The Sleep Cycle Modelled as a Cortical Phase Transition

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Abstract. We present a mean-field model of the cortex that attempts to describe the gross changes in brain electrical activity for the cycles of natural sleep. We incorporate within the model two major sleep modulatory effects: slow changes in both synaptic efficiency and in neuron resting voltage caused by the ~90-min cycling in acetylcholine, together with even slower changes in resting voltage caused by gradual elimination during sleep of somnogens (fatigue agents) such as adenosine. We argue that the change from slow-wave sleep (SWS) to rapid-eye-movement (REM) sleep can be understood as a first-order phase transition from a low-firing, coherent state to a high-firing, desynchronized cortical state. We show that the model predictions for changes in EEG power, spectral distribution, and correlation time at the SWS-to-REM transition are consistent not only with those observed in clinical recordings of a sleeping human subject, but also with the on-cortex EEG patterns recently reported by Destexhe *et al.* [*J. Neurosci.* **19**(11), (1999) 4595–4608] for the sleeping cat.

Key words: cortical model, sleep cycle, adenosine, acetylcholine, phase transition, SWS, REM, EEG, Langevin equation, fluctuations, correlation, critical slowing down

Abbreviations: 2-D – two-dimensional; ACh – acetylcholine; EEG – electroencephalogram; EMG – electromyogram; EOG – electro-oculogram; LFP – local field potential; OU – Ornstein–Uhlenbeck; PSP – postsynaptic potential; REM sleep – rapid-eye-movement sleep; SWS – slow-wave sleep

1. Introduction

It has long been known that mammalian sleep consists of two distinct phases. *Quiet* or *SWS* sleep has a cortical signal (scalp electroencephalogram, EEG) that is characterised by low-frequency voltage fluctuations that have higher amplitude and greater coherence than the EEG patterns of the awake state. The opposite phase of sleep is known as *REM* (rapid eye-movement) or *paradoxical* sleep – so called because its EEG closely resembles the high-frequency, low-voltage, desynchronized patterns of the awake state. During a typical night's rest, a sleeping adult human cycles between SWS and REM sleep states at ~90-min. intervals, accumulating

Figure 1. Cortical activity for a cat transitioning from awake to SWS to REM sleep, as reported by Destexhe *et al.* (see Figure 5 of [2]). LFP is the local field potential or cortical EEG. The abrupt change from SWS to REM is marked by reappearance of *eye movements* (EOG, electrooculogram) and *loss of muscle tone* (EMG, electromyogram). Prior to transition there are pronounced increases in both low-frequency power and space-constant (correlation length for EEG fluctuations). [Copyright 1999 by Society for Neuroscience; reprinted with permission]

a total of 4 to 6 SWS–REM cycles. The sleeping cat shows similar patterns of SWS–REM alternation, but with a faster cycling time of ~ 20 min.

These opposed phases of sleep are well illustrated by the 16-min recording of the local field potential (LFP, the on-cortex EEG), shown in Figure 1, for a cat transitioning from wake into slow-wave sleep and then into REM sleep. The wake and REM stages show high-frequency, low-amplitude voltage fluctuations, while the intervening SWS stage is distinguished by low-frequency activity whose amplitude

and spatial correlation grow markedly with time, only to collapse dramatically at the transition into REM. We will argue in this paper that this remarkably abrupt change in cortical activity is well modelled as a first-order phase transition in the average membrane voltage of the population of excitatory neurons. Such a model provides a natural explanation for the gross changes in EEG characteristics seen during the SWS→REM transition, namely the slow growth, followed by abrupt collapse, in low-frequency fluctuation power and coherence.

