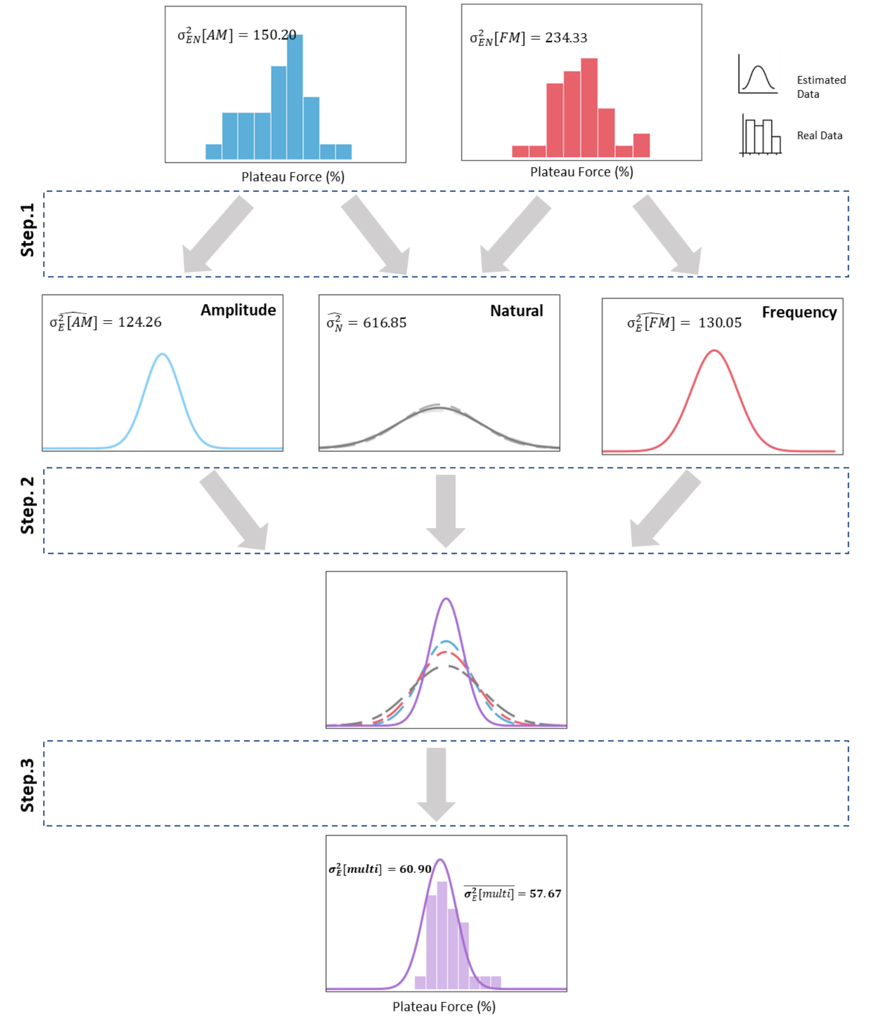



Figure 9. A representative illustration of how the variance of the plateau force in multimodal modulation condition was predicted using the variances of the experimentally observed distributions of $f_{mt}$ in unimodal conditions. In the first step, the variance of each sensory input (electrotactile feedback: AM and FM; natural feedback) were computed using Eq.4.2 & 4.3. In step.2 three sensory inputs, were then integrated based on MLE-framework (the predicted variance). Finally, in step.3 we compared the predicted value with the experimentally observed variance for the multimodal condition for each subject.

Additionally, the predicted weight assigned to electrotactile feedback in multimodal condition ($\overline{W_E[multi]}$) was determined through rearranging Eq.4.4. In this case, $\sigma_E^2[multi]$ was estimated by combining the estimated values of $\sigma_E^2$ from the AM and FM conditions based on MLE-framework:

$$\boldsymbol{\sigma_E^2[multi]} = \frac{\boldsymbol{\sigma_E^2[AM]\sigma_E^2[FM]}}{\boldsymbol{\sigma_E^2[AM] + \sigma_E^2[FM]}} \qquad \textbf{(4.7)}$$

As depicted in Figure 10, comparing the predicted and measured variance as well as weight of electrotactile feedback in the multimodal modulation across all subjects, we observed significant correlations for both parameters ($\sigma_E^2[multi]$: $r^2 = 0\ 67, p < 0.001$, $W_E[multi]$: $r^2 = 0.73, p < 0.001$), indicating that the performance with multimodal modulation can be modelled accurately by the MLE-integration of amplitude and frequency modulation as two separate inputs.

In previous studies [113], [146], the underlying the reason of proposing multimodal modulation was probably to resemble the characteristics of natural sensory feedback, assuming that it is easier for us to recognize the feedback evoked by multimodal stimulation as a meaningful sensory signal. In study III, however, we have found another evidence that may justify the superiority of multimodal condition from a sensory integration point of view. The fact that the plateau force variance and weight of electrotactile feedback in multimodal modulation could be predicted from the data recorded with only frequency or amplitude modulation, indicates that the subjects might have perceived the modulation in amplitude and frequency as two independent feedback sources conveying the same information (grasping force). Consequently, by integrating the two sources in accordance with MLE, the nervous system would obtain a better estimate of the feedback information, which might lead to improved performance and user experience.

