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Introduction
1.1 Neural synchronization for information processing

The brain is the most complex organ in our body. With roughly $10^{11}$ neurons and about $10^{15}$ connections it forms a very large and complicated network. A central question in neuroscience is how the activity of all these neurons is coordinated in order to generate and support human behavior. According to the traditional view, the rate at which neurons emit signals (action potentials) constitutes a primary mechanism of information transfer, as there is a plenitude of empirical evidence that this rate modulates with behavioral tasks. However, more recent theories stress the additional importance of the timing of neural spikes relative to those of other neurons. In fact, properly timed and synchronized neural activity appears to be omnipresent in the nervous system. In particular neurons within a population that share a functional specialization, so-called neural assemblies, often fire simultaneously. It is believed that by this orchestration the population elicits larger effects on its target neurons as compared to random, non-synchronous firing.

Synchronization may not only occur between neurons within a population but also between different populations. Key evidence for between-population synchrony has been provided by studies addressing the ‘binding problem’ in the visual system. Distinct neural assemblies in visual cortex respond to different stimulus features such as color, shape, and motion. In order to form a single percept, this information needs to be integrated or ‘bound’. Many studies indicate that this binding is achieved through synchronization between assemblies that encode properties of the same stimulus. This is referred to as the binding-by-synchrony hypothesis.

The first conceptual (and empirical) study of synchronization dates back to the seventeenth century. While searching for a perfect clock, the Dutch scientist Christiaan Huygens observed in 1665 that two pendulum clocks quickly swing in unison once suspended on the same wooden beam. One may say that in the nervous system, the pendulum clocks are replaced by individual neurons or populations of neurons and the wooden beam by the synaptic connections or neural pathways, respectively. Returning to the idea that synchronization serves neural information transfer, it is important to realize that, like the mere firing rate, also the amount of synchronization modulates with the task currently performed by the nervous system. That is, neural synchronization correlates with neural functioning. In my thesis I particularly focus on the functional role of synchronization within and between regions of the motor system in generating voluntary movements.

Throughout this thesis I will use the word ‘synchronization’ as synonym for phase entrainment or phase-locking as used in the theory of coupled oscillators. This implies that I consider neural synchronization not to be restricted to coinciding neural spikes (‘in-phase’) but generalizable to any constant phase difference.
1.2 The motor system

Neural activity in various brain regions accompanies the generation of movements (see Figure 1.1). The main output to the spinal cord stems from primary motor cortex (M1). M1 receives direct input from premotor areas, thalamus, and sensory (including association) areas. The premotor areas consist of the supplementary motor area (SMA), ventral and dorsal premotor cortex (PMv and PMd) and the cingulate motor areas (CMA). Although each of these areas also has projections to the spinal cord, they are all considered ‘higher-order’ motor areas that are involved in movement planning. Activity in PMv and PMd is primarily related to movements that are triggered by external cues, whereas activity in the SMA is related to self-initiated movements. SMA is also believed to play an important role in the coordination of bimanual movements. Input from parietal sensory and association areas is used for the integration of motor commands with sensory information. Especially in the cerebellum this integration is used in the context of motor timing and learning. The basal ganglia form a circuit of nuclei that is thought to be involved in action selection and initiation. This view mainly relies on observations in patients with Parkinson’s or Huntington’s disease in whom these circuits malfunction. Nuclei in the thalamus and brain stem act as relay

Figure 1.1. The human motor system comprises several cortical, subcortical, and spinal regions. Its organization is largely bilateral with contralateral control of the limbs. Left and right corticospinal pathways are connected on several levels: through the corpus callosum, via uncrossed pyramidal pathways, and in the spinal cord.
centers between cortex, basal ganglia, cerebellum, and spinal cord. Finally, neural circuits in the spinal cord underlie reflexes and more automatized forms of rhythmic motor behavior like locomotion. Taken together, the motor system consists of a network of many functionally specialized regions that are intricately connected.

The experiments reported in my thesis pertain to motor tasks that involve a brisk increase in force, the generation of a constant or dynamic force pattern, or self-paced rhythmic opening and closing of the hand. These tasks were deliberately chosen for their ‘simplicity’ to ensure that (primary) motor cortex and spinal cord were the main neural controllers. The activity from other regions was substantially less pronounced rendering interpretation of the synchronization patterns in cortex and spinal cord easier than it might have been in more complex daily life tasks. In order to relate cortical activity to motor output, the exerted force was measured and the muscle activity was recorded with surface electromyography (EMG).

