

Chapter 2

Modelling Sleep and General Anaesthesia

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2.1 Introduction

There is active controversy concerning the ideas about the relationship between the states of natural sleep and general anaesthesia (Hudetz 2008; Lu et al. 2008; Zecharia et al. 2009). Because, by definition, general anaesthetic drugs act to diminish the conscious state of the central nervous system—they are said to bias the central nervous system to enter natural sleep-like modes of operation (Franks 2008; Lancel 1999; Lin et al. 1989). This is manifest in the many similarities between the electroencephalogram (EEG) of natural sleep and the EEG when the patient is receiving modest doses of general anaesthetic. Further evidence to support this idea is found in a number of studies in which a sedated state may be induced (or reversed) by microinjection of various anaesthetic (and anti-anaesthetic) substances into some discrete areas of the brain-stem and midbrain which have been shown to be critical in the co-ordination of natural sleep-wake transitions (Hudetz et al. 2003; Nelson et al. 2002; Alkire et al. 2007, 2009; Sukhotinsky et al. 2007). These sub-cortical arousal structures facilitate wakefulness by providing ongoing depolarizing neuromodulatory input to the cortex. It is hard to imagine a more evolutionarily important behavior for an animal than the ability to achieve the state of wakefulness. Therefore, it is not surprising that there exist many overlapping brain-stem systems that can activate the cerebral cortex—acting via a number of different chemical substances such as glutamate, acetylcholine, amines, and orexin. Presumably this huge redundancy makes the animal relatively insensitive to natural neuromodulator toxins. However, there is a problem. The sleep state seems, also, to be essential for the survival of animals with adaptive nervous systems. Therefore,

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in tandem with the robust systems required to maintain wakefulness, the animal must also be able to reliably achieve sleep. In mammals the ability to be ‘properly awake’ or ‘properly asleep’ seems to have been achieved by the evolutionary development of neuronal mechanisms that interact over a variety of different scales of size. If we want to model the processes of sleep and anaesthesia, the challenge is to include the processes that are occurring at many different spatial scales. The global behavioral states of wakefulness and sleep reflect large-scale alterations in activity encompassing virtually the entire cerebral cortex. At the scale of traditional anatomic ‘brain-centers’ (millimetre-to-centimetre size) we could envisage the cerebral cortex as being strongly influenced by distant brain-stem servo-controlling systems based on mutual inhibition. These models typically have sets of equations that hope to capture the dynamics of the interacting groups of brain-stem neurons (Behn et al. 2007; Rempe et al. 2010; Fulcher et al. 2008; Phillips and Robinson 2008); and thus replicate observed activity in various wake-ON, sleep-ON, wake-OFF, and sleep-OFF neuronal populations (Leung and Mason 1999; Lin et al. 1988; Saint-Mleux et al. 2004; Saito et al. 1977). However, the complexity of the thalamo-cortical response to the brain-stem neuromodulator input cannot be ignored; and should be included in the modelling process. At the smaller cellular and molecular scale (sub-millimeter), there is also a strong tendency for thalamo-cortical neuronal populations to abruptly jump between active and silent modes of operation—without externally derived driving. This bistability is probably driven by both intrinsic neuronal ion currents, and synaptic effects (Fuentelba et al. 2005; Hill and Tononi 2005; Compte et al. 2003; Contreras et al. 1996; Steriade et al. 2001; Steriade and Amzica 1998). The modelling of sleep has thus developed in two somewhat divergent directions, reflecting these diversity of scales. On one hand are the ideas that the brain-stem control is pre-eminent, and the cortical responses are just subservient to the brain-stem neuromodulator outputs (Clearwater et al. 2008; Phillips and Robinson 2008). The opposing body of work, does not look at how the neuromodulator milieu is generated, but assumes that it is simply an externally imposed parameter; and instead looks in great detail at the cortical (and sometimes thalamic) responses to the change in neuromodulator environment (Wilson et al. 2005, 2006). As yet there does not seem to be a single comprehensive model of both brain-stem and neocortical interactions. The diagram in Fig. 2.1 summarizes the components that would be included in such a model.

At higher concentrations of anaesthetic drugs, the similarities between general anaesthesia and natural sleep are less obvious. In particular, the ability for painful (nociceptive) stimuli to activate awakening is markedly suppressed by general anaesthetic drugs. With further increases in anaesthetic dosage, the EEG tends toward a burst-suppression pattern—which is not found in natural sleep states; and the animal becomes behaviorally impervious to all nociceptive arousal. It is unclear exactly how general anaesthetic drugs cause this suppression of responsiveness in the animal. In this chapter we will address this question using a neocortical mean-field model. We explicitly concentrate on modelling cerebro-cortical dynamics. Brain-stem neuromodulation is limited to exogenously imposed variations in cortical neuronal resting membrane potential, with no attempt to quantify the complex multimodal brain-stem feedback mechanisms. With this cortico-centric model

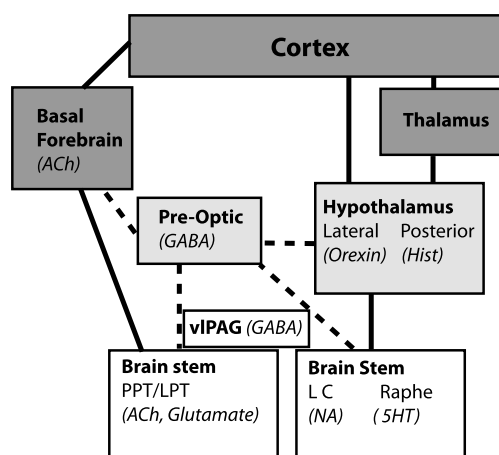


Fig. 2.1 Diagram of various components of sleep processes in the brain. For clarity the circadian and limbic inputs have not been included. The *non-italic* lettering indicates the various anatomical brain regions and nuclei (viPAG = ventro-lateral peri-aqueductal gray matter, PPT = pedunculo-pontine-tegmentum, LPT = lateral pontine tegmentum, LC = locus ceruleus)). The *black lines* indicate excitatory interactions, and the *dashed lines* indicate inhibitory interactions. The *italic* lettering indicates the various neuromodulators (ACh = acetylcholine, Hist = histamine, NA = Noradrenaline, 5HT = serotonin, GABA = gamma-amino-butyric acid)

we propose that the gamma-amino-butyric-acid (GABA)-ergic effect of common general anaesthetic drugs is a sufficient explanation of both:

1. the ability of general anaesthetic drugs to precipitate the central nervous system into a sleep-like state, and is also
2. the mechanism by which general anaesthetic drugs obtund nociceptive arousal.

2.2 Mechanisms of Natural Sleep

Sleep is a phenomenon that is ubiquitous in the animal kingdom. It is essential for survival; even though—from a superficial evolutionary viewpoint—the act of becoming unresponsive to the outside world for a considerable period each day would not appear to be very advantageous. The investigation of the control mechanisms in mammalian sleep has been very intense in recent years and we would refer the reader to a number of excellent reviews (Rosenwasser 2009; McCarley 2007; McCarley and Chokroverty 2007; Saper et al. 2005; Fuller et al. 2006, 2007), and also the Chap. 1 in this volume. In brief, there is an interlinked system of mutually inhibitory neuronal populations—located in the brain stem and basal forebrain—that will tend to cause the state of the animal to be either awake or asleep. This has been described as being analogous to a ‘flip-flop’ electrical circuit. These neuronal populations are made up of relatively few cells (perhaps only a few thousand), but

have a very wide projection, and so are able to influence huge areas of the neocortex. The systems are set up so that an intermediate state is not inherently stable—the animal does not remain in a half-asleep state.

Traditionally sleep has been described as being under the control of two processes: (i) homeostatic and (ii) circadian. Sleep is then further classified into rapid-eye-movement (REM) or paradoxical sleep; and non-REM (NREM) or slow-wave sleep states. REM sleep is associated with relatively high levels of activity in cholinergic and glutamatergic neurons, whereas NREM sleep is predominantly a GABAergic state (Fuller et al. 2007; Goutagny et al. 2008; Luppi et al. 2006). The amount of sleep varies widely between different species of mammals. A mathematical model of the brain-stem control of circadian and ultradian sleep rhythms of V. Booth et al. can be found in Chap. 5. The various states of sleep and wakefulness have been defined mainly by using stereotypical heuristic EEG patterns. These changes in EEG pattern are usually quite clear. Questions arise as to what is the real biological significance to the animal of these EEG changes, and also how they can be quantified. An accurate mathematically based model of sleep would go a long way toward answering both these questions.

There is increasing evidence that ‘sleep’ is a phenomenon that can occur in quite small localized populations of neurons (Krueger et al. 2008). As a homeostatic response to periods of prolonged neuronal activity, neurons show a propensity to enter a state where they undergo fluctuations of hyperpolarized quiescence and depolarized activity that are indistinguishable from those seen in classical slow-wave sleep. The reason for this phenomenon is not known with certainty, but probably involves some synaptic re-organization which is required for more efficient information handling (Tononi 2009; Tononi and Cirelli 2006; Vyazovskiy et al. 2008). This process has been modeled (Roy et al. 2008; Riedner et al. 2007). There is therefore a tension between the requirements for local populations of neurons to engage in a period of sleep for their efficient operation, and the requirements for the whole mammal to function as safely as possible in a dangerous world. The solution appears to be utilization of the primitive brain-stem systems as controllers of mammalian sleep. The process of falling asleep involves the interaction of many large-scale brain systems. It can be easily imagined that the roles of these systems are to:

- Minimize the tendency for small parts of the brain to fall asleep, while the rest of the brain is awake. In aquatic mammals half the brain sleeps at any one time. Presumably this occurs because some responsiveness is required for the continued swimming and breathing necessary for survival in dolphins and whales (Siegel 2009). In land mammals, it seems that there is a preference for the whole brain to sleep synchronously. This is probably because higher forms of mammalian consciousness require co-ordination and synchrony within neuronal assemblies that span widely separated parts of the brain (Harris 2005; Massimini et al. 2009). Thus the maintenance of function within these spatially disparate assemblies would require that these large portions of the brain enter the sleep state at the same time. This requirement for total-brain sleep would suggest that localized unsynchronized sleep episodes are not sufficient for the large-scale

synaptic re-modelling required for effective mammalian cognition. Also spatially synchronous EEG activity is a notable feature of slow-wave sleep (Destexhe et al. 1999).

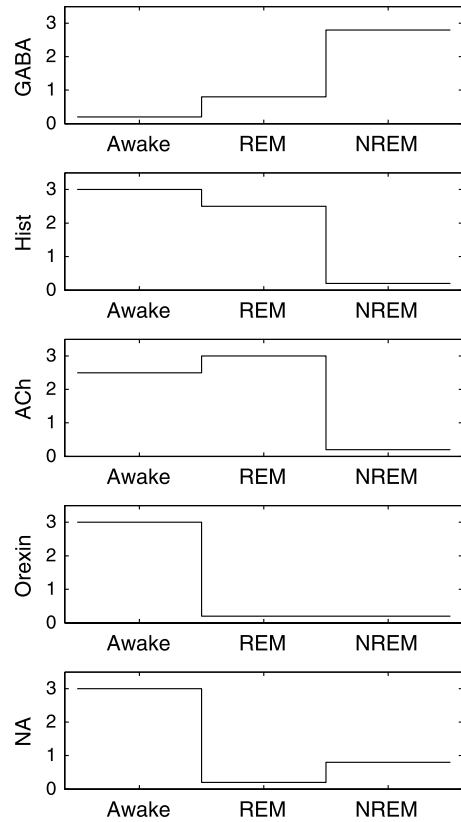
- Co-ordinate the sleep phase with the part of the day that the animal is least active. Thus predominantly visual animals (like man) tend to sleep at night, and predominantly smell-oriented animals (like rats) tend to sleep in the day.