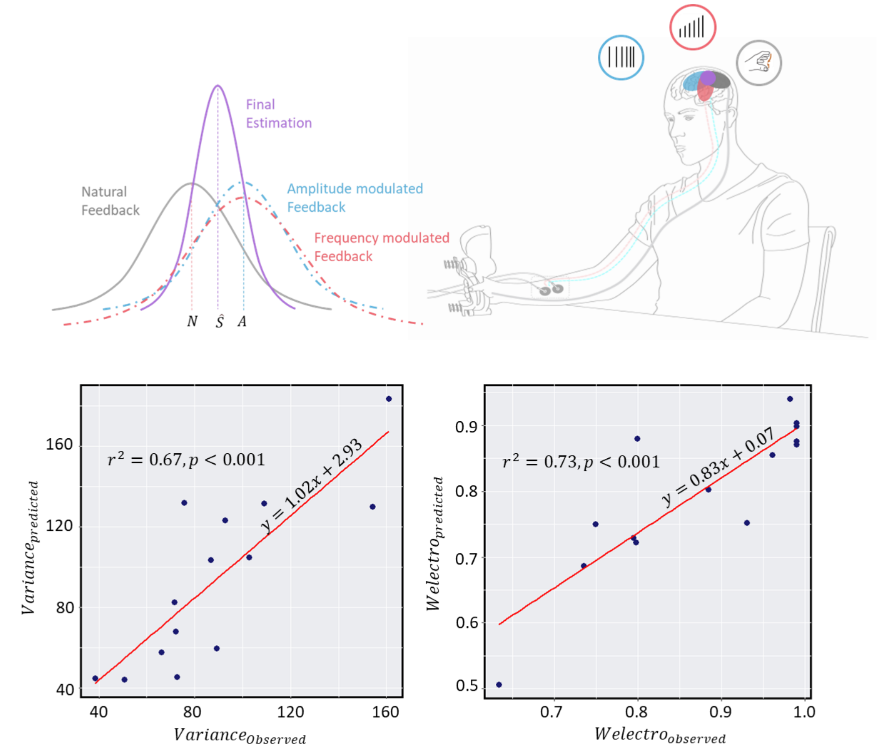



Figure 10. Summary of study III. In the multimodal condition, three sensory inputs are fed into integration process. In this way, we hypothesized that the final estimation depends on the integration of three feedback channels: natural force feedback, amplitude and frequency modulated electrotactile feedback (assumed as two independent input). To test this hypothesis, the empirical sensory weights in multimodal condition for each subject are statistically compared with the MLE-predicted weights computed from variance of plateau forces obtained from unimodal condition. Scatter plot showing the relation between observed and predicted values for variance of plateau force (bottom left) and weight assigned to electrotactile feedback (bottom right) for multimodal modulation condition.
The high correlation between predicted and observed values suggests that human observer integrates the two streams of information delivered by electrical stimulation as two independent sensory cues.

## 4.5. SENSORY INTEGRATION OF ELETROTACTILE FEEDBACK IS FEASIBLE WHILE DELIVERING STIMULATION THROUGH STUMP

In this study, we also included a trans-radial amputee to investigate whether the sensory integration of the electrotactile feedback still occurs while the electrodes are placed on the stump as opposed to an intact forearm. To do this, the amputee participated in one session with multimodal modulation. The result revealed that the sensation threshold, JND and the electrotactile weight ($W_E[multi] = 0.84$; shown by a star in Figure 8) were similar to those obtained in able-bodied subjects. These findings are consistent with previous studies that did not identify differences in the touch-pressure sensibility in the stump and intact arms of adults with acquired upper extremity amputations [149], [150]. Although verification in a larger population of amputee subjects is needed, this finding suggests that the main findings of the study can be also applied for prosthesis users.

# CHAPTER 5. FUTURE WORK AND SUMMARY

## 5.1. FUTURE WORK

### 5.1.1. TRANSLATION FROM HAND TO PROSTHESIS CONTROL

In this Ph.D. project we have shown that sensory substitution feedback is included included in the central nervous system estimation process. These findings may have an impact on how sensory feedback systems should be designed, in order to enhance performance while minimizing the added cognitive load. The translation of this insight into clinical applications could serve as a future direction. For example, the tactile stimulation can be transmitted through the value of the EMG signal recorded from the amputee residual muscles [26], [51]. The EMG signal is normally used to control prosthesis by applying simple processing (smoothing). In this way, the amputee receives online feedback on the myoelectric signal to control the level of their muscle contraction, allows the user to control the force predictive. We would encourage future research to investigate sensory integration of the EMG biofeedback with intact natural sense of activation of the residual muscles.

### 5.1.2. MULTI-VARIABLE FEEDBACK

Alternative direction for future study would be to explore whether the nervous system is able to handle more feedback variables without compromising neural integration. Modern developments of prostheses involve increasing the number of degrees of freedom (DoF). There are efforts to provide feedback that can transmit larger bandwidth of information (multi variables) [40], [52], as a simple feedback interface based on single stimulation channel may not provide sufficient information for prosthetic control. For example in [52] the information of wrist rotation and hand aperture were simultaneously transmitted to the user through multichannel electrotactile stimulation while performing an online myoelectric control of two DoF positioning task. In this respect, our results from study III are encouraging, indicating that the nervous system is effectively able to identify single-channel electrotactile multimodal modulation as two independent signal, so that the redundant information provided by two streams of information could improve overall estimation in accordance with MLE. The ability to convey more variables through one feedback channel might reduce cost, power consumption, and need for maintenance, however increasing the number of feedback channels, would allow the larger bandwidth of the transmitted information. Whether this is indeed possible, however, needs to be investigated in future research. For example, to investigate the effects of simultaneous transmission of multiple feedback on sensory integration, one can record two force signals generated by two different fingers in which each force signal is individually encoded in a stimulation pattern and delivered to subject's forearm via two feedback channels. In this setup, the target and matching tasks will be applied to the force of both fingers, while there would be a mismatch between the two stimulation channels (based on perturbation technique). By comparing the results with previous outcomes, it can be deducted if transmitting more feedback variables would degrade sensory integration or not.

## 5.2. SUMMARY AND REMARKS

This thesis has endeavored to provide a better understanding of how feedback based on sensory substitution is included in the estimation process of the central nervous system. We have shown that human observers attribute a very high credibility to the electrotactile stimulation, and it can thus significantly improve the estimation of the condition of a prosthesis. In addition, the results showed that this contribution could be increased when the feedback contained redundant information (e.g., modulation in both amplitude and frequency).

Overall, we advocate that insights from sensory integration theory around principles of motor control may facilitate the design of bidirectional human-machine interfaces.