1.3 Synchronization within regions

In this thesis I have used magnetoencephalography (MEG) and electroencephalography (EEG) to record neural activity. Rather than spikes of individual neurons, M/EEG picks up intra-/extracellular currents related to postsynaptic potentials on the dendrites of spatially aligned pyramidal cells, lumped over a large neural population in the cortex. Moreover, activity is only visible when large numbers of neurons within a cortical region are active at the same time. In other words, the signals recorded with M/EEG already represent regionally synchronized activity. The amplitude of the signals increases when the activity of individual neurons is more synchronous as well as when more neurons are involved – a fact that complicates the interpretation of activation patterns, as I will discuss later in this thesis.

Brain activity recorded with M/EEG displays rhythmic components, i.e., oscillations that can be divided into different frequency regimes, each with characteristic modulations in relation to behavior. For example, oscillations in the delta band (1-4 Hz) can be observed during sleep, the theta band (4-7 Hz) is associated with memory, the alpha band (8-12 Hz) with arousal, beta (13-30 Hz) with movement and gamma (30-100 Hz) with the integration of sensory information. However, the functional association may depend on which brain region is considered. For example, alpha activity above motor areas, referred to as the Rolandic mu rhythm, is clearly related to movement. The typical movement-related modulations of oscillatory activity in motor cortex are a decrease in mu and beta band power during movement preparation and execution, followed by an increase in power after movement termination (see Figure 1.2).
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Figure 1.2. Example of movement-related modulations in synchronization. Left panels: power and coherence spectra. Typically, M1 power in the mu (8-12 Hz) and beta (15-30 Hz) bands decreases during movement compared to in rest. In contrast, beta band synchronization between M1 and EMG of contralateral hand muscles arises during tonic muscle contractions. Right panels: event-related synchronization patterns. The gray patch indicates the period of time in which force production increases. Prior and during this dynamic force pattern, the beta power in M1 drops (event-related desynchronization, ERD). It returns to baseline when force is held constant again, even showing a power overshoot (event-related synchronization, ERS). Synchronization between M1 and contralateral EMG only builds up during tonic force production and is abolished during movement.

1.4 **Synchronization between regions**

Connectivity in the brain can be studied at three levels – structural, functional, and effective. First, anatomical or structural connectivity concerns the organization of synaptic connections. This organization may change over time but every (non-traumatic) change can be considered slow or even constant, in view of the millisecond time scale of neural firing. Second, functional connectivity, in contrast, can exhibit rapid task-related modulations. Two or more neural units are functionally connected whenever their activity is correlated (over time). Such correlations are considered indicative for communication between units because their activity patterns are related. Third, so-called effective connectivity goes beyond mere correlations by specifying directionality of interaction: does region A influence region B and/or vice versa? In fact, the relation between anatomical and functional/effective connectivity (structure vs. function) is far from straightforward (see, e.g., Daffertshofer and van Wijk 2011). Two units may be connected anatomically without showing any evidence
for a functional relation. Conversely, two units that are not anatomically connected may show correlated activity because they are both strongly linked to a common third one.

In this thesis I primarily focus on functional connectivity expressed as between-regional synchronization. In addition to synchronization between cortical regions, I investigated corticospinal synchronization, i.e., between neurons in the motor cortex and motoneurons in the spinal cord. As the latter is inferred from (surface) EMG recordings, the synchronization is also denoted as corticomuscular. It typically arises during isometric muscle contractions and is abolished during movement (see Figure 1.2). In healthy subjects significant synchronization can only be observed between the EMG and contralateral M1, which supports its role of information carrier.

1.5 Extracting synchronization patterns from recorded signals

How can synchronization within and between regions be detected in recorded data? Within-regional synchronization is usually assessed in the (time-)frequency domain using, e.g., Fourier or wavelet analysis. The spectral content typically has a $1/f$-like profile, i.e., with large power at low frequencies and little power at high frequencies. This frequency-based (or temporal) distinction generally agrees with a spatial one, i.e., the observation that large cortical areas may be involved in low-frequency oscillations, whereas gamma oscillations may be more focal. The evolution of spectral power over time can be studied by using a moving time window. Event-related time-frequency spectra are obtained when spectra are averaged over epochs that have been aligned in time with regard to a specific event.

