Chapter 18
Shaping Brain Rhythms: Dynamic and Control-Theoretic Perspectives on Periodic Brain Stimulation for Treatment of Neurological Disorders



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Abstract Rhythmic, collective activity is a fundamental feature of neural systems. As a result of this, many of the challenges and opportunities involved in developing clinical tools from basic neuroscience knowledge come down to questions about control of dynamic, oscillatory networks. In this chapter we review a range of experimental and theoretical work on control of neural oscillations, in healthy brains and in relation to various clinical conditions. We highlight the main types of qualitative system behaviour that can result from application of periodic stimulation and present a simple case study on this using a mathematical model of rhythmogenesis in thalamocortical circuits. The concepts discussed here may, we hope, help provide some guidelines and principles for the development of future generations of more physiologically and dynamically informed brain stimulation techniques, paradigms, and researchers.

18.1 Background

Synchronous neural activity has been identified as a hallmark of neural communication and information processing. These rhythmic electrical fluctuations, which occur at frequencies spanning several orders of magnitude, have been linked to numerous neurophysiological and cognitive processes, including atten-

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tion [1], memory [2], spatial navigation [3, 4], sensory processing [1, 5–7], and a wide variety of perceptual and motor tasks (see [8] and references therein). Abnormal neural synchrony and altered oscillatory activity are hallmarks of many neurological disorders [9] such as Parkinson's [10], dementia [11, 12], stroke [13–15], tumours [16–18], and neurogenic pain [19, 20]. These observations, together with recent technological developments and increasingly widespread availability of noninvasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) and transcranial direct and alternating current stimulation (TDCS, TACS), have led to a surge of interest in the use of electromagnetic neuromodulation to engage and manipulate brain oscillations, as a means of enhancing cognitive function and improving treatment of central nervous system disorders [21, 22]. Painless, inexpensive, and relatively easy to use, TMS, TDCS, and TACS protocols have already become popular to support a wide variety of clinical interventions [23–25]. These trends are most apparent in the fields of stroke rehabilitation [26, 27] and treatment of depression [28, 29], with promising results also being obtained in Alzheimer's [30, 31], Parkinson's [32], and epileptic [33, 34] cohorts. Noninvasive stimulation has also been used to interfere with brain oscillations in order to enhance working memory [35] and other cognitive functions (see [22] and references therein) and has been proposed as a tool to help slow down cognitive decline in the elderly [12].

Collectively, these results hold great promise. However, despite the rapid growth in recent years of applied and basic research in this area, the mechanisms by which noninvasive stimulation interferes with brain oscillations to modify neural and cognitive function remain poorly understood. This knowledge gap constitutes a major limitation in the development of new paradigms aimed at enhancing and/or restoring healthy brain dynamics through selective manipulation of synchrony and oscillatory activity. Mathematical and computational approaches represent increasingly central tools in efforts by scientists and clinicians to address these questions. For example, appropriately formulated mathematical models allow us to estimate and quantify the relationship between stimulation parameters (e.g. waveform, frequency, and intensity) and observed neural responses, at both the individual cell and neural population scales. These relationships can then be used to tune stimulation parameters in order to achieve the desired output in a clinical setting. In this chapter, we shall review some of the existing science about the effects of stimulation on brain rhythms and examine some of the mechanisms involved.

18.2 Brain Stimulation: Insights from Electrophysiology, Imaging, and Computational Models

From the perspective of individual cells, most information we have about how neurons (cortical and non-cortical) respond to stimulation comes from slice preparation studies [36]. The influence of static and varying electric fields on both extra- and