# LITERATURE LIST


[1] H. Imamizu *et al.*, "Human cerebellar activity reflecting an acquired internal model of a new tool," *Nature*, vol. 403, no. 6766, pp. 192–195, 2000.

[2] M. O. Ernst and M. S. Banks, "Humans integrate visual and haptic information in a statistically optimal fashion," *Nat. 2002 4156870*, vol. 415, no. 6870, pp. 429–433, Jan. 2002.

[3] R. C. Miall, O. Rosenthal, K. Ørstavik, J. D. Cole, and F. R. Sarlegna, "Loss of haptic feedback impairs control of hand posture: a study in chronically deafferented individuals when grasping and lifting objects," *Exp. Brain Res.*, vol. 237, no. 9, pp. 2167–2184, Sep. 2019.

[4] J. C. Rothwell, M. M. Traub, B. L. Day, J. A. Obeso, P. K. Thomas, and C. D. Marsden, "Manual motor performance in a deafferented man," *Brain*, vol. 105, no. 3, pp. 515–542, Sep. 1982.

[5] R. Shadmehr and S. Mussa-Ivaldi, "Biological Learning and Control: How the Brain Builds Representations, Predicts Events, and Makes Decisions," p. 400, 2012.

[6] P. Hernigou, "Ambroise Paré IV: The early history of artificial limbs (from robotic to prostheses)," *Int. Orthop.*, vol. 37, no. 6, p. 1195, Jun. 2013.

[7] M. Asghari Oskoei and H. Hu, "Myoelectric control systems-A survey," *Biomed. Signal Process. Control*, vol. 2, no. 4, pp. 275–294, 2007.

[8] J. S. Schofield, K. R. Evans, J. P. Carey, and J. S. Hebert, "Applications of sensory feedback in motorized upper extremity prosthesis: a review," *https://doi.org/10.1586/17434440.2014.929496*, vol. 11, no. 5, pp. 499–511, 2014.

[9] J. Davidson, "A survey of the satisfaction of upper limb amputees with their prostheses, their lifestyles, and their abilities," *J. Hand Ther.*, vol. 15, no. 1, pp. 62–70, 2002.

[10] E. Biddiss, D. Beaton, and T. Chau, "Consumer design priorities for upper limb prosthetics," *Disabil. Rehabil. Assist. Technol.*, vol. 2, no. 6, pp. 346–357, 2007.

[11] R. D. Lipschutz, B. Lock, J. Sensinger, A. E. Schultz, and T. A. Kuiken, "Myoelectric forearm prostheses: state of the art from a user-centered perspective," *J. Rehabil. Res. Dev.*, vol. 48, no. 6, pp. 719–737, 2011.

[12] S. Salminger *et al.*, "Current rates of prosthetic usage in upper-limb amputees - have innovations had an impact on device acceptance?," *Disabil. Rehabil.*, 2020.

[13] E. A. Biddiss and T. O. M. T. Chau, “Upper limb prosthesis use and abandonment: A survey of the last 25 years,” *Prosthet. Orthot. Int.*, vol. 31, no. 3, pp. 236–257, Sep. 2007.

[14] E. Biddiss and T. Chau, “Upper-limb prosthetics: critical factors in device abandonment,” *Am. J. Phys. Med. Rehabil.*, vol. 86, no. 12, pp. 977–987, Dec. 2007.

[15] P. Svensson, U. Wijk, A. Björkman, and C. Antfolk, “A review of invasive and non-invasive sensory feedback in upper limb prostheses,” *Expert Rev. Med. Devices*, vol. 14, no. 6, pp. 439–447, Jun. 2017.

[16] D. S. Childress, “Closed-loop control in prosthetic systems: Historical perspective,” *Ann. Biomed. Eng. 1981 84*, vol. 8, no. 4, pp. 293–303, Jul. 1980.

[17] G. F. Shannon, “A myoelectrically-controlled prosthesis with sensory feedback,” *Med. Biol. Eng. Comput.*, vol. 17, no. January, pp. 73–80, Jan. 1979.

[18] J. Hermsdörfer, Z. Elias, J. D. Cole, B. M. Quaney, and D. A. Nowak, “Preserved and impaired aspects of feed-forward grip force control after chronic somatosensory deafferentation,” *Neurorehabil. Neural Repair*, vol. 22, no. 4, pp. 374–384, Jul. 2008.

[19] M. A. Wilke, C. Niethammer, B. Meyer, D. Farina, and S. Dosen, “Psychometric characterization of incidental feedback sources during grasping with a hand prosthesis,” *J. Neuroeng. Rehabil.*, vol. 16, no. 1, Dec. 2019.

[20] M. Markovic, M. A. Schweisfurth, L. F. Engels, D. Farina, and S. Dosen, “Myocontrol is closed-loop control: Incidental feedback is sufficient for scaling the prosthesis force in routine grasping,” *J. Neuroeng. Rehabil.*, vol. 15, no. 1, pp. 1–11, Sep. 2018.

[21] M. Lundberg, K. Hagberg, and J. Bullington, “My prosthesis as a part of me: a qualitative analysis of living with an osseointegrated prosthetic limb,” *Prosthet. Orthot. Int.*, vol. 35, no. 2, pp. 207–214, Jun. 2011.

[22] C. Antfolk, M. D’alonzo, B. Rosén, G. Lundborg, F. Sebelius, and C. Cipriani, “Sensory feedback in upper limb prosthetics,” *https://doi.org/10.1586/erd.12.68*, vol. 10, no. 1, pp. 45–54, Jan. 2014.

[23] J. W. Sensinger and S. Dosen, “A Review of Sensory Feedback in Upper-Limb Prostheses From the Perspective of Human Motor Control,” *Front. Neurosci.*, vol. 14, p. 345, Jun. 2020.

[24] N. Jorgovanovic, S. Dosen, D. J. Djozic, G. Krajoski, and D. Farina, “Virtual grasping: closed-loop force control using electrotactile feedback,” *Comput. Math. Methods Med.*, vol. 2014, 2014.