The two primary methods I applied in my thesis to detect between-regional synchronization are coherence and relative phase uniformity. Coherence is the equivalent of a cross-correlation in the frequency domain and is defined as

$$C_{xy}(f) = \frac{|P_{xy}(f)|^2}{P_{xx}(f)P_{yy}(f)}$$

where $P_{xy}$ denotes the cross-spectral density between signals $x(t)$ and $y(t)$, and $P_{xx}$ and $P_{yy}$ their corresponding power spectral densities. The outcome values range between 0 (no coherence) and 1 (perfect coherence). Coherence provides an estimate of the combined correlation of power and phase between two signals.

In contrast, relative phase uniformity is a true measure of phase synchronization (see Figure 1.3). It captures the variability of the difference in phase between two signals for a given frequency. Perfect synchronization occurs when the phase difference is constant. When looking at a time series, the signal $x(t)$ is first band-pass
filtered around a particular frequency of interest. Then, the instantaneous phase $\phi_x(t)$ is estimated using the analytic signal $a(t)$ defined via the Hilbert-transform $H\{\ldots\}$ in terms of

$$a(t) = x(t) + iH\{x(t)\} = x(t) + \frac{1}{\pi} PV \int_{-\infty}^{\infty} \frac{x(\tau)}{t - \tau} d\tau$$

and

$$\phi(t) = \tan^{-1} \left( \frac{\Re\{a(t)\}}{\Im\{a(t)\}} \right)$$

The Cauchy principal value ($PV$) ensures that the integral is defined in spite of the singularity at $t = \tau$. For two signals $x(t)$ and $y(t)$ the phase difference $\Delta \phi(t) = \phi_x(t) - \phi_y(t)$ is computed and, subsequently, its circular variance $R$

$$R = \sqrt{C^2 + S^2}$$

with

$$C = \frac{1}{N} \sum_{k=1}^{N} \cos \Delta \phi_k \quad \text{and} \quad S = \frac{1}{N} \sum_{k=1}^{N} \sin \Delta \phi_k$$

Finally, the relative phase uniformity is defined as $1 - R$, which forms a measure of phase locking that is 0 in the case of no coupling and 1 for perfect coupling. Synonyms used for this measure in literature are the phase locking index and phase coherence.

I used the analytic signal also to estimate the spectral power for the band-pass filtered frequency using the Hilbert amplitude:

$$A(t) = |a(t)| = \sqrt{(\Re\{a(t)\})^2 + (\Im\{a(t)\})^2}$$

Both coherence and relative phase uniformity can be estimated over time and over trials. For the latter, individual trials are aligned in time and the coherence or relative phase uniformity is computed for each time sample across trials. This provides an estimate of synchronization as a function of time.
**Figure 1.3.** Illustration for estimating phase synchronization. Signals of two sensors are band-pass filtered around a frequency of interest, their instantaneous Hilbert phases are calculated, and the variability of their relative phase is determined. Left panels: the distribution of relative phases within a time interval for a single trial. The indicated envelope of the band-pass filtered signal equals the Hilbert amplitude as a measure of spectral power. Right panels: the distribution of relative phases across trials at a certain time point. The in-phase locking observed at \( t_1 \) has disappeared at \( t_2 \) where the relative phases are uniformly distributed.
1.6 Reconstructing source activity from recorded signals

Several source localization techniques are available to pinpoint the origin of non-invasively recorded brain activity. Throughout this thesis I applied a linearly constrained minimum variance beamformer approach, which, in general, yields spatial filters that localize spectral power in a pre-selected frequency band in a certain time window. By contrasting activity that is recorded during task performance with the resting state one can identify regions that are significantly activated as a result of task performance. Subsequently, signals can be projected from sensor space to source space to estimate the activity at the source.