2.2.1 The Neurobiology of Falling Asleep and Waking up

The sensation of sleepiness can arise from at least two sources; (1) either directly from circadian inputs (the suprachiasmatic nucleus of the hypothalamus (Fuller et al. 2006; Saper et al. 2005)), or (2) from other less well-specified, homeostatically derived, neuromodulator somnogens (such as adenosine) (Krueger 2008; Basheer et al. 2007; Arrigoni et al. 2006). These chemicals can be generated as the result of prolonged neuronal activity, or from other pathological origins—such as is found in the drowsiness of septic encephalopathy. In the awake state, the gamma-amino-butyric-acid(GABA)-ergic neurons of the ventro-lateral preoptic nucleus (VLPO) of the hypothalamus (Winsky-Sommerer 2009) are suppressed by many excitatory arousal substances (amines, glutamate, acetylcholine, orexin). If the somnogen levels—or the suprachiasmatic circadian input—are sufficient to reduce the effect of these arousal neuromodulators, the sleep-active GABAergic neurons in the VLPO become active and these cells then further suppress the activity in the excitatory arousal systems. Thus a positive feedback is set up leading to rapid and almost complete suppression of activity in the arousal systems (Lin et al. 1988; Luppi et al. 2004; Moreno-Balandran et al. 2008; Ohno and Sakurai 2008; Saito et al. 1977; Verret et al. 2006; Villablanca 2004). Removal of the tonic neuromodulator-induced depolarization of the cortico-thalamic circuits allows these circuits to enter hyperpolarized silent ‘DOWN’ states that are characteristic of slow-wave, or NREM sleep (Steriade et al. 2001). The EEG signature of these modes of operation are sleep spindles, delta waves, and the slow oscillation (Steriade and Amzica 1998; Amzica and Steriade 1998). These patterns are associated with inability to form the spatially dispersed large synchronous networks (Massimini et al. 2005; Sakurai 2007) that are presumably the prerequisite of the wakeful state. At the scale of individual neurons, the hyperpolarized state causes sequential activation of a variety of slow intrinsic currents, which are primarily responsible for the various aforementioned EEG oscillations observed in NREM sleep (Crunelli and Hughes 2010). It is well established that GABAergic drugs act to decrease sleep latency, inhibit REM sleep, and increase stage 2 type NREM sleep (Lancel 1999). Figure 2.2 shows a summary diagram of the changes in activity amongst the various neuromodulators in the Awake, REM, and NREM states.

The reverse process is involved in waking up. The GABAergic neurons (principally in the VLPO, but also in the thalamus and elsewhere) are, for some reason,

Fig. 2.2 A diagram of changes in neuromodulators in different states of sleep and wakefulness. The *vertical axes* are arbitrary units (REM = rapid-eye-movement sleep, NREM = non-rapid-eye-movement sleep, ACh = acetylcholine, Hist = histamine, GABA = gamma-amino-butyric acid, NA = noradrenaline). The main Awake–Sleep differentiators are orexin and noradrenaline, whereas acetylcholine and histamine differentiate active (= REM and Awake) from inactive (NREM) states



switched off. This removal of suppression of the brain-stem nuclei allows the activation of the, previously quiescent, excitatory aminergic, glutamatergic, cholinergic, and orexinergic systems. Acting via various receptors, these neuromodulators cause closure of potassium channels and neural depolarization. Thus this brain-stem reticular activation induces a depolarized active ‘UP’ state in the cortex; which in turn, allows the formation of spatially dispersed large synchronous networks, and hence the wakeful state (Massimini et al. 2009; Tononi and Sporns 2003). The obvious question is: ‘What could cause the VLPO to switch off?’ In the natural course of the day, this is primarily a question about the influences of the homeostatic and circadian processes. At the end of a good night’s sleep, the hyperpolarizing somnogen and circadian input has diminished to such an extent that the balance shifts in favor of the aminergic activating systems; which then inhibit the VLPO and initiate a positive feedback of arousal that is the inverse of that described above when the person falls asleep (Rempe et al. 2010; Riedner et al. 2007; Wilson et al. 2005). It is tempting to speculate that the increase in REM activity later in the night is acting as a ‘ping’ to test the progress of the sleep-induced synaptic remodelling. Unlike in the awake state, in REM sleep the brain aminergic and orexinergic systems are quiescent, and the cortex is partially activated with acetyl-

choline only. There is a good case to be made for the orexin system as performing the up-stream ‘executive function’ controlling wakefulness.