[25] J. L. Segil, I. Cuberovic, E. L. Graczyk, R. F. f. Weir, and D. Tyler, “Combination of Simultaneous Artificial Sensory Percepts to Identify Prosthetic Hand Postures: A Case Study,” *Sci. Reports 2020 101*, vol. 10, no. 1, pp. 1–15, Apr. 2020.

[26] S. Dosen, M. Markovic, K. Somer, B. Graimann, and D. Farina, “EMG Biofeedback for online predictive control of grasping force in a myoelectric prosthesis,” *J. Neuroeng. Rehabil.*, vol. 12, no. 1, pp. 1–13, Jun. 2015.

[27] C. Antfolk *et al.*, “Sensory feedback in upper limb prosthetics,” *Expert Rev. Med. Devices*, vol. 10, no. 1, pp. 45–54, Jan. 2013.

[28] D. S. Childress, “Closed-loop control in prosthetic systems: Historical perspective,” *Ann. Biomed. Eng.*, vol. 8, no. 4–6, pp. 293–303, Jul. 1980.

[29] S. Micera, J. Carpaneto, and S. Raspopovic, “Control of hand prostheses using peripheral information,” *IEEE Rev. Biomed. Eng.*, vol. 3, pp. 48–68, 2010.

[30] G. S. Dhillon, T. B. Krüger, J. S. Sandhu, and K. W. Horch, “Effects of short-term training on sensory and motor function in severed nerves of long-term human amputees,” *J. Neurophysiol.*, vol. 93, no. 5, pp. 2625–2633, May 2005.

[31] P. E. Patterson and J. A. Katz, “Design and evaluation of a sensory feedback system that provides grasping pressure in a myoelectric hand,” *J. Rehabil. Res. Dev.*, vol. 29, no. 1, pp. 1–8, 1992.

[32] E. Raveh, S. Portnoy, and J. Friedman, “Adding vibrotactile feedback to a myoelectric-controlled hand improves performance when online visual feedback is disturbed,” *Hum. Mov. Sci.*, vol. 58, no. July 2017, pp. 32–40, Apr. 2018.

[33] S. Dosen *et al.*, “Multichannel Electrotactile Feedback With Spatial and Mixed Coding for Closed-Loop Control of Grasping Force in Hand Prostheses,” *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 25, no. 3, pp. 183–195, Mar. 2017.

[34] C. Cipriani, J. L. Segil, F. Clemente, R. F. Richard, and B. Edin, “Humans can integrate feedback of discrete events in their sensorimotor control of a robotic hand,” vol. 232, no. 11, pp. 3421–3429, Oct. 2014.

[35] Conzelman JE , Ellis HB , O'Brian CW : Prosthetic Device Sensory Attachment , U.S. Patent 2,656,545 , Oct. 27 , 1953.

[36] A. Chatterjee, P. Chaubey, J. Martin, and N. Thakor, “Testing a Prosthetic Haptic Feedback Simulator With an Interactive Force Matching Task,” *J. Prosthetics Orthot.*, vol. 20, no. 2, pp. 27–34, Apr. 2008.

[37] C. E. Stepp and Y. Matsuoka, “Vibrotactile sensory substitution for object manipulation: amplitude versus pulse train frequency modulation,” *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 20, no. 1, pp. 31–37, Jan. 2012.

[38] M. D. M. Atique and S. E. Rabbani, “A cost-effective myoelectric prosthetic hand,” *J. Prosthetics Orthot.*, vol. 30, no. 4, pp. 231–235, Oct. 2018.

[39] C. Cipriani, M. Dalonzo, and M. C. Carrozza, “A miniature vibrotactile sensory substitution device for multifingered hand prosthetics,” *IEEE Trans. Biomed. Eng.*, vol. 59, no. 2, pp. 400–408, Feb. 2012.

[40] H. J. B. Witteveen, H. S. Rietman, and P. H. Veltink, “Vibrotactile grasping force and hand aperture feedback for myoelectric forearm prosthesis users,” *Prosthet. Orthot. Int.*, vol. 39, no. 3, pp. 204–212, Jun. 2015.

[41] J. M. Walker, A. A. Blank, P. A. Shewokis, and M. K. Omalley, “Tactile Feedback of Object Slip Facilitates Virtual Object Manipulation,” *IEEE Trans. Haptics*, vol. 8, no. 4, pp. 454–466, Oct. 2015.

[42] H. J. B. Witteveen, F. Luft, J. S. Rietman, and P. H. Veltink, “Stiffness feedback for myoelectric forearm prostheses using vibrotactile stimulation,” *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 22, no. 1, pp. 53–61, Jan. 2014.

[43] J. Tchimino, M. Markovic, J. L. Dideriksen, and S. Dosen, “The effect of calibration parameters on the control of a myoelectric hand prosthesis using EMG feedback,” *J. Neural Eng.*, vol. 18, no. 4, Aug. 2021.

[44] P. Mamidanna, J. L. Dideriksen, and S. Dosen, “The impact of objective functions on control policies in closed-loop control of grasping force with a myoelectric prosthesis,” *J. Neural Eng.*, vol. 18, no. 5, Oct. 2021.

[45] L. A. Jones and N. B. Sarter, “Tactile displays: guidance for their design and application,” *Hum. Factors*, vol. 50, no. 1, pp. 90–111, Feb. 2008.

[46] K. A. Kaczmarek, J. G. Webster, P. Bach-y-Rita, and W. J. Tompkins, “Electrotactile and Vibrotactile Displays for Sensory Substitution Systems,” *IEEE Trans. Biomed. Eng.*, vol. 38, no. 1, pp. 1–16, 1991.

[47] M. D’Alonzo, F. Clemente, and C. Cipriani, “Vibrotactile stimulation promotes embodiment of an alien hand in amputees with phantom sensations,” *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 23, no. 3, pp. 450–457, May 2015.