The paper is structured as follows. We explain the heritage and mean-field philosophy underpinning the model, then present a mathematical description for the cortex in terms of convolution integrals of spike-activity fluxes impinging on the neuron dendrite and cell membrane. We transform the integral equations to differential equations in order to locate the steady states of the cortex, and to quantify their stability with respect to small perturbations about equilibrium. We introduce white-noise driving from the sub-cortex, and simplify the system equations by adopting an adiabatic approximation that recognises a separation of time-scales between “fast” rapidly-evolving synaptic events and the relatively slow evolution of neuron voltages registered at the soma. While this simplification effectively eliminates cortical dynamics, it allows us to focus on the near-equilibrium stochastic behaviours of the cortex. We bring sleep to our model by identifying two major modulatory effects that are important for sleep: the slow reduction in cell resting voltage brought on by the gradual accumulation of adenosine and other “somnogens” during waking hours; and the alterations in synaptic efficiency caused by the neuromodulator acetylcholine (ACh), a substance that is completely absent in SWS, yet abundant in REM. This allows us to design a theoretical sleep cycle as an “elliptical tour” over a manifold of cortical steady states. We linearise the stochastic differential equations about steady state, then compute exact expressions for fluctuation statistics: power, correlation time, and spectral distribution, tracing their evolution as a function of position on the elliptical sleep cycle. We test these theoretical predictions against stochastic simulation runs, and conclude by comparing our findings with clinical recordings for a human sleeper.

2. Theoretical Model for the Sleeping Cortex

2.1. MEAN-FIELD MODEL

Rather than considering the detailed interactions of individual neurons in the cortex, we adopt a mean-field philosophy that describes the average behaviours of populations of cooperating excitatory and inhibitory neurons. We picture the cortex as a 2-D homogeneous collection of *macrocolumns*: aggregates of approximately 100 000 neurons, each aggregate occupying a cortical volume of $\sim 1 \text{ mm}^3$ that defines the spatial extent over which cortical parameters are averaged (see Figure 2).

While our approach builds on, and freely borrows ideas from, earlier cortical-continuum models developed by Freeman [4], Wright and Liley [23], Liley *et al.*

Figure 2. Schematic “wiring diagram” for a cortical macrocolumn showing two excitatory neurons (triangles) and two inhibitory neurons (circles). Total number of neurons per macrocolumn is $\sim 10^5$. The numeric labels identify synaptic connection types which can be *within* macrocolumn: ϕ_{jk}^β (1...4); from *other* macrocolumns: ϕ_{ek}^α (5, 6); and *subcortical*: ϕ_{ek}^{sc} (7, 8). [For clarity, subcortical connections ϕ_{ik}^{sc} (9, 10) are not shown.]

[10], Robinson *et al.* [14], and Rennie *et al.* [13], to our knowledge this is the first mean-field formulation that attempts to describe the gross changes in brain electrical activity for the cycles of *natural* sleep. The present model is similar in form and philosophy to that developed previously by the authors to describe the abrupt “anaestheto-dynamic” transition into unconsciousness for a cortex subdued by general anaesthetic agent ([15–18]; see [19] for an overview), albeit with an obvious and interesting contrast: here we are concerned with a natural, self-generated “rousing” transition from deep sleep (SWS) to an activated cortical state (REM sleep).

Cortical and scalp potentials are primarily generated by the activity of excitatory neurons. This is because excitatory neurons tend to have their dendrites aligned parallel to each other and perpendicular to the scalp [11], whereas inhibitory neurons are smaller and have a more random orientation. Our working assumption is that the scalp-measured EEG is proportional to V_e , the macrocolumn-averaged soma voltage of the excitatory neural population, and that the ac component of the EEG

signal is generated by fluctuations in V_e about a steady-state value. We now develop equations of motion for V_e and V_i , the soma voltages for the excitatory and inhibitory neural populations.