Perhaps the more intriguing question is: ‘What is happening when the person wakes in response to a strange noise in the house?’ This implies that the natural sub-conscious circadian and homeostatic rhythms have been overruled by a particular circumstance, which may be of specific importance to the person. The neurobiological details in this situation are not well understood at present, but there is clearly some degree of unconscious cognitive control of arousal during natural sleep in adults (Lovejoy and Krauzlis 2010). For example an unusual noise like a telephone ringing will be recognized and result in the adult waking (although anyone who has had children can tell you that a deeply asleep child is much more difficult to waken). It would seem that the arousal signal has originated from some sort of low-grade attention process that clearly functions quite well during natural sleep. This ‘top-down’ input—probably originating in the amygdala (Alkire et al. 2008)—is then able to switch off the GABAergic VLPO suppression of the aminergic and orexinergic arousal systems. At its heart, the final common pathway of natural waking is the activation of various arousal systems to alter intrinsic currents within the neurons to make them more depolarized and excitable. In contrast the defining feature of general anaesthesia is the complete inability to waken—even in response to the most severe painful stimulus imaginable. As is further elaborated below, general anaesthesia has at least two pharmacological effects to impair arousal:

1. The person is not able to turn the arousal-suppressing VLPO switch to the ‘off’ position; and thus set in train the downstream aminergic cortical activation processes (Plourde et al. 2006).
2. The anaesthesia also directly prevents the effector-organ of wakefulness (the neo-cortex) from responding to these aminergic depolarizing inputs with a suitable increase in spike-rate.

2.3 Mechanisms of General Anaesthesia

Surprisingly, general anaesthesia—like sleep—is also a phenomenon that is ubiquitous in the animal kingdom. Why this should be so is unknown, but it would seem likely that general anaesthesia is—in part—a chemical hijacking of natural sleep mechanisms (Franks 2008; Pang et al. 2009). At the molecular level this would involve interactions with evolutionarily conserved protein ion channels and pumps that are necessary for homeostatic control of nervous system activity. It is noteworthy that—while drugs which antagonize the excitatory neuromodulators, e.g. antihistamines, clonidine, antimuscarinics, will augment sleepiness—they are not, on their own, capable of inducing a state of proper anaesthesia. It seems that the ability to directly open the chloride channels is a prerequisite for a sedative drug to be an anaesthetic drug. There are clearly both similarities and differences between the two states:

- Similarities between sleep and general anaesthesia
 - Behavioral effects (unconsciousness/unawareness)

- EEG patterns (spindles, K-complexes, delta waves) (Ferenets et al. 2006; Koskinen et al. 2001)
- fMRI distribution metabolism (Peltier et al. 2005)
- Demonstration of general anaesthetic drug action on specific sleep nuclei (Kerssens et al. 2005; Nelson et al. 2002)
- some functional effect—restfulness/sleep rebound studies (Nelson et al. 2004).
- Differences between general anaesthesia and sleep
 - Unrousability
 - EEG burst suppression
 - Circadian rhythm disturbance
 - Side effects of general anaesthesia—nausea, etc.

As is described in the rest of this book, modelling of sleep and anaesthesia can be done at a variety of different levels. In the following sections we will explicitly concentrate on modelling the neocortical dynamics. We have used a mean-field method, but other neuron-by-neuron models have been published (Esser et al. 2009; Hill and Tononi 2005; Compte et al. 2003). The recently published paper by Esser and co-workers came to very similar conclusions about the neurophysiological mechanism of unconsciousness as those we have obtained from our model in this chapter. They compared various possible intrinsic neuronal current effects, with an increase in effective inhibitory post-synaptic potential (IPSP). They found that the increase in IPSP is the most likely mechanism to cause ‘gating’ of propagation of information flow between different neocortical regions in NREM. They suggested that this occurs during natural sleep as a result of the reduction in cholinergic tone. Acetylcholine acts via M1 and M2 receptors to inhibit GABA release in the supra-granular cortical layers (Salgado et al. 2007). As is described below, the critical point of difference between natural sleep and general anaesthesia is that activation of the cholinergic arousal systems on waking from natural sleep causes the IPSP to return to normal amplitude. In contrast, if the patient has an appreciable concentration of general anaesthetic drug present, the IPSP cannot be reduced in amplitude; because the drug is directly holding the chloride channels open—and hence the cortical ‘gating’ is held closed.

2.3.1 Mean-Field Modelling of General Anaesthesia and Sleep

In recent years variations of a mean-field model have been used with some success to model the cortical effects of both sleep and general anaesthesia (Steyn-Ross et al. 1999; Bojak and Liley 2005; Liley and Bojak 2005; Robinson et al. 2003; Sleight and Galletly 1997; Steyn-Ross et al. 2001; Steyn-Ross et al. 2004; Wilson et al. 2006; Wright and Liley 1995). The usual output from these models is the change in time of the mean soma potential—which can be related to the EEG signal. Since the EEG (or local field potential) is the most commonly observed experimental output, the output from the theoretical model can be directly compared to experimental results. In the following description, however, we will be using

the mean firing rate as the primary model output. The reason for choosing this is that the firing rate is clearly related to anaesthetic blockade of arousal (Antkowiak 1999). If the brain cannot achieve an active state, it does not have the information flux capacity to be complex enough to be conscious. The technical details of this model have been previously published (Sleigh et al. 2009; Wilson et al. 2006; Sleigh et al. 2010), but are described briefly below. The model has been parameterized using information about cortical anatomy, but the ideas could apply more generally to any suitably large interacting populations of inhibitory and excitatory neurons. We term the computer instantiation of this set of equations as the ‘pseudo-cortex’.