[48] M. I. Johnson, “Transcutaneous Electrical Nerve Stimulation (TENS),” *eLS*, Oct. 2012.

[49] E. Krueger, J. C. Da Cunha, E. M. Scheeren, and P. Nohama, “Electrical and mechanical technologies in sensory system feedback and control: Cybernetics in physical rehabilitation,” *J. Control. Autom. Electr. Syst.*, vol. 25, no. 4, pp. 413–427, 2014.

[50] J. S. Schofield, K. R. Evans, J. P. Carey, and J. S. Hebert, “Applications of sensory feedback in motorized upper extremity prosthesis: a review,” *Expert Rev. Med. Devices*, vol. 11, no. 5, pp. 499–511, 2014.

[51] M. A. Schweisfurth, M. Markovic, S. Dosen, F. Teich, B. Graimann, and D. Farina, "Electrotactile EMG feedback improves the control of prosthesis grasping force," *J. Neural Eng.*, vol. 13, no. 5, p. 056010, Aug. 2016.

[52] M. A. Garenfeld, C. K. Mortensen, M. Strbac, J. L. Dideriksen, and S. Dosen, "Amplitude versus spatially modulated electrotactile feedback for myoelectric control of two degrees of freedom," vol. 17, no. 4, p. 46034, Aug. 2020.

[53] G. Lundborg, B. Rośn, K. Lindström, and S. Lindberg, "Artificial Sensibility Based on the Use of Piezoresistive Sensors: Preliminary observations,"vol. 23, no. 5, pp. 620–626, Aug. 2016.

[54] G. K. Patel, S. Dosen, C. Castellini, and D. Farina, "Multichannel electrotactile feedback for simultaneous and proportional myoelectric control," *J. Neural Eng.*, vol. 13, no. 5, p. 056015, Sep. 2016.

[55] G. Wang, X. Zhang, J. Zhang, and W. A. Gruver, "Gripping force sensory feedback for a myoelectrically controlled forearm prosthesis," *Proc. IEEE Int. Conf. Syst. Man Cybern.*, vol. 1, pp. 501–504, 1995.

[56] L. P. Paredes, S. Dosen, F. Rattay, B. Graimann, and D. Farina, "The impact of the stimulation frequency on closed-loop control with electrotactile feedback," *J. Neuroeng. Rehabil.*, vol. 12, no. 1, pp. 1–16, Apr. 2015.

[57] G. F. Shannon, "A comparison of alternative means of providing sensory feedback on upper limb prostheses," *Med. Biol. Eng.*, vol. 14, no. 3, pp. 289–294, 1976.

[58] K. A. Kaczmarek, M. E. Tyler, A. J. Brisben, and K. O. Johnson, "The afferent neural response to electrotactile stimuli: preliminary results," *IEEE Trans. Rehabil. Eng.*, vol. 8, no. 2, pp. 268–270, Jun. 2000.

[59] G. L. Aiello, "Multidimensional electrocutaneous stimulation," *IEEE Trans. Rehabil. Eng.*, vol. 6, no. 1, pp. 95–101, Mar. 1998.

[60] A. Akhtar, J. Sombeck, B. Boyce, and T. Bretl, "Controlling sensation intensity for electrotactile stimulation in human-machine interfaces," *Sci. Robot.*, vol. 3, no. 17, Apr. 2018.

[61] S. Dosen, M. C. Schaeffer, and D. Farina, "Time-division multiplexing for myoelectric closed-loop control using electrotactile feedback," *J. Neuroeng. Rehabil.*, vol. 11, no. 1, Sep. 2014.

[62] Y. Sasaki, Y. Nakayama, and M. Yoshida, "Sensory feedback system using interferential current for EMG prosthetic hand," *Annu. Int. Conf. IEEE Eng. Med. Biol. - Proc.*, vol. 3, pp. 2402–2403, 2002.

[63] M. A. Garenfeld *et al.*, "A compact system for simultaneous stimulation and recording for closed-loop myoelectric control," *J. Neuroeng. Rehabil.*, vol.

18, no. 1, pp. 1–17, Dec. 2021.

[64] J. Wheeler, K. Bark, J. Savall, and M. Cutkosky, “Investigation of rotational skin stretch for proprioceptive feedback with application to myoelectric systems,” *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 18, no. 1, pp. 58–66, Feb. 2010.

[65] G. Lundborg, B. Rosén, and S. Lindberg, “Hearing as substitution for sensation: a new principle for artificial sensibility,” *J. Hand Surg. Am.*, vol. 24, no. 2, pp. 219–224, 1999.

[66] D. Alais, F. N. Newell, and P. Mamassian, “Multisensory processing in review: from physiology to behaviour,” *Seeing Perceiving*, vol. 23, no. 1, pp. 3–38, 2010.

[67] M. O. Ernst and H. H. Bülthoff, “Merging the senses into a robust percept,” *Trends Cogn. Sci.*, vol. 8, no. 4, pp. 162–169, Apr. 2004.

[68] D. C. Knill, “Discrimination of planar surface slant from texture: human and ideal observers compared,” *Vision Res.*, vol. 38, no. 11, pp. 1683–1711, Jun. 1998.

[69] M. S. Landy, L. T. Maloney, E. B. Johnston, and M. Young, “Measurement and modeling of depth cue combination: in defense of weak fusion,” *Vision Res.*, vol. 35, no. 3, pp. 389–412, Feb. 1995.

[70] J. J. Clark and A. L. Yuille, “Data Fusion for Sensory Information Processing Systems,” *Data Fusion Sens. Inf. Process. Syst.*, 1990.

[71] A. Blake, H. H. Bülthoff, and D. Sheinberg, “Shape from texture: Ideal observers and human psychophysics,” *Vision Res.*, vol. 33, no. 12, pp. 1723–1737, Aug. 1993.

[72] Z. Ghahramani, D. M. Wolpert, and J. Michale I., “Computational models of sensorimotor integration,” *Adv. Psychol.*, vol. 119, no. C, pp. 117–147, Jan. 1997.