intracellular potentials have been studied extensively in recent years, notably using computational and forward models [37, 38] and biophysical models [39, 40]. As a general rule, neurons subjected to varying electric fields will display fluctuations in membrane polarization mirroring the waveform applied. However, the connection between stimulation waveform and neural spiking activity is more challenging to establish and depends on many parameters that are difficult to determine in practice [41]. Weak electrical stimulation, such as that delivered to the brain by TDCS, cannot usually make neurons fire. Rather, it generates a diffuse electrical current that influences the firing probability by either hyperpolarizing or depolarizing neuronal membranes, hence causing subthreshold voltage fluctuations. Other forms of stimulation (e.g. direct cortical stimulation) do induce suprathreshold effects due to the greater proximity of the electrodes and more intense fields. Periodic stimulation triggers an alternation of depolarization and hyperpolarization periods across neuronal compartments [42], whose magnitude and phase depend on the relative position and orientation of the cell (and its arborization) with respect to the cathode/anode, as well as the frequency of the carrier signal. Due to synaptic delays and current leakage, neurons also exhibit filtering properties that make them more susceptible to low-frequency inputs if intensity is kept constant [41]. Some of these synaptic filtering effects are responsible for cell type-specific frequency tuning and resonances that have been suggested to direct the flow of information across the cortex [43, 44].

Macro-scale brain oscillations, such as the high-amplitude and low-frequency alpha rhythms that dominate human EEG and MEG recordings, are a collective phenomenon. It is therefore critical to understand how stimulation impacts populations and circuits, as opposed to individual neurons. Experimental studies have repeatedly demonstrated the ability of periodic brain stimulation to engage specific brain circuits in a frequency-specific manner, as well as its ability to both up- and downregulate performance on cognitive tasks [2, 45, 46].

The literature on computational models of brain stimulation is vast and spans the full range of spatial scales and neuroscience measurement modalities, from individual cells to whole-brain networks. For present purposes we focus on the meso-/macro-scale commensurate with both the brain stimulation techniques and recording techniques available in human subjects. Studies of microcircuits of recurrently connected excitatory and inhibitory spiking neurons [47, 48] and coupled bistable networks [49, 50] have demonstrated that periodic stimulation can evoke persistent large-scale oscillatory activity over prolonged time scales. Often however it is preferable for practical purposes to work with lower-dimensional neural population models (generally termed neural mass, mean field, or neural field models) than with detailed spiking networks, once the correspondence between simpler and more complex models has been established [51, 52]. Popular neural mass models such as those of Wilson and Cowan [53] or Jansen and Rit [54–56] represent entire brain regions by one or several excitatory and one or several inhibitory populations in a cortical column. Researchers deploying neural mass models to study brain stimulation have tended to focus on two things: (i) modulation of intrinsic brain rhythms by periodic stimulation [48, 57–62] and (ii) propagation

of stimulation-evoked responses away from stimulated areas to downstream cortical and subcortical locations [63]. The power and precision of these large-scale modelling approaches have been improved considerably in recent years by developments in data acquisition and analysis tools for noninvasive estimation of individual subjects' white matter connectivity structure and geometry using diffusion-weighted MRI tractography [58, 63–66].

18.3 Restoring Brain Synchrony: A Control Problem

How can stimulation be used to compensate for disease-related loss in neural synchrony [9]? This control problem naturally depends on the pathology concerned, the impact it has on brain oscillations, and the cellular populations involved. Many physiological mechanisms may lead to the same change in neural synchrony. Irrespective of these details, our goal remains to restore collective brain activity by enhancing the amplitude of brain oscillations, speeding them up, or even suppressing them (as for example in the case of Parkinson's disease).

External signals (control signals) can engage and interact with these intrinsic oscillations via several specific, mathematically well-defined mechanisms. We list the main ones here:

1. ***Resonance.*** Stimuli with frequencies close to the system's natural frequency amplify the power of intrinsic oscillations. The proximity of the stimulation frequency to the intrinsic system frequency, and/or its harmonics, will dictate the amplitude of the responses.
2. ***Entrainment.*** The system is frequency- and phase-locked to the stimulus. The neuron or network of neurons is said to be *driven* by the stimulation, and phase alignment between the system's activity and the input must be observed. Entrainment of a nonlinear system is a function of stimulation frequency and amplitude, and regions in parameter space where entrainment occurs are called *Arnold Tongues*.
3. ***Nonlinear acceleration.*** High-frequency and/or random stimuli interact with the system's nonlinearities to provoke a *shift in intrinsic frequency*.
4. ***Destabilization.*** Application of an anti-phasic signal or a strong irregular (i.e. noisy) waveform transiently or permanently destabilizes (and thereby suppresses) intrinsic oscillations, effectively preventing the system from establishing stable synchronous states. This suppression can occur through a variety of ways (bifurcations).