2.3.1.1 Mathematical Description of the Mean-Field Model

The model consists of a set of partial differential equations that describe the time evolution of the mean soma potential in a homogeneous, isotropic 2-dimensional sheet of macrocolumns. The macrocolumns contain a population of excitatory pyramidal neurons (denoted with subscript e), and a population inhibitory interneurons (subscript i). The two populations interact by means of ‘fast’ chemical synapses; that simulate AMPA and GABAA kinetics. We do not explicitly model the effects of gap junctions, glia, slow synaptic currents (NMDA or GABAB), or slower modulation of synaptic receptor trafficking. We have used the convention of $a \rightarrow b$ indicating that the direction of transmission in the synaptic connections is from the presynaptic nerve a , to post-synaptic nerve b . The model cortex is driven by a subcortical random white noise input (superscript sc), which is independent of the neocortical membrane potential. The time evolutions of the mean neuronal soma membrane potential (V_a) in each population of neurons, in response to synaptic input ($\rho_a \Psi_{ab} \Phi_{ab}$) are given by the following set of equations:

$$\tau_e \frac{\partial V_e}{\partial t} = V_e^{\text{rest}} - V_e + \delta V_e^{\text{rest}} + \rho_e \Psi_{ee} \Phi_{ee} + \rho_i \Psi_{ie} \Phi_{ie} \quad (2.1)$$

$$\tau_i \frac{\partial V_i}{\partial t} = V_i^{\text{rest}} - V_i + \rho_e \Psi_{ei} \Phi_{ei} + \rho_i \Psi_{ii} \Phi_{ii} \quad (2.2)$$

where τ_a are the neuron soma time constants, ρ_a are the strength of the post-synaptic potentials (they are multipliers of the total area under the post-synaptic potentials), Ψ_{ab} are the weighting functions that allow for the effects of reversal potentials and are described by the equation:

$$\Psi_{ab} = \frac{V_a^{\text{rev}} - V_b}{V_a^{\text{rev}} - V_a^{\text{rest}}}. \quad (2.3)$$

V^{rev} are the reversal potentials for chloride or sodium (as appropriate), and V^{rest} is the resting soma potential. (For clarity in later sections we have put the ‘rest’ as a subscript instead of a superscript). The Φ_{ab} are the synaptic input spike-rate densities which are described by the following equations (2.4) to (2.7). These are a set of second-order differential equations which describe the post-synaptic (dendritic) impact of a delta-function spike of activity at the synapse. The shape of the

post-synaptic potential is given by the solution (Green's function) to the differential equation, and is a so-called 'alpha-function'.

$$\left(\frac{\partial^2}{\partial t^2} + 2\gamma_{ee} \frac{\partial}{\partial t} + \gamma_{ee}^2 \right) \Phi_{ee} = \gamma_{ee}^2 (N_{ee}^\alpha \phi_{ee} + N_{ee}^\beta Q_e + \phi_{ee}^{sc}) \quad (2.4)$$

$$\left(\frac{\partial^2}{\partial t^2} + 2\gamma_{ei} \frac{\partial}{\partial t} + \gamma_{ei}^2 \right) \Phi_{ei} = \gamma_{ei}^2 (N_{ei}^\alpha \phi_{ei} + N_{ei}^\beta Q_e + \phi_{ei}^{sc}) \quad (2.5)$$

$$\left(\frac{\partial^2}{\partial t^2} + 2\gamma_{ie} \frac{\partial}{\partial t} + \gamma_{ie}^2 \right) \Phi_{ie} = \gamma_{ie}^2 (N_{ie}^\beta Q_i + \phi_{ie}^{sc}) \quad (2.6)$$

$$\left(\frac{\partial^2}{\partial t^2} + 2\gamma_{ii} \frac{\partial}{\partial t} + \gamma_{ii}^2 \right) \Phi_{ii} = \gamma_{ii}^2 (N_{ii}^\beta Q_i + \phi_{ii}^{sc}) \quad (2.7)$$

where γ_{ab} are the synaptic rate constants, N^α are the typical number of long-range connections between macrocolumns, and N^β the number of local intra-macrocolumn connections. It should be noted that these equations are describing the average impact of the excitatory and inhibitory dendritic input onto the soma of the neuron; and thus would include dendritic modulation and summation of pure synaptic input. The mean axonal velocity is given by v , and the characteristic length (the length at which the connectivity between neuronal populations decays to $1/e$) is $1/\Lambda_{ea}$. These spatial interactions amongst the macrocolumns are described by the two equations (2.8) and (2.9):

$$\left(\frac{\partial^2}{\partial t^2} + 2v\Lambda_{ee} \frac{\partial}{\partial t} + v^2\Lambda_{ee}^2 - v^2\nabla^2 \right) \phi_{ee} = v^2\Lambda_{ee}^2 Q_e \quad (2.8)$$

$$\left(\frac{\partial^2}{\partial t^2} + 2v\Lambda_{ei} \frac{\partial}{\partial t} + v^2\Lambda_{ei}^2 - v^2\nabla^2 \right) \phi_{ei} = v^2\Lambda_{ei}^2 Q_e. \quad (2.9)$$

The relationship between the mean neuronal population firing rate and the mean soma potential is given by sigmoidal functions (see (2.10) and (2.11)). An alternative interpretation is the probability of a neuron firing at a particular membrane potential.

$$Q_e(V_e) = \frac{Q_e^{\max}}{1 + \exp(-\pi(V_e - \theta_e)/\sqrt{3}\sigma_e)} \quad (2.10)$$

$$Q_i(V_i) = \frac{Q_i^{\max}}{1 + \exp(-\pi(V_i - \theta_i)/\sqrt{3}\sigma_i)} \quad (2.11)$$

where θ_a describes the inflection point membrane potential, and σ_a the standard deviation of the threshold potential. This parameter is a composite indicator of both: (i) the degree of homogeneity within the population of neurons, and (ii) whether the neurons show 'bursting' vs. 'regular-spiking' responses to injected current. The parameters and ranges used in our simulations are shown below in Table 2.1. The parameter values are a composite, derived from numerous different published papers in which the real neurophysiological values for individual neurons have been measured. The parameters are not freely adjusted post-hoc. Real nervous systems seem to tolerate quite a lot of variation in parameter values. A good argument could be made that the real nervous system will homeostatically adjust its connectivity