[73] K. Körding, *Decision theory: What “should” the nervous system do?*, vol. 318, no. 5850. 2007, pp. 606–610.

[74] J. Trommershäuser, K. P. Körding, and M. S. Landy, “Sensory Cue Integration,” *Sens. Cue Integr.*, pp. 1–464, Sep. 2012.

[75] D. C. Knill and A. Pouget, “The Bayesian brain: The role of uncertainty in neural coding and computation,” *Trends Neurosci.*, vol. 27, no. 12, pp. 712–719, 2004.

[76] A. K. C. Lee, M. T. Wallace, A. B. Coffin, A. N. Popper, and R. R. Fay, “Multisensory processes : the auditory perspective.”

[77] D. Alais and D. Burr, “The Ventriloquist Effect Results from Near-Optimal

Bimodal Integration," *Curr. Biol.*, vol. 14, no. 3, pp. 257–262, Feb. 2004.

[78] S. G. Meek, S. C. Jacobsen, and P. P. Goulding, "Extended physiologic taction : Design and evaluation of a proportional force feedback system."

[79] H. B. Helbig and M. O. Ernst, "Optimal integration of shape information from vision and touch," *Exp. Brain Res.*, vol. 179, no. 4, pp. 595–606, Jun. 2007.

[80] J. M. Hillis, S. J. Watt, M. S. Landy, and M. S. Banks, "Slant from texture and disparity cues: Optimal cue combination," *J. Vis.*, vol. 4, no. 12, pp. 1–1, Dec. 2004.

[81] D. R. Wozny, U. R. Beierholm, and L. Shams, "Human trimodal perception follows optimal statistical inference," *J. Vis.*, vol. 8, no. 3, pp. 24–24, Mar. 2008.

[82] J. H. Hillis, M. O. Ernst, M. S. Banks, and M. S. Landy, "Combining sensory information: mandatory fusion within, but not between, senses," *Science*, vol. 298, no. 5598, pp. 1627–1630, Nov. 2002.

[83] H. B. Helbig and M. O. Ernst, "Visual-haptic cue weighting is independent of modality-specific attention," vol. 8, no. 1, pp. 21–21, Jan. 2008.

[84] G. Risso *et al.*, "Optimal integration of intraneural somatosensory feedback with visual information: a single-case study," *Sci. Rep.*, vol. 9, no. 1, pp. 1–10, Dec. 2019.

[85] G. Risso *et al.*, "Multisensory stimulation decreases phantom limb distortions and is optimally integrated," *iScience*, vol. 25, no. 4, p. 104129, Apr. 2022.

[86] P. D. Marasco *et al.*, "Illusory movement perception improves motor control for prosthetic hands," *Sci. Transl. Med.*, vol. 10, no. 432, p. 6990, Mar. 2018.

[87] M. C. Dadarlat, J. E. O'Doherty, and P. N. Sabes, "A learning-based approach to artificial sensory feedback leads to optimal integration," *Nat. Neurosci.*, vol. 18, no. 1, pp. 138–144, Jan. 2015.

[88] S. M. Engdahl, B. P. Christie, B. Kelly, A. Davis, C. A. Chestek, and D. H. Gates, "Surveying the interest of individuals with upper limb loss in novel prosthetic control techniques," *J. Neuroeng. Rehabil.*, vol. 12, no. 1, pp. 1–11, Jun. 2015.

[89] R. J. Van Beers, A. C. Sittig, and J. J. Denier Van Der Gon, "How humans combine simultaneous proprioceptive and visual position information," vol. 111, no. 2, pp. 253–261, 1996.

[90] R. J. Van Beers, D. M. Wolpert, and P. Haggard, "When feeling is more important than seeing in sensorimotor adaptation," *Curr. Biol.*, vol. 12, no. 10, pp. 834–837, May 2002.

[91] M. J. Young, M. S. Landy, and L. T. Maloney, "A perturbation analysis of

depth perception from combinations of texture and motion cues," vol. 33, no. 18, pp. 2685–2696, Dec. 1993.

[92] L. A. Jones and H. Z. Tan, "Application of Psychophysical Techniques to Haptic Research," *IEEE Trans. Haptics*, vol. 6, no. 3, pp. 268–284, Jul. 2013.

[93] G. A. Gescheider and H. College, "Psychophysics : The Fundamentals Third Edition," 1997.

[94] W. A. Simpson, "The method of constant stimuli is efficient," *Percept. Psychophys.*, vol. 44, no. 5, pp. 433–436, Sep. 1988.

[95] S. A. Klein and N. A. Macmillan, "Threshold estimation: The state of the art," *Percept. Psychophys. 2001 638*, vol. 63, no. 8, pp. 1277–1278, 2001.

[96] A. B. Watson and A. Fitzhugh, "The method of constant stimuli is inefficient," vol. 47, no. 1, pp. 87–91, Jan. 1990.

[97] T. N. Cornsweet, "The staircrase-method in psychophysics.," *Am. J. Psychol.*, vol. 75, pp. 485–491, 1962.

[98] W. J. Dixon and A. M. Mood, "A Method for Obtaining and Analyzing Sensitivity Data," *J. Am. Stat. Assoc.*, vol. 43, no. 241, pp. 109–126, 1948.

[99] G. B. Wetherill and H. Levitt, "SEQUENTIAL ESTIMATION OF POINTS ON A PSYCHOMETRIC FUNCTION," *Br. J. Math. Stat. Psychol.*, vol. 18, no. 1, pp. 1–10, 1965.

[100] C. Kaernbach, "Simple adaptive testing with the weighted up-down method," *Percept. Psychophys. 1991 493*, vol. 49, no. 3, pp. 227–229, May 1991.

[101] F. A. A. Kingdom and N. Prins, *Psychophysics: A Practical Introduction: Second Edition*. Elsevier Inc., 2016, pp. 1–331.