2.2. INTEGRAL EQUATIONS FOR THE MACROCOLUMN

In the absence of synaptic inputs, the soma voltage of neuron population k (where $k = e$ for the excitatory population, and $k = i$ for the inhibitory population) will sit at a *resting voltage* $V_k^{\text{rest}} \approx -64$ mV. This negative potential (cell interior negative relative to the surrounding ionic sea) is generated by the action of ion pumps that maintain Na^+ and K^+ concentration differentials across the cell membrane. Any spike activity invading the dendritic tree will be integrated at the soma, imposing a time-dependent perturbation about V_k^{rest} :

$$V_k(t) = V_k^{\text{rest}} + \int_{-\infty}^t L_k(t-t')[E_k(t') + I_k(t')] dt', \quad k = e, i \quad (1)$$

where $L_k(t)$ is the impulse response of the soma (defined below in Eq. (7)), and the $E_k(t)$ and $I_k(t)$ terms are, respectively, the excitatory and inhibitory voltage inputs to the soma “capacitor”. More precisely, $E(t)$ represents the dendritically-integrated accumulation of excitatory post-synaptic potentials (PSPs) that tend to raise the V_k soma voltage, making the cell more likely to fire; while $I(t)$ is the accumulation of inhibitory PSPs whose effect is to lower the soma voltage and reduce the likelihood of firing. These E and I input terms are expressed as the product of a synaptic strength ρ [units: mV·s] with an input flux rate Φ [spikes/s],

$$E_k(t) = \rho_e \psi_{ek}(t) \Phi_{ek}(t), \quad (\rho_e > 0) \quad (2)$$

$$I_k(t) = \rho_i \psi_{ik}(t) \Phi_{ik}(t), \quad (\rho_i < 0) \quad (3)$$

Note that the “flow of action” implied by our double-subscripting is left-to-right, thus Φ_{ek} is to be read $\Phi_{e \rightarrow k}$, and indicates the rate of transmission of PSPs *from* an excitatory source *to* a neuron of type k .

The ψ_{jk} factors appearing in Eqs. (2–3) are dimensionless weighting functions that scale the effectiveness of the Φ_{jk} input flux in proportion to the difference between the cell voltage V_k of the receiving neuron and the relevant ionic reversal potential V_j^{rev} [10, 13],

$$\psi_{jk}(t) = \frac{V_j^{\text{rev}} - V_k(t)}{V_j^{\text{rev}} - V_k^{\text{rest}}}. \quad (4)$$

In the present work we take $V_e^{\text{rev}} = 0$ mV, appropriate for AMPA (excitatory) receptors, and $V_i^{\text{rev}} = -70$ mV for GABA (inhibitory) receptors (see Table I for a full list of model constants). Graphs of ψ_{ek} and ψ_{ik} are shown in Figure 3.

Table I. Model constants for the neural macrocolumn. Subscript label k means destination cell can be either of type e (excitatory) or i (inhibitory)

Symbol	Description	Value	Unit
$\tau_{e,i}$	membrane time constant	0.050, 0.050	s
$V_{e,i}^{\text{rev}}$	cell reversal potential	0, -70	mV
$V_{e,i}^{\text{rest}}$	cell resting potential	-64, -64	mV
$\rho_{e,i}$	synaptic gain	$(1.00, -1.05) \times 10^{-3}$	mV.s
$N_{ee,ei}^{\alpha}$	$e \rightarrow k$ connections from other macrocolumns	3710, 3710	–
$N_{ee,ei}^{\beta}$	local $e \rightarrow k$ synaptic connections	410, 410	–
$N_{ie,ii}^{\beta}$	local $i \rightarrow k$ synaptic connections	800, 800	–
$N_{ee,ei}^{\text{sc}}$	subcortical $e \rightarrow k$ synaptic connections	50, 50	–
$N_{ie,ii}^{\text{sc}}$	subcortical $i \rightarrow k$ synaptic connections	50, 50	–
v	axonal conduction speed	9	m s^{-1}
$\Lambda_{ee,ei}$	axonal inverse-length scale	40, 40	m^{-1}
$\gamma_{ee,ei}$	rate constant for $e \rightarrow k$ synaptic input	70, 70	s^{-1}
$\gamma_{ie,ii}$	rate constant for $i \rightarrow k$ synaptic input	58.6, 58.6	s^{-1}
$Q_{e,i}^{\text{max}}$	maximum firing rate for sigmoid function	30, 60	s^{-1}
$\theta_{e,i}$	inflection-point voltage for sigmoid function	-58.5, -58.5	mV
$\sigma_{e,i}$	sigmoid width	4, 6	mV