Table 2.1 Parameters for model cortex

Symbol	Description	Value
τ_e, τ_i	membrane time constant	15, 15 ms
$Q_{e,i}$	maximum firing rates	30, 60 Hz
$\Theta_{e,i}$	sigmoidal thresholds	−58, −58 mV
$\sigma_{e,i}$	standard deviation of thresholds	3, 5 mV
$\rho_{e,i}$	gain per synapse at resting voltage	0.001, −0.001 mV s
$V_{e,i}^{\text{rev}}$	cell reversal potential	0, −70 mV
$V_{e,i}^{\text{rest}}$	cell resting potential	−64, −64 mV
$N_{e,a}^\alpha$	long-range e to e or i connectivity	2500, 1000
N_{ea}^β	short-range e to e or i connectivity	1000
$N_{i,a}^\beta$	short-range i to e or i connectivity	500, 250
ϕ_{ea}^{sc}	mean e to e or i subcortical flux	80/s
γ_{ea}	baseline excitatory synaptic rate constant	100/s
γ_{ia}	baseline inhibitory synaptic rate constant	50/s
$L_{x,y}$	spatial length of cortex	25 cm
a_{mac}	area of macrocolumn	0.5 mm ²
Λ_{ea}	Inverse length connection scale	14/cm
ν	mean axonal conduction speed	140 cm/s

(via synaptic up- and down-regulation) and excitability (via intrinsic ion channel expression) to maximize flexibility in its responses and activity regimes—and thus its ability to generate information.

2.3.2 *Modelling Nociceptive Arousal*

The neurobiological effects of a surgical stimulus are surprisingly poorly understood, but can be plausibly modeled as pain-induced activation of the various nuclei of the reticular activating system (as described above in Sect. 2.2). These ascending nuclei then act both:

1. indirectly to switch off the GABAergic neurons (in the VLPO, peri-aqueductal gray matter, and reticular thalamus) that are dominant in the state of slow-wave sleep; and also,
2. directly to depolarize the thalamo-cortical structures.

The increase in excitatory neuromodulatory substances (amines, orexin, acetylcholine) closes various potassium channels (Arrigoni et al. 2006; Espinosa et al. 2008; Leonard and Llinas 1994; McCormick 1989; McCormick et al. 1991; Rowell et al. 2003; Saint-Mleux et al. 2004; Wu et al. 2004), and thus causes the resting membrane potential to become more depolarized. This is easily incorporated in the

model as a depolarization of the resting soma potential V^{rest} (by setting the δV_{rest} offset to a positive value). We examined the effects of altering the resting membrane potential values over quite a large range, from -68 mV to -56 mV. Alternatively the arousal effect could also be included in the model as increased excitatory sub-cortical input flux (ϕ^{sc}). This approach has mathematically equivalent effects on the dynamics of the pseudo-cortex.

2.3.2.1 Modelling Anaesthetic-Induced Suppression of Arousal

There is ongoing debate about the exact molecular mechanisms of action of general anaesthetics, but it is widely acknowledged that—for intravenous drugs like propofol and etomidate—they have fairly specific actions to increase the area under the inhibitory post-synaptic potential (IPSP), and thus increase inhibition within the brain (Campagna et al. 2003; Grasshoff et al. 2006; Rudolph and Antkowiak 2004; Antkowiak 1999). This effect is mainly the result of prolongation of the IPSP, rather than an increase in the peak amplitude of the IPSP. In higher concentrations this action is independent of the presence of endogenous GABA. At the dose required to suppress awakening to a surgical incision, propofol increases the area of the IPSP between 1.5-fold and 3-fold. The opening of the chloride channels in the post-synaptic membrane also increases the effective membrane conductance. This has the effect of decreasing the degree of depolarization induced by excitatory post-synaptic currents—which magnifies the inhibition effects. We have not included this in our modelling; and thus have tended to underestimate the inhibitory effects of propofol. We have also not included the hyperpolarizing effects in tonic non-synaptic GABA receptors. While we have concentrated on the GABAergic synaptic effects of general anaesthetic drugs, we acknowledge other possible effects on intrinsic neuronal channels; especially by volatile anaesthetic agents. This group of drugs is well known to have a multitude of actions, including opening various 2-pore-domain potassium channels, and NMDA receptor antagonism (Franks 2008). The effects on the model are more fully explored later in this chapter.

The most obvious and important question is whether the simple IPSP augmentation by propofol, is sufficient to explain the extraordinary ability of general anaesthetic drugs to block extreme nociceptive arousal of the cerebral cortex. Assuming that the model has at least some fidelity in representing the dynamics of the cerebral cortex, we may then use this model to explore possible answers to this question. Accordingly, the natural space to envisage the competing effects of the general anaesthetic drug and those of painful arousal has three axes:

- IPSP magnitude, which is an indicator of the general anaesthetic effect.
- Change in resting membrane potential (via δV_{rest}) which reflects the input of brain-stem neuromodulator activation. This \hat{V}_{rest} parameter will be a composite indicator of the balance between activation of the sleep systems (to decrease δV_{rest}) and their opposition by nociceptive input (to increase δV_{rest}).
- The mean neuronal firing rate is the output variable on the vertical axis.