The procedure for source localization is illustrated in Figure 1.4. In a nutshell, the brain volume is divided into a 3D grid of voxels. This is realized by using a head model that approximates the brain’s shape (convex hull), be it through a single sphere, multiple local spheres or a more realistic model based on an individual structural MRI scan, for which the different layers of tissue have been segmented. For each of these voxels, a so-called lead-field is constructed that maps the activity of a unit dipole within this voxel to the recording sensors. For EEG this is based on a forward model of how electric current spreads through the different tissues between the brain and the electrodes. The model is much simpler in case of MEG as the magnetic field spread is largely unaffected by these tissues. This model is inverted to estimate the source activity from the signals recorded at the sensors. It is important to realize that there are typically many more voxels, and thus potential sources, than the number of recording sites. Inverting the model hence has no unique solution and requires additional constraints to be solved. These constraints are usually defined for the source activity: in the case of the linearly constrained minimum variance beamformer it is assumed that the sources are linearly independent. By this, for each voxel an optimal spatial filter is constructed that preserves the activity estimated by its lead-field while minimizing leakage of activity from other sources.

For the so-defined source activities, a (pseudo-) $t$-test can be performed to test for differences in activation between conditions. The (most) significant voxels yield the locations of the sources of interest. The mapping from sensor to source space is finally realized via a weighted sum of the signals on sensor level, for which the beamformer weights determine the relative contribution of each of the sensors to the signal at the source. This source activity can be used for further processing.
**Figure 1.4.** From sensor data to source data. A beamformer approach can be applied to estimate the source location in the brain where recorded M/EEG signals originate. The goal is to construct a spatial filter that specifies the relation between sensor and source signals. To this end, the brain is divided into a grid of voxels (possible source locations). For each of these voxels a lead-field is constructed that describes the activation pattern that can be observed on the scalp when the source is active, using a forward model of how electromagnetic activity propagates from the brain to the sensors. Subsequently, again for each voxel, an inverse calculation is performed with the constraint of no linear correlations between sources and by suppressing leakage from other sources as much as possible. This amounts to a spatial filter with weights assigned to each sensor that indicate the contribution to the source. The estimated source activity can be compared between movement and rest in order to identify task-related activity. This yields (pseudo-) t-values for each voxel in the grid and significant sources can be selected. Finally, the time series at the location of the source can be estimated by a linear weighted summation of the sensor signals.
1.7 Research questions

In the previous subsections I provided a brief introduction to the topic of my thesis and the most important methods that I applied in the various studies that will be presented in coming chapters. As said, with the research described in my thesis I aim to understand the functional role of synchronization within and between regions of the motor system in generating voluntary movements. In particular I was interested in the following research questions:

- *Are both increases and decreases in synchronization used to control motor output?*
- *What movement-related information is encoded by synchronization?*
- *Is there a 1:1 mapping between synchronization patterns and movement?*
- *What methodology should be used to study connectivity in the brain?*

The answers to these questions would advance our comprehension of the neural mechanisms underlying motor control and, more general, information processing in the brain. Such fundamental knowledge can in turn prove useful for understanding motor skill learning, improving the treatment of movement disorders, and perhaps sparking research in related neuroscientific fields. Given that some of these questions are admittedly quite broad, it will not be feasible to provide definite answers to all of them in a handful of chapters. Rather, specific aspects will be tested that will be described in the next section.

1.8 Outline of the thesis

The remainder of this thesis is divided into three parts, each of which contributes in a different way to answering the research questions.

*Part I – Literature*

First, a literature overview will be provided reflecting the current knowledge on synchronization in the motor system. Chapter 2 presents a review of key findings on synchronization patterns within and between regions of the motor system (also referred to in this thesis as *local* and *long-range* synchronization). Modulations in synchronization patterns in relation to movement parameters are important for understanding the neural mechanisms of motor control. These are discussed for synchronization within M1, between M1 and the spinal cord, as well as between cortical regions. In addition, several examples of abnormal synchronization patterns in motor disease states are highlighted.
Part II – Experimental observations

In this part three studies will be presented in which the role of synchronization within and between regions of the motor system has been investigated.

There is wide consensus that a decrease in beta band oscillations in motor cortex is associated with the preparation and execution of movement. In contrast, a functional role for elevated beta synchronization has been ascribed only in recent years. Early work marked post-movement synchronization as a mere ‘idling’ state serving to recover from previous action (Pfurtscheller et al. 1996). However, an up-regulation of beta synchrony can also be used as an active mechanism to suppress unwanted motor output, hence inhibiting initiation of new movements (Androulidakis et al. 2007). The study described in Chapter 3 investigates whether a down- and upregulation of beta synchrony is used in response selection. This was assessed not only at the cortical level but also in the interaction between cortex and spinal cord.