Each incoming spike (action potential) releases a quantum of neurotransmitter into the synaptic cleft, altering the dendritic conductance and causing a momentary change in voltage in the postsynaptic neuron as a result of charge transfer through the opened ion channels. Following Tuckwell [20], the time-course for this momentary postsynaptic potential (PSP) is well represented by an “alpha”-function impulse

Figure 3. Flux weighting functions defined in Eq. (4). For our modelling we set $V_e^{\text{rest}} = V_i^{\text{rest}} \approx -64$ mV; consequently the upper graph (a) describes both ψ_{ee} and ψ_{ei} ; similarly the lower graph (b) describes ψ_{ie} and ψ_{ii} . Both graphs pass through unity when $V_k = V_k^{\text{rest}}$ (indicated with circled cross-hairs), and cross zero at the V_k^{rev} reversal potentials.

response $H(t)$ (defined below in Eq. (8)), so we write the total excitatory (inhibitory) input flux Φ_{ek} (Φ_{ik}) at neuron k as the temporal convolution of the dendrite impulse response H with the per-synapse spike-rate ϕ_{ek} (ϕ_{ik}), scaled by the number of one-way $e, i \rightarrow k$ synaptic connections N_{ek} (N_{ik}),

$$\Phi_{ek}(t) = \int_{-\infty}^t H_{ek}(t-t') \left[\underbrace{N_{ek}^{\beta} \phi_{ek}^{\beta}(t')}_{\text{local}} + \underbrace{\phi_{ek}^{\text{sc}}(t')}_{\text{subcortical}} + \underbrace{N_{ek}^{\alpha} \phi_{ek}^{\alpha}(t')}_{\text{distant}} \right] dt' \quad (5)$$

$$\Phi_{ik}(t) = \int_{-\infty}^t H_{ik}(t-t') [N_{ik}^{\beta} \phi_{ik}^{\beta}(t') + \phi_{ik}^{\text{sc}}(t')] dt' \quad (6)$$

in which the superscripts identify distinct spike-rate contributions from *local* (superscript β : *within* macrocolumn), *distant* (α : cortico-cortical excitatory connections from *other* macrocolumns), and *subcortical* (sc: input from subcortical structures such as thalamus and brain-stem). Note that there are no distant inhibitory connections from other macrocolumns, hence the lack of a cortico-cortical ϕ_{ik}^{α} term in Eq. (6).

The impulse response functions $L_k(t)$ for the soma and $H_{jk}(t)$ for the dendrite appearing in Eqs. (1) and (5), (6) are modelled respectively as an exponential decay with membrane time-constant τ_k , and an alpha-function pulse with dendrite rate-constant γ_{jk} :

$$L_k(t) = \frac{1}{\tau_k} \exp[-t/\tau_k], \quad t \geq 0 \quad (\text{soma response}) \quad (7)$$

$$H_{jk}(t) = t \gamma_{jk}^2 \exp[-t \gamma_{jk}], \quad t \geq 0 \quad (\text{dendrite response}) \quad (8)$$

with $L_k(t) = H_{jk}(t) = 0$ for $t < 0$; see Figure 4. We note that both the membrane (7) and the dendrite (8) impulse-response functions have been normalised to have unit area on the interval $0 \leq t < \infty$.