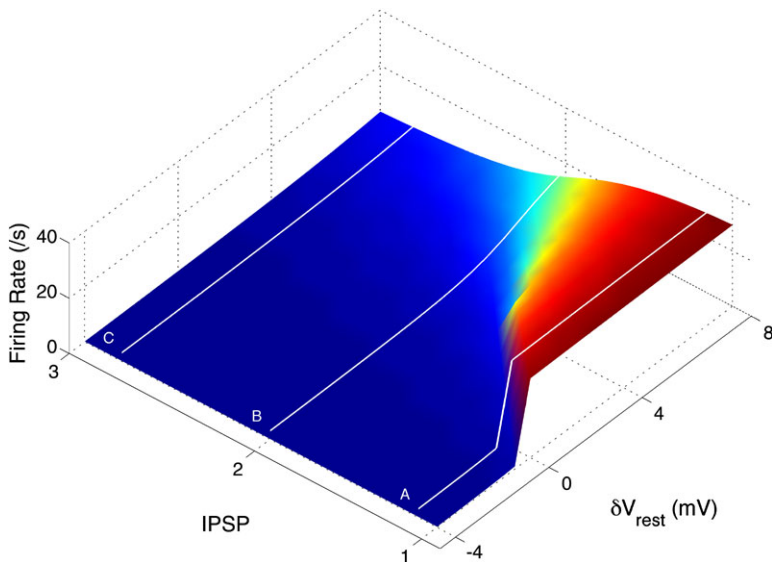


Fig. 2.3 Diagram of model steady-state solutions in neuronal firing rate (vertical axis) versus changes in inhibitory post-synaptic potential (IPSP) and resting membrane potential (δV_{rest}), on the horizontal axes. The trajectories of steady states followed by increasing δV_{rest} at three fixed magnitudes of IPSP are shown by the white lines, ‘A’ (Sleep-wake), ‘B’ (Sedation), and ‘C’ (Anaesthesia). These correspond to the diagrams ‘A’, ‘B’, and ‘C’ in Fig. 2.4

We obtained the steady-state solutions to the set of equations that comprise the model at various input parameter values (IPSP and δV_{rest}). We assume that a high-firing state is a necessary (but not sufficient) condition for wakefulness to occur in a real animal. Conversely a low-firing state is thought to be consonant with unconscious states—and precludes wakefulness. Using parameters as shown in Table 2.1, the resultant output from the model is shown in Figs. 2.3 and 2.4. The subplots (Figs. 2.4A to 2.4C) show trajectories indicated by the white lines on the manifold in Fig. 2.3. These are the response of the model cortex to a progressive increase in δV_{rest} such as might occur with painful stimulation.

- Figure 2.4A: If there is no increase in IPSP magnitude (i.e. in a state of natural sleep—in the absence of general anaesthesia), it can be seen that a small neuromodulator-induced depolarization of the resting membrane potential ($\delta V_{\text{rest}} \approx 2\text{--}3$ mV) results in an abrupt jump from a low-firing state to an active state (firing rate 25/s). This would correspond to the cortex moving from NREM to the wakeful state in response to activation of the aforementioned brain-stem neuromodulator systems. It is interesting to note that this abrupt change is a property that is intrinsic to the cortical population behavior, and does not require a separate mutually inhibitory brain-stem flip-flop system.
- Figures 2.4B, and 2.4C show the effects if propofol is included in the model and the magnitude (and duration) of the IPSP is increased. The region of interest shifts to the left of the manifold in Fig. 2.3. We see that there has to be a much

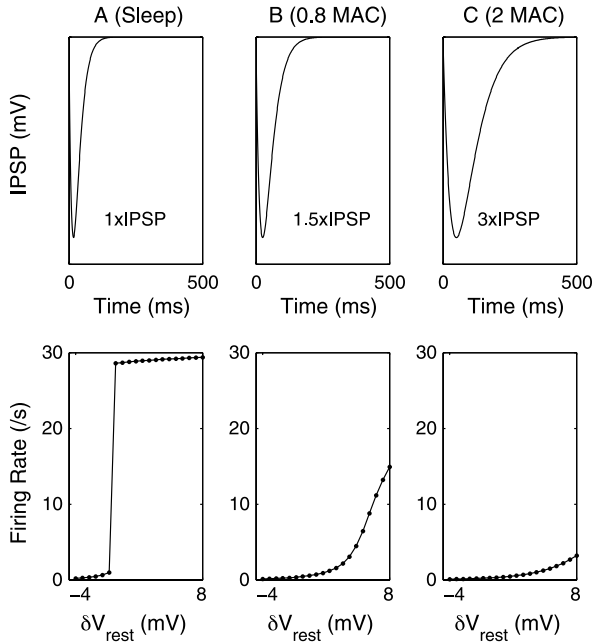


Fig. 2.4 Changes in firing rate with changes in resting membrane potential (*lower graphs*) for three different values of IPSP magnitude (shown in *upper graphs*). MAC = minimal alveolar concentration of anaesthetic vapor that prevents movement in response to a surgical incision in 50% patients. This concept has been loosely applied to the effects of the intravenous drug propofol. There are data to support the assertion that the concentration of propofol (2 μ M) that is required to increase the IPSP area to 150% of the starting values is associated with sedation/light anaesthesia, and that required (8 μ M) to increase the IPSP area to 300% of the starting value is associated with deep burst-suppression pattern anaesthesia

greater arousal-induced activation of neuromodulators ($\delta V_{rest} \approx 10$ mV) to allow the cortex to achieve some sort of active state, and once the IPSP magnitude is greater than about twice normal, the firing rate of the active state is much diminished (5/s)—no matter how much the soma potential is depolarized. The synaptic effects of the general anaesthesia always ‘trump’ the intrinsic effects of the nociceptive activation of the neuromodulators. This makes intuitive sense. The effect of the increased IPSP area is to amplify negative feedback on excitatory neurons. Thus any increased activity in the excitatory/pyramidal cells quickly translates into increased activity in their ‘downstream’ inhibitory interneurons which then ‘chokes’ the possible ceiling of activity in the model cortex. More excitatory activity simply results in more inhibitory activity. To the extent that the model reflects reality, we may conclude that; if the IPSP is increased by general anaesthetic drugs, the cortex become increasingly difficult to activate by the usual arousal mechanisms of potassium channel closure and neuronal depolarization. Once the IPSP is greater than double the baseline amplitude, it becomes almost impossible to activate the cortex by increasing intrinsic neuronal excitability. The low-firing

coma state can only be reversed by blockade of chloride conductance, or possibly be an increased EPSP.