For a comprehensive discussion of these different mechanisms, see [48]. We now turn to a didactic example of a simple model for EEG brain rhythms and their response to periodic stimulation, demonstrating aspects of mechanisms 1 and 2 outlined above.

18.4 Case Study: Tuning Thalamocortical Alpha Oscillations

Alpha oscillations, a cortical rhythm of roughly 8–12 Hz in humans, have been shown to play a key role in a wide variety of cognitive and perceptual functions [8, 67, 68] and, for that reason, have been a prime target for noninvasive stimulation [48]. To get some insights about the effect of patterned stimulation on alpha oscillations, let us consider the simplified thalamocortical network model shown diagrammatically in Fig. 18.1.

Numerous experimental and computational studies have shown that alpha oscillations are, least in part, of thalamocortical origin [69–71]. As such, in this nonlinear neural oscillator model, the dynamics are governed by a combination of corticocortical interactions and thalamocortical feedback. A similar network has recently been used to explain some state-dependent effects of repetitive stimulation on cortical activity in humans [62], and similar models have been used extensively by other authors [59, 72–76].

The basic building block of the model is a minimal four-component corticothalamocortical motif that describes the interconnections between excitatory ($\mathbf{u}_e$) and inhibitory ($\mathbf{u}_i$) neuronal populations in a given patch of cortical tissue and two thalamic nuclei: the reticular nucleus ($\mathbf{u}_r$) and specific relay nucleus ($\mathbf{u}_s$). Both relay and reticular nuclei receive inputs from the cortical excitatory population, following a corticothalamic conduction delay (τ_1). However only the relay nucleus sends excitatory input back to the cortex, again received following a corticothalamic delay. The reticular nucleus, which is widely known to have an inhibitory influence on other thalamic regions, plays a similar role to the cortical inhibitory population, inhibiting the relay nucleus and thereby generating oscillatory dynamics. Multiple adjacent patches of cortical tissue are modelled by repeating this basic circuit motif and coupling patches together through their excitatory neuronal populations. The

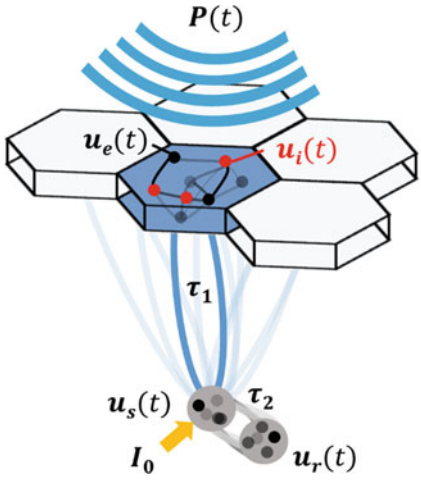


Fig. 18.1 ***Thalamocortical model***. Schematic of the thalamocortical model structure. Cortical ($\mathbf{u}_e$,$\mathbf{u}_i$) and thalamic ($\mathbf{u}_s$,$\mathbf{u}_r$) populations interact through a delayed feedback loop. Entrainment of the network activity through electromagnetic stimulation P applied to $\mathbf{u}_e$ depends on the amplitude and frequency of the stimulation pulse, as well as the network state, controlled by I_o

dynamics for the model are given by the following set of Wilson-Cowan-type stochastic delay-differential equations:

$$\frac{d\mathbf{u}_e(t)}{dt} = -\mathbf{u}_e(t) + g_{ee}\mathbf{F}[\mathbf{u}_e(t)] + g_{ei}\mathbf{F}[\mathbf{u}_i(t)] + g_{es}\mathbf{F}[\mathbf{u}_s(t-\tau_1)] + g_{cc}CCI + \mathbf{P}(t) + \sqrt{2D}\boldsymbol{\xi}_e(t) \tag{18.1}$$

$$\frac{d\mathbf{u}_i(t)}{dt} = -\mathbf{u}_i(t) + g_{ii}\mathbf{F}[\mathbf{u}_i(t)] + g_{ie}\mathbf{F}[\mathbf{u}_e(t)] + g_{is}\mathbf{F}[\mathbf{u}_s(t-\tau_1)] + \sqrt{2D}\boldsymbol{\xi}_i(t) \tag{18.2}$$

$$\frac{d\mathbf{u}_r(t)}{dt} = -\mathbf{u}_r(t) + g_{re}\mathbf{F}[\mathbf{u}_e(t-\tau_1)] + g_{rs}\mathbf{F}[\mathbf{u}_s(t-\tau_2)] + \sqrt{2D}\boldsymbol{\xi}_r(t) \tag{18.3}$$

$$\frac{d\mathbf{u}_s(t)}{dt} = -\mathbf{u}_s(t) + g_{sr}\mathbf{F}[\mathbf{u}_r(t-\tau_2)] + g_{se}\mathbf{F}[\mathbf{u}_e(t-\tau_1) + \sqrt{2D}\boldsymbol{\xi}_s(t) + I_o \tag{18.4}$$

where the population vectors $\mathbf{u}_p(t) = (u_{p1}(t), u_{p2}(t), \ldots u_{pN}(t))$ denote the mean somatic membrane activity of neuronal population $p \in \{e, i, r, s\}$ and $N = 100$ units per population. Nonlinear interactions between neuronal populations are mediated by a steep sigmoidal response function $\mathbf{F}[u] = (1 + exp(-150))^{-1}$ and in the cases of intrathalamic and corticothalamic/thalamocortical connections are retarded by conduction delays $\tau_1 = 5$ ms and $\tau_2 = 20$ ms, respectively. The summed influence of the N excitatory populations in adjacent patches of cortical tissue on each other is given by the cortico-cortical input term $CCI = N^{-1}\sum_{k=1}^{N}\mathbf{F}[\mathbf{u}_e^k]$. Irregular and independent fluctuations are also present in the network, modelled by the zero mean Gaussian white noise processes ξ_p. Stimulation is applied evenly to all excitatory cortical units $\mathbf{u}_e$ through the continuous stimulation pulse $\mathbf{P} = M\sin(2\pi\omega t)$ with frequency ω and intensity M. Finally, the level of sensory drive to the thalamus is represented by the parameter I_o. As has been demonstrated previously [61], increasing this parameter past a critical point triggers suppression of resting state alpha oscillations and results in a greater susceptibility of cortical neural populations to entrainment by exogenous inputs or noninvasive stimulation.

Despite its simplicity, the base cortico-thalamocortical circuit motif in this model combines what are widely considered the two most important rhythmogenic mechanisms responsible for large-scale oscillatory activity observable in human extracranial recordings such as scalp EEG: low-frequency (i.e. alpha) oscillations generated by thalamocortical loops and higher-frequency (e.g. gamma) oscillations generated by local (intra-columnar) excitatory-inhibitory interactions in the cortex. Moreover, through variation of I_o, the model naturally accommodates the widely reported phenomenon of alpha suppression observed in response to sensory inputs [8, 77], during cognitive tasks requiring top-down control, and which is reduced in anaesthesia [78] and during sleep [73].