By including two distinct impulse response functions – one for the dendrite response $H_{jk}(t)$ (Eq. (8)) and another for the overall membrane response $L_k(t)$ (Eq. (7)) – we have constructed a “two-compartment” neuron model in which the dendritic inputs evolve on a time-scale that is typically *faster* than that of the soma response: $\gamma_{jk}^{-1} < \tau_k$. In this paper we will examine the simplified system that results from the extreme *adiabatic* or “slow-membrane” assumption $\gamma_{jk}^{-1} \ll \tau_k$. This simplification will be discussed in Section 2.5 below.

2.3. DIFFERENTIAL EQUATIONS FOR THE MACROCOLUMN

Because we wish to locate the steady states of our model cortex, and then quantify their stability properties, we transform the integral Eqs. (1) and (5), (6) to differential form. Taking the time-derivative of the $k = e$ and $k = i$ convolutions indexed

Figure 4. Impulse response functions for (a) soma and (b) dendrite. The soma time-constant is $\tau_k = 50$ ms (Eq. 7) and the dendrite rate-constant is $\gamma_{jk} = 200 \text{ s}^{-1}$ (Eq. 8), giving a time-to-peak $1/\gamma_{jk} = 5$ ms. In the adiabatic limit, we assume $\tau_k \gg \gamma_{jk}^{-1}$.

by Eq. (1) (using the calculus theorem for differentiation under an integral with time-dependent end-points; e.g., see p. 77 of [1]), we obtain a pair of first-order equations of motion for $V_{e,i}$, the macrocolumn-average excitatory and inhibitory soma voltages:

$$\tau_e \frac{dV_e}{dt} = V_e^{\text{rest}} - V_e(t) + \rho_e \psi_{ee}(t) \Phi_{ee}(t) + \rho_i \psi_{ie}(t) \Phi_{ie}(t) \quad (9)$$

$$\tau_i \frac{dV_i}{dt} = V_i^{\text{rest}} - V_i(t) + \rho_e \psi_{ei}(t) \Phi_{ei}(t) + \rho_i \psi_{ii}(t) \Phi_{ii}(t). \quad (10)$$

Twice-differentiating the four dendrite convolutions of Eqs. (5) and (6) produces four second-order differential equations for the rate-change of the Φ_{jk} input-flux terms. The equation pair for inputs into the excitatory population read

$$\left(\frac{d}{dt} + \gamma_{ee} \right)^2 \Phi_{ee} = [N_{ee}^\alpha \phi_{ee}^\alpha(t) + N_{ee}^\beta Q_e(t) + \phi_{ee}^{\text{sc}}(t)] \gamma_{ee}^2 \quad (11)$$

$$\left(\frac{d}{dt} + \gamma_{ie} \right)^2 \Phi_{ie} = [N_{ie}^\beta Q_i(t) + \phi_{ie}^{\text{sc}}(t)] \gamma_{ie}^2 \quad (12)$$

and the corresponding pair for inhibitory-population input read

$$\left(\frac{d}{dt} + \gamma_{ii} \right)^2 \Phi_{ii} = [N_{ii}^\beta Q_i(t) + \phi_{ii}^{\text{sc}}(t)] \gamma_{ii}^2 \quad (13)$$

$$\left(\frac{d}{dt} + \gamma_{ei}\right)^2 \Phi_{ei} = [N_{ei}^\alpha \phi_{ei}^\alpha(t) + N_{ei}^\beta Q_e(t) + \phi_{ei}^{\text{SC}}(t)] \gamma_{ei}^2. \quad (14)$$

Consistent with our spatial coarse-graining approach, the within-macrocolumn fluxes $\phi_{jk}^\beta(t)$ appearing in Eqs. (5) and (6) have been replaced in Eqs. (11–14) by $Q_j(t)$, an empirical sigmoidal mapping from membrane voltage to neuronal firing rate [13],

$$Q_{e,i}(t) = \frac{Q_{e,i}^{\max}}{1 + \exp[-C(V_{e,i}(t) - \theta_{e,i})/\sigma_{e,i}]} \quad (15)$$

where $\theta_{e,i}$ is the population-average threshold voltage for firing, $\sigma_{e,i}$ is a measure of its spread, and $Q_{e,i}^{\max}$ is the maximal firing rate for the macrocolumn. The constant $C = \pi/\sqrt{3}$, allowing $\sigma_{e,i}$ to be interpreted as the standard deviation of the sigmoid-derivative curve $dQ_{e,i}/dV_{e,i}$.