Although movements of distal muscles are controlled primarily by the contralateral motor cortex, activity in ipsilateral motor cortex is also commonly observed during unimanual movement. The role of this ipsilateral activity is investigated in Chapter 4. One point of view is that ipsilateral activity reflects interhemispheric ‘cross-talk’ from contralateral motor cortex that facilitates synchronous bimanual actions. Evidence for this phenomenon is the presence of mirror movements in healthy individuals, i.e., small activations of the homologous hand that mimic those of the active hand, despite the fact that the homologous hand is not intended to move. On the other hand, to prevent unwanted motor output the interhemispheric cross-talk needs to be suppressed. Comparing synchronization patterns between ipsilateral and contralateral motor cortices during unimanual movement can reveal whether ipsilateral activity does merely reflect that in the contralateral motor cortex or whether it involves additional processes.

One way to gain insight into brain function is by perturbing its activity. In this regard, cases of brain lesions have provided a wealth of information on functional specialization. Abnormal synchronization patterns may arise in a variety of pathologies. A well-known example is Parkinson’s disease, in which abundant beta oscillations in the basal ganglia lead to the slowing of movement that is characteristic of this disease. In Chapter 5 I study the influence of glioma (a type of brain tumor) on oscillatory activity in the motor cortex. As can be seen in Figure 1.5, glioma may grow excessively. In this process it exerts pressure on surrounding tissue, which as a result can become damaged and may lose its functional capacity. Typical EEG activity in glioma patients shows low-frequency oscillations in the immediate vicinity of the tumor. However, when white matter fibers are disrupted, alterations in brain activity may be more widespread because these fibers serve communication between distant
regions. The motor system seems especially prone to this, with its intricate connections between (pre-)frontal, parietal, cerebellar, and subcortical areas.

**Figure 1.5.** Axial view of a structural MRI scan of a patient with a low-grade glioma. The tumor is visible as a gray area on the left side of the scan. The volume occupied by a tumor can become very large with damage to both gray and white matter. In this example it compresses one of the lateral ventricles. In addition to the tumor bulk, gliomas widely infiltrate healthy tissue, rendering complete surgical removal impossible.

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**Part III – Data-driven versus model-driven approaches**

The third part of my thesis will be devoted to two state-of-the-art methodologies for studying brain interactions that I have evaluated during my research. On the one hand, *graph theory* provides a powerful framework to analyze structural properties of a network. Its strength resides in describing a complex network organization with just a handful of scalar measures. These topological measures can for example indicate whether the connections in a network are organized in a random or ordered way (see Figure 1.6). The application of graph theory to neuroscience has become very popular in recent years, both in the study of anatomical and functional connectivity. Regarding functional connectivity, it does not require any a priori assumptions about which brain regions are active or even anatomically connected. Networks are simply constructed by correlating activity from all pair-wise combinations of recording sites. The correlation strength determines whether regions are connected. Subsequently, a variety of topological measures can be employed to uncover properties of network organization that might be informative on brain function. As such, it is a data-driven approach for which results are subject to interpretation.

The power of graph theory is nicely illustrated by the anecdotal phenomenon of ‘six degrees of separation’: as the story goes, everyone is connected to everyone else by just six handshakes between acquaintances. Whether the number six is correct is irrelevant. The crux is that it is an astonishingly low number, given the roughly 7 billion people living in this world. This can be ascribed to a ‘small-world’ organization of the network of social interactions, in which most of someone’s friends come from a local group and a few connections are random between people belonging to different social groups. Furthermore, a few persons are acquainted to a very large number of people and act as hubs in the network. In graph theoretical terms, this results in a high
clustering coefficient and a short path length. In the brain, such an organization might be very efficient as regions can specialize into different functions, while by the same token information from distant regions can be rapidly exchanged. Indeed, a small-world organization of both anatomical and functional connections has been observed repeatedly. Pathologies like Alzheimer’s disease and schizophrenia might alter the brain network’s structure towards a more random organization. Despite these advances, one should keep in mind that graph theory is a well-developed field in mathematics where it is mainly used to study theoretical problems. The application to real data, however, may not be without difficulties. In **Chapter 6** I demonstrate that there are serious drawbacks when it comes to comparing the structure of networks that have a different size and/or number of connections. This is problematic indeed because most, if not all, empirical networks differ in either one or both aspects. I will present an overview of various methods that can be applied to compare network structures and discuss their benefits and pitfalls.