[102] R. Boldt, J. Gogulski, J. Gúzman-Lopéz, S. Carlson, and A. Pertovaara, "Two-point tactile discrimination ability is influenced by temporal features of stimulation," *Exp. Brain Res.*, vol. 232, no. 7, pp. 2179–2185, Mar. 2014.

[103] S. VA *et al.*, "Spatial and temporal influences on discrimination of vibrotactile stimuli on the arm," vol. 237, no. 8, pp. 2075–2086, Aug. 2019.

[104] S. Convento, K. A. Wegner-Clemens, and J. M. Yau, "Reciprocal Interactions Between Audition and Touch in Flutter Frequency Perception," *Multisens. Res.*, vol. 32, no. 1, pp. 67–85, Jan. 2019.

[105] D. J. Djozic, D. Bojanic, G. Krajoski, N. Popov, and V. Ilic, "Psychophysical characteristics of electrotactile stimulation: The impact of changes in stimulation pulse width and frequency on human perception," *undefined*, Dec. 2015.

[106] R. J. Sinclair and H. Burton, "Discrimination of vibrotactile frequencies in a

delayed pair comparison task," vol. 58, no. 5, pp. 680–692, 1996.

[107] C. J. Dallmann, M. O. Ernst, and A. Moscatelli, "The role of vibration in tactile speed perception," vol. 114, no. 6, pp. 3131–3139, 2015.

[108] M. Štrbac *et al.*, "Integrated and flexible multichannel interface for electrotactile stimulation," *J. Neural Eng.*, vol. 13, no. 4, p. 046014, Jun. 2016.

[109] J. A. George, M. R. Brinton, P. C. Colgan, G. K. Colvin, S. J. Bensmaia, and G. A. Clark, "Intensity Discriminability of Electrocutaneous and Intraneural Stimulation Pulse Frequency in Intact Individuals and Amputees," *Proc. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. EMBS*, vol. 2020-July, pp. 3893–3896, Jul. 2020.

[110] C. M. Goeke, S. Planera, H. Finger, and P. Kï¿½nig, "Bayesian Alternation during Tactile Augmentation," *Front. Behav. Neurosci.*, vol. 10, no. OCT, p. 187, Oct. 2016.

[111] E. L. Graczyk, M. A. Schiefer, H. P. Saal, B. P. Delhaye, S. J. Bensmaia, and D. J. Tyler, *The neural basis of perceived intensity in natural and artificial touch*, vol. 8, no. 362. 2016, p. 362ra142.

[112] L. E. Crommett, A. Pérez-Bellido, and J. M. Yau, "Auditory adaptation improves tactile frequency perception," vol. 117, no. 3, pp. 1352–1362, Mar. 2017.

[113] G. Valle *et al.*, "Biomimetic Intraneural Sensory Feedback Enhances Sensation Naturalness, Tactile Sensitivity, and Manual Dexterity in a Bidirectional Prosthesis," *Neuron*, vol. 100, no. 1, pp. 37-45.e7, Oct. 2018.

[114] B. Geng, J. Dong, W. Jensen, S. Dosen, D. Farina, and E. N. Kamavuako, "Psychophysical Evaluation of Subdermal Electrical Stimulation in Relation to Prosthesis Sensory Feedback," *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 26, no. 3, pp. 709–715, Mar. 2018.

[115] J. Dideriksen, M. Markovic, S. Lemling, D. Farina, and S. Dosen, "Electrotactile and Vibrotactile Feedback Enable Similar Performance in Psychometric Tests and Closed-loop Control," vol. PP, 2021.

[116] K. A. Kaczmarek, J. G. Webster, P. Bach-y-Rita, and W. J. Tompkins, "Electrotactile and vibrotactile displays for sensory substitution systems," *IEEE Transactions on Biomedical Engineering*, vol. 38, no. 1. pp. 1–16, 1991.

[117] J. A. Harris, C. Miniussi, I. M. Harris, and M. E. Diamond, "Transient Storage of a Tactile Memory Trace in Primary Somatosensory Cortex," *J. Neurosci.*, vol. 22, no. 19, pp. 8720–8725, Oct. 2002.

[118] S. Dosen, M. Markovic, C. Hartmann, and D. Farina, "Sensory feedback in prosthetics: A standardized test bench for closed-loop control," *IEEE Trans.*

*Neural Syst. Rehabil. Eng.*, vol. 23, no. 2, pp. 267–276, 2015.

[119] V. G. Macefield and R. S. Johansson, “Control of grip force during restraint of an object held between finger and thumb: responses of muscle and joint afferents from the digits,” *Exp. brain Res.*, vol. 108, no. 1, pp. 172–184, 1996.

[120] T. R. Farrell and R. F. Weir, “The optimal controller delay for myoelectric prostheses,” *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 15, no. 1, pp. 111–118, Mar. 2007.

[121] R. B. Welch and D. H. Warren, “Immediate perceptual response to intersensory discrepancy,” *Psychol. Bull.*, vol. 88, no. 3, pp. 638–667, Nov. 1980.

[122] H. Mcgurk and J. Macdonald, “Hearing lips and seeing voices,” vol. 264, no. 5588, pp. 746–748, 1976.

[123] B. Bonath *et al.*, “Neural basis of the ventriloquist illusion,” *Curr. Biol.*, vol. 17, no. 19, pp. 1697–1703, Oct. 2007.

[124] L. Jami, “Golgi tendon organs in mammalian skeletal muscle: functional properties and central actions,” *Physiol. Rev.*, vol. 72, no. 3, pp. 623–666, 1992.

[125] R. S. Johansson and J. R. Flanagan, Coding and use of tactile signals from the fingertips in object manipulation tasks, vol. 10, no. 5. 2009, pp. 345–359.

[126] M. L. Latash, J. P. Scholz, and G. Schöner, “Motor control strategies revealed in the structure of motor variability,” vol. 30, no. 1, pp. 26–31, 2002.

[127] F. J. Valero-Cuevas, M. Venkadesan, and E. Todorov, “Structured variability of muscle activations supports the minimal intervention principle of motor control,” vol. 102, no. 1, pp. 59–68, Jul. 2009.