Following Robinson *et al.* [14], the long-range excitatory flux ϕ_{ek}^α in (11) and (14) are modelled as damped waves generated by sources $Q_e(\vec{r}, t)$, obeying the 2-D wave equation,

$$\left[\left(\frac{d}{dt} + v\Lambda_{ek}\right)^2 - v^2\nabla^2\right]\phi_{ek}^\alpha(\vec{r}, t) = (v\Lambda_{ek})^2 Q_e(\vec{r}, t) \quad (16)$$

where v is the average axonal conduction speed, and Λ_{ek} is an inverse-length scale for the long-range connections. The wave equation is stated here for completeness, and is relevant to cortical spatio-temporal dynamics. However, because the present work focuses on the homogeneous adiabatic limit, the wave equation for distant fluxes can be collapsed to the direct equality $\phi_{ek}^\alpha(t) = Q_e(t)$.

Each of the four subcortical sources ϕ_{jk}^{SC} in (11–14) is modelled as a mean level of spike-rate input with additive Gaussian white noise:

$$\phi_{jk}^{\text{SC}}(t) = s_{jk} Q_j^{\max} + \sqrt{s_{jk} Q_j^{\max}} \cdot \xi_m(t), \quad m = 1 \dots 4 \quad (17)$$

where the four $\xi_m(t)$ stochastic terms are independent, zero-mean, delta-correlated white-noise sources:

$$\langle \xi_m(t) \rangle = 0 \quad (18)$$

$$\langle \xi_m(t) \xi_n(t') \rangle = \delta_{mn} \delta(t - t') \quad (19)$$

and the s_{jk} are dimensionless scale-factors that allow us to vary the level of subcortical driving. This phenomenological inclusion of white-noise stimulation is motivated by physiological evidence that the cortex requires a continuous background “wash” of input noise to function normally: for over 50 years it has been

known that the conscious state can only be maintained while the cortex receives an ongoing flux of non-specific excitatory input from the reticular activating system within the brainstem [8]. This brainstem input can be modelled as the sum of many individual Poisson-distributed neuronal processes, which, by the central limit theorem, we approximate as Gaussian-distributed noise.

2.4. THE SLEEPING CORTEX

The 90-min. SWS–REM cycling of natural sleep represents a modulation of the cortical parameters on a time-scale that is vastly slower – by about five orders of magnitude – than the ~ 50 -ms relaxation time of our “slow neuron” macrocolumn. We now describe how these extremely slow sleep-induced changes in cortical milieu are incorporated into the macrocolumn equations.

There exists a complex system of brainstem neuromodulators whose concentrations change markedly between the awake, SWS and REM states. In the interests of simplicity, our sleep model will assume that the cortical state is controlled by just two significant neurochemical effects: (a) *adenosine fatigue* and (b) *acetylcholine activation*.¹

(a) During waking hours, adenosine and other *somnogens* or “fatigue agents”, steadily accumulate in the cortex [3]. Then, during subsequent recovery sleep, these somnogen concentrations slowly diminish. Adenosine acts to *decrease* cortical activity by increasing a K^+ leak-current, thus lowering the neuron resting voltage V_e^{rest} , making the neuron less likely to fire [6].