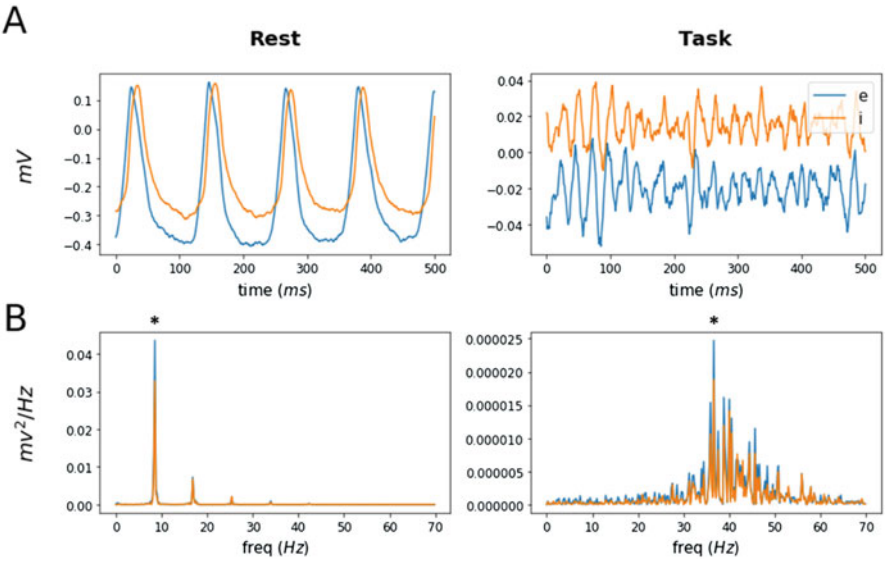


Fig. 18.2 ***Baseline activity of the thalamocortical circuit in the rest and task states***. Time series (**a**) and power spectra (**b**) of cortical excitatory (blue) and inhibitory (orange) neural populations during rest (left column) and task (right column) states, in the absence of stimulation. The rest state ($I_o = 0$) is dominated by slow, high-amplitude alpha (around 10 Hz) rhythms, whereas the task state ($I_o = 1.5$) is dominated by lower amplitude gamma (around 40 Hz) oscillations. Asterisks indicate locations of spectral peaks

Figure 18.2 shows examples of the time series and power spectra generated by the model in 'rest' and 'task' states, in the absence of external stimulation ($\mathbf{P}(t) = 0$). The power spectrum in the rest state is dominated by high-amplitude, low-frequency (around 10 Hz) oscillations and their harmonics. As we shall see, this state-dependence of oscillatory activity has major implications for how we understand and model the effects of periodic brain stimulation. It has been shown that cortical systems are more prone to entrainment in regimes of strong sensory drive where the power of alpha is suppressed, suggestive of mechanisms such as stochastic resonance [61]. This has been repeatedly demonstrated in both noninvasive [79] and intracranial [62] experiments, highlighting the need to develop closed-loop systems where such fluctuations can be tracked – and compensated for – in real time. This dependence on baseline fluctuations is illustrated in Fig. 18.3, where the peak frequency and peak amplitude of the system in response to a sine wave stimulation are plotted as a function of stimulation amplitude and frequency. For both rest and task states, the lowest amplitude stimulation has no effect on the dominant rhythms, and so the plots are dominated by the endogenous natural frequency associated with that state (power spectral peaks from Fig. 18.2). As stimulation amplitude is increased, a triangular pattern known as an *Arnold Tongue* appears in panel A of Fig. 18.3. These patterns represent stimulation parameters for which