[128] M. Dimitriou and B. B. Edin, “Discharges in human muscle receptor afferents during block grasping,” *J. Neurosci.*, vol. 28, no. 48, pp. 12632–12642, Nov. 2008.

[129] W. R. Kunst-Wilson and R. B. Zajonc, “Affective discrimination of stimuli that cannot be recognized,” *Science (80-. ).*, vol. 207, no. 4430, pp. 557–558, 1980.

[130] M. Markovic *et al.*, “The clinical relevance of advanced artificial feedback in the control of a multi-functional myoelectric prosthesis,” *J. Neuroeng. Rehabil.*, vol. 15, no. 1, Mar. 2018.

[131] M. Markovic, H. Karnal, B. Graimann, D. Farina, and S. Dosen, “GLIMPSE: Google Glass interface for sensory feedback in myoelectric hand prostheses,” *J. Neural Eng.*, vol. 14, no. 3, Mar. 2017.

[132] F. Clemente, M. D’Alonzo, M. Controzzi, B. B. Edin, and C. Cipriani, “Non-

Invasive, Temporally Discrete Feedback of Object Contact and Release Improves Grasp Control of Closed-Loop Myoelectric Transradial Prostheses," vol. 24, no. 12, pp. 1314–1322, Dec. 2016.

[133] S. Raspopovic *et al.*, "Restoring natural sensory feedback in real-time bidirectional hand prostheses," *Sci. Transl. Med.*, vol. 6, no. 222, Feb. 2014.

[134] A. Ninu, S. Dosen, S. Muceli, F. Rattay, H. Dietl, and D. Farina, "Closed-loop control of grasping with a myoelectric hand prosthesis: which are the relevant feedback variables for force control?," *IEEE Trans. Neural Syst. Rehabil. Eng.*, vol. 22, no. 5, pp. 1041–1052, Sep. 2014.

[135] M. D'Alonzo and C. Cipriani, "Vibrotactile Sensory Substitution Elicits Feeling of Ownership of an Alien Hand," *PLoS One*, vol. 7, no. 11, p. e50756, 2012.

[136] A. W. Shehata, M. Rehani, Z. E. Jassat, and J. S. Hebert, "Mechanotactile Sensory Feedback Improves Embodiment of a Prosthetic Hand During Active Use," *Front. Neurosci.*, vol. 14, no. 263, 2020.

[137] S. Lewis, M. F. Russold, H. Dietl, and E. Kaniusas, "User demands for sensory feedback in upper extremity prostheses," in *MeMeA 2012 - 2012 IEEE Symposium on Medical Measurements and Applications, Proceedings*, 2012.

[138] J. L. Dideriksen, I. U. Mercader, and S. Dosen, "Task-Dependent Adaptations in Closed-Loop Motor Control Based on Electrotactile Feedback," *IEEE Trans. Human-Machine Syst.*, 2022.

[139] J. L. Dideriksen, I. U. Mercader, and S. Dosen, "Closed-loop Control using Electrotactile Feedback Encoded in Frequency and Pulse Width," *IEEE Trans. Haptics*, vol. PP, no. 4, pp. 818–824, Oct. 2020.

[140] P. D. Marasco *et al.*, "Neurorobotic fusion of prosthetic touch, kinesthesia, and movement in bionic upper limbs promotes intrinsic brain behaviors," *Sci. Robot.*, vol. 6, no. 58, p. 3368, Sep. 2021.

[141] V. Mathiowetz, G. Volland, N. Kashman, and K. Weber, "Adult norms for the Box and Block Test of manual dexterity," *Am. J. Occup. Ther.*, vol. 39, no. 6, pp. 386–391, 1985.

[142] L. A. Miller *et al.*, "Control of a six degree of freedom prosthetic arm after targeted muscle reinnervation surgery," *Arch. Phys. Med. Rehabil.*, vol. 89, no. 11, pp. 2057–2065, Nov. 2008.

[143] D. T. Beckler, Z. C. Thumser, J. S. Schofield, and P. D. Marasco, "Using sensory discrimination in a foraging-style task to evaluate human upper-limb sensorimotor performance," *Sci. Rep.*, vol. 9, no. 1, Dec. 2019.

[144] H. Bouwsema, C. K. Van Der Sluis, and R. M. Bongers, "Changes in

performance over time while learning to use a myoelectric prosthesis," *J. Neuroeng. Rehabil.*, vol. 11, no. 1, p. 16, Feb. 2014.

[145] S. Gholinezhad, S. Dosen, and D. Jakob, "Electrotactile feedback outweighs natural feedback in sensory integration during control of grasp force," *J. Neural Eng.*, vol. 18, no. 5, Oct. 2021.

[146] J. A. George *et al.*, "Biomimetic sensory feedback through peripheral nerve stimulation improves dexterous use of a bionic hand," *Sci. Robot.*, vol. 4, no. 32, pp. 1–12, Jul. 2019.

[147] J. Diedrichsen, R. Shadmehr, and R. B. Ivry, "The coordination of movement : optimal feedback control and beyond," *Trends Cogn. Sci.*, vol. 14, no. December, pp. 31–39, Jan. 2009.

[148] P. M. Bays and D. M. Wolpert, "Computational principles of sensorimotor control that minimize uncertainty and variability.," *J. Physiol.*, vol. 578, no. Pt 2, pp. 387–96, 2007.

[149] J. P. Hunter, J. Katz, and K. D. Davis, "Dissociation of phantom limb phenomena from stump tactile spatial acuity and sensory thresholds," *Brain*, vol. 128, no. 2, pp. 308–320, 2005.

[150] W. Van Gils, H. A. Reinders-Messelink, F. Smit-Klaij, R. M. Bongers, P. U. Dijkstra, and C. K. Van Der Sluis, "Sensibility of the stump in adults with an acquired major upper extremity amputation," *Arch. Phys. Med. Rehabil.*, vol. 94, no. 11, pp. 2179–2185, Nov. 2013.

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