It is also of interest that the bistability of the pseudo-cortex is reduced as the IPSP increases—and the transition between silent and firing modes becomes continuous rather than discontinuous.

2.3.3 Robustness of Parameters and Drug Interactions

The conclusions are largely independent of parameter values. The important point of all this is the fact that the high-firing state exists as a sort of ‘hilltop’ in the back right-hand side of the manifold. Changes in various parameters alter the size of the ‘hilltop’ in a predictable fashion. Increase in excitability (increases in N_{ee} , N_{ii} , sub-cortical input ($\langle \phi_{ea}^{sc} \rangle$), EPSP magnitude (ρ_e), and decreases in N_{ei} , and N_{ie}) will increase the area of the ‘hilltop’ and shift it forward and to the left—thus increasing the propensity for activity and wakefulness. Parameter changes in the opposite direction will decrease the size of the ‘hilltop’ and shift it backwards and to the right—thus increasing the propensity for coma. However, the basic shape of the ‘hilltop’ is unchanged; with increasing IPSP always reducing the peak firing rate.

The known anaesthetic drug interactions are consonant with this model. Drugs that open potassium channels and hence hyperpolarize V_{rest} (opioids), and drugs that reduce ρ_e (ketamine) will potentiate the GABAergic anaesthesia of propofol. Indeed volatile anaesthetic agents are known to have a significant potassium channel opening activity themselves (Franks 2008). Drugs that inhibit the aminergic arousal systems (such as dexmedetomidine) also potentiate general anaesthesia. Drugs that close potassium channels (such a physostigmine (Meuret et al. 2000; Plourde et al. 2003)), and enhance ρ_e (pentylenetetrazole, or direct glutamate application) will tend to antagonize GABAergic general anaesthesia. However, the ability of these antagonists to recover the conscious state is limited to sedative doses of propofol. Alkire and co-workers have done some seminal work on the behavioral reversal of anaesthesia (Alkire et al. 2007, 2009). They injected the cholinergic drug nicotine into the central medial thalamus, and found that rats, which had received about 0.5MAC sevoflurane (i.e. just enough to eliminate their loss-of-righting reflex) woke-up. That is they regained normal behavior patterns, even in the ongoing presence of sevoflurane. There are various interpretations of these results, but we would suggest that the sevoflurane had impaired the rats’ cortical activity so as to move off the active state ‘hilltop’ (i.e. back along the Fig. 2.4A–B trajectory). The injection of nicotine in a crucial area of the thalamus with widely diverging cortical projection, was enough to depolarize the cortex back up the ‘hilltop’, and thus the rat regained wakefulness. Although it is not explicitly described in the paper, it appears that the nicotine-induced awakening is not successful if a full one-MAC dose of sevoflurane was used, i.e. trajectory 2.4C in Figs. 2.3 and 2.4. We can conclude that at higher doses of propofol, the IPSP-induced suppression of firing rate is not able to be effectively opposed by potassium channel closure by boosting (δV_{rest}).

The model thus explains the experimental observation that deep anaesthesia could only be reversed chemically by direct chloride channel blockade.

This exposes one problem with our model. As mentioned previously, an active cortex is necessary but not sufficient for wakefulness. We do not distinguish between the state of REM sleep and wakefulness. On both states the cortex is in an active state—however, in REM sleep the ‘consciousness’ is entirely internally directed; whereas in the wakeful state input from the external world is included in the consciousness. Analogous states are often seen during recovery from general anaesthesia. The patient commonly has an active cortex—as measured by an EEG monitor—but has no interaction with the external world, and is unresponsive to verbal command. The reasons for this lack of perception are unknown at present; but presumably are related in some way to aminergic and orexinergic functions. For anyone who wants to develop a monitor of anaesthesia, this question is clearly of utmost relevance.

2.4 Conclusions

If this model has some correspondence with reality, we may summarize the relationship between natural sleep and GABAergic anaesthesia as follows.

- In natural sleep there is activation of specific GABAergic pathways involving hypothalamic and brain-stem systems that cause hyperpolarization of the thalamo-cortical systems, which in turn, precipitates the state of slow-wave sleep. This state is characterized primarily by increased firing rates in GABAergic neurons, and an increase in effective IPSP that is contingent on low levels of acetylcholine. In this state the GABAergic systems are under normal homeostatic control, and even mild stimuli are able to switch them off and allow normal neuromodulator-induced cortical depolarization, and the transition to wakefulness (or REM sleep); see Figs. 2.3 and 2.4A.
- At low (sedative) doses of propofol, the IPSPs are moderately increased by the drug; which allows the GABAergic brain systems to become dominant and the subject has an increased tendency to enter the sleep state. However, an increased intensity of nociceptive stimuli may still induce sufficient depolarization to achieve the awake state; see Figs. 2.3 and 2.4B.
- At a higher (anaesthetic) dose of propofol, the large-scale global increase in inhibitory gain within the brain is of such a magnitude that no amount of nociceptive-induced closure of potassium channels is able to counteract the IPSP effects and the cortex is denied the possibility of reaching a high-firing state that is necessary for the state of wakefulness. This absolute resistance to nociceptive arousal is the sine qua non of the state of general anaesthesia: see Figs. 2.3 and 2.4C.

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