**Figure 1.6.** In graph theory networks are represented as nodes and edges. Shown are examples of four network archetypes. Their structural properties can be captured with graph measures like the average path length and clustering coefficient. The path length indicates the average number of steps it takes to get from one point in the network to another. The clustering coefficient represents the probability that two neighbors of a node are also connected themselves, hence the occurrence of clusters. All nodes in a ring-lattice are connected in an ordered way, which results in a high clustering coefficient but also in a long path length. Rewiring a small percentage of these ordered edges to random nodes in the network drastically reduces the path length while preserving high clustering (small-world network as defined by Watts and Strogatz 1998). In the Erdős-Rényi network all edges are distributed randomly, which results in a short path length and a low clustering coefficient. The same holds for the Barabási-Albert scale-free network but here the degree distribution (number of edges per node) follows a power law: a small number of nodes contain a lot of edges while many nodes just have a few.
On the other hand, *dynamic causal modeling (DCM)* can be used to study interactions between a few sources within a small network. First developed for fMRI (Friston et al. 2003), this method relies on a generative model of neural dynamics. For EEG, MEG, and LFPs, the model can be based on either neurophysiology or could have a phenomenological nature for which the dynamics of a specific data feature is modeled directly. Different DCMs have been developed depending on the data feature of interest: event-related potentials (David et al. 2006), time-frequency modulations (Chen et al. 2008b), cross-spectral densities underlying steady-state responses (Moran et al. 2009), complex-valued cross-spectra underlying steady-state responses (Friston et al. 2012), and synchronization by means of phase coupling (Penny et al. 2009). In contrast to graph-theoretical approaches, the networks for DCM are constructed based on underlying anatomy and expected source-involvement in the task that the subject performed. The generative model describes how activity in one source responds to input from other sources, its intrinsic dynamics, and (if appropriate) an external stimulus. The parameters of this model are then estimated by fitting the model to observed data. By this, one can compare the performance of models with different configurations of effective connections and select the one that most likely underlies the empirical observations. The parameter values of this model can be further used to assess the connection strength between sources. Moreover, comparing different conditions can reveal how the task under study affects the connectivity. To give an example, DCM can be used to test the directionality of a connection (does source A influence source B and/or vice versa?) and whether the connection strength increases during task-performance.

In Chapter 7 I illustrate the use of DCM in revealing the mechanisms behind time-frequency modulations (induced responses). A generative model is sketched and employed to reproduce the modulations in induced power that occurred during a motor imagery task. More specifically, subjects used mental rotation of hand images in order to determine whether a left or right hand had been presented. This task results in longer reaction times when a hand image is displayed with a larger rotation angle. During the mental rotation, a strong increase in gamma oscillations in visual areas was observed and accompanied by a decrease in alpha and beta power in both visual and motor areas. As will be shown, DCM can reveal directed cross-frequency interactions between visual and motor cortex. Furthermore, the difference between trials with a short and long reaction time can be reproduced by altered ‘bottom-up’ and ‘top-down’ connectivity that gave rise to a more pronounced gamma increase in trials with a longer reaction time. Despite these promising findings, however, the results are not fully consistent for slightly different time-frequency spectra, at least for the data set under study. Some methodological caveats and potential directions for improvement are discussed. Nevertheless, the use of generative models can, in
general, help extracting information from experimental data that may remain opaque in mere data-driven approaches. Therefore, I believe that the approach is an invaluable technique to study effective connectivity.

Epilogue

Finally, I reflect on the main results from all chapters and revisit my leading research questions in Chapter 8. The functional role of neural synchronization in controlling voluntary movements is discussed in light of the current state of literature and my experimental findings described in this thesis. In addition, I discuss the methodologies applied in my thesis to study brain connectivity. I will go into more detail on the application of graph theory in neuroscience and its prospects and limitations. This final chapter ends with a brief conclusion and a future outlook.