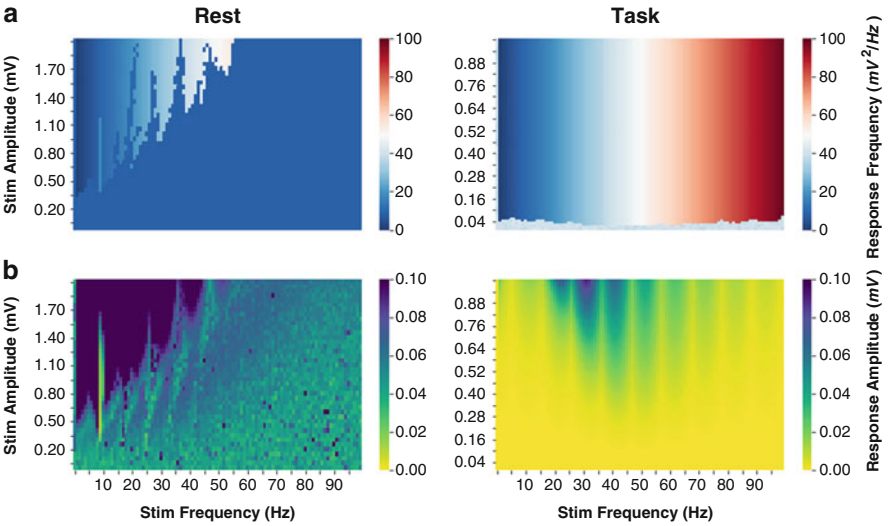


Fig. 18.3 ***Entrainment region in both rest and task regimes***. Shown are maximum frequencies (**a**) and corresponding maximum amplitudes (**b**) of the cortical excitatory population in rest and task states as a function of stimulation frequency and stimulation amplitude. In both task and rest states, the system oscillates at its natural frequency (cf. Fig. 18.2, panel b), observable as a contiguous domain of constant dominant frequency in the lower portions of the frequency response heatmaps. Increasing stimulus level results in the emergence of Arnold Tongues (**a**) and resonance peaks (**b**), centred on the natural frequency

the system's activity is frequency- and phase-locked to the stimulus. Moreover, such susceptibility to entrainment is greatest at the system's natural frequency, which is around 10 Hz in the rest state and around 40 Hz in the task state (cf. Fig. 18.2, panel a). In addition to the difference in natural frequencies, the rest and task states differ markedly in their susceptibility to exogenous control. This can be seen by the fact that the stimulus level needed to entrain network oscillatory activity – i.e. the lower tip of the Arnold Tongues in Fig. 18.3 panel a – is much higher for the rest state than the task state. Resonance also shapes the amplitude of the responses, as seen in Fig. 18.3 panel b, where the amplitude of the solutions is increased near the system's endogenous frequency and/or its harmonics. Taken together, these results show that the presence of the alpha rhythm in the thalamocortical circuit can be understood as 'suppressing' higher-frequency exogenous oscillatory fluctuations, consistent with multiple empirical observations in the M/EEG literature.

18.5 Summary

In this chapter we have reviewed several key dynamical systems and control-theoretic concepts that, when combined with appropriate mathematical descriptions of macro-scale neural circuit properties, hold great promise in the development

of precision brain stimulation therapies for neurological and neuropsychiatric disorders. The case study served to demonstrate several of these concepts in a schematic model exhibiting two distinct rhythmogenic mechanisms, both believed to play an important role in the genesis of macro-scale oscillations in the human brain: (i) intra-columnar excitatory-inhibitory interactions within the cortex and (ii) recurrent, delayed inhibitory feedback in thalamocortical loops. For the purposes of this chapter, we have focused on providing the reader with a clear exposition of some of this system's behavioural repertoire, rather than, e.g. matching precisely power spectrum traces from specific TMS/TACS-EEG datasets. Details of the full model implementation – including the use of optimization routines to accurately fit individual patients' whole-head power spectra, electromagnetic forward models (both brain-to-sensor and stimulus-to-brain), whole-brain white matter connectivity (anatomical macro-connectome), and integration with the virtual brain modelling and neuroinformatics platform [80, 81] – was beyond the scope of this chapter and shall be the subject of future work. It is nevertheless essential when constructing complex, multicomponent models to first have a detailed characterization of the dynamic behaviour of the individual building blocks – which in our case is the base thalamocortical motif shown in Fig. 18.1. The scientific value of such models lies in their ability to capture, in a mathematically compact way, some essential properties of large-scale neural dynamics and thereby provide insight into both normal activity and potential for control with brain stimulation techniques.

18.6 Software Note

Python code and additional documentation for the simulations presented in this chapter is freely available online at www.github.com/Lefebvrelab/ShapingBrainRhythms.

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