(b) Acetylcholine (ACh) is an excitatory neuromodulator that is abundant during REM, and absent during other stages of sleep [3]. Thus we identify REM sleep with periods of high ACh concentration, and SWS with periods of low ACh. Acetylcholine activates the cortex by reducing the K^+ leak-current, so raising V_e^{rest} and making the cell more excitable. But in addition to its adenosine-antagonising excitatory action, ACh has the paradoxical effect of simultaneously *reducing* the amplitude of the excitatory PSP [6]. In our model, this corresponds to a reduction in ρ_e , the excitatory synaptic gain.

Taking both (a) and (b) into account, we apply the following mappings to Eqs. (9), and (10):

$$V_e^{\text{rest}} \rightarrow V_e^{\text{rest}} + \Delta V_e^{\text{rest}} \quad (20)$$

$$\rho_e \rightarrow \lambda_{\text{ACh}} \rho_e \quad (21)$$

where λ_{ACh} is a dimensionless scale factor; an *increase* in λ_{ACh} corresponds to a *decrease* in ACh concentration. (Note that the Eq. (20) additive change to the

¹Serotonin is another neuromodulator that regulates behavioural state, but its modes of action are complex and remain poorly understood [7]. While early studies indicated serotonergic involvement in the production of sleep, more recent observations show that serotonin actually promotes wakefulness [3]. For these reasons we have not attempted to include serotonin effects in our sleep model.

Figure 5. Distribution of steady-state cortical voltages over the sleep domain. The vertical axis is the equilibrium excitatory soma voltage V_e ; the sleep domain is defined by a “fatigue” axis ΔV_e^{rest} and a “synaptic efficiency” axis λ_{ACh} . There are three steady-state values for V_e within the green $\supset$ -shaped region adjoining the left edge, and single steady-states elsewhere. The arrowed trajectory shows an elliptical tour (as viewed from above – see Figure 6) on the manifold, commencing at the point marked (+), then making a jump transition (dashed vertical line) from SWS into REM at the point marked $\odot$.

excitatory resting voltage is applied only to the V_e^{rest} term of Eq. (9), and not to the denominators of the ψ_{je} weighting functions of Eq. (4): for simplicity, we choose to leave normalizations for these reversal-potential functions unchanged.) These mappings (20, 21) define our sleep domain (illustrated in Figures 5 and 6) in terms of a “fatigue” axis ΔV_e^{rest} and a “synaptic-gain” axis λ_{ACh} . Because the neuron resting voltage is affected by both neurochemicals, the position on the ΔV_e^{rest} axis at any given time will depend on the concentrations of ACh and adenosine.

2.5. THE “SLOW NEURON” ADIABATIC LIMIT

The “slow neuron” adiabatic simplification assumes that, relative to voltage changes occurring at the soma of the neuron, the synaptic-input events at the dendrite are fast and rapidly equilibrating. This means that the synaptic time-scale, γ_{jk}^{-1} is taken to be much smaller than the membrane time-constant τ_k (see Figure 4). Although the adiabatic limit suppresses cortical dynamics, it allows us to investigate the dramatic changes in the noise-perturbed near-equilibrium “statics” as the cortical system approaches a change of sleep state. (In a subsequent paper [22] we will report on the dynamical behaviours that emerge when we remove the “fast-synapse, slow-soma” restriction.)

Figure 6. Bird's-eye view of cortical manifold of Figure 5. In this view, the $\supset$ -shaped region in Figure 5 showing the locus of manifold turning points sharpens into the green $>$ -shaped cusp. The elliptical tour starts in SWS at $+$, then makes an abrupt transition, out of the plane of the page, into REM at $\odot$.

To implement the homogeneous adiabatic limit, we set the time- and space-derivatives in Eqs. (11–14) and (16) to zero, but retain the subcortical noise terms. We then solve for the four synaptic fluxes, expressing each of the Φ_{jk} as a noise-driven variation about its steady-state value, and substitute these back into the soma equations of motion (9) and (10). The result is a pair of coupled first-order stochastic differential equations for V_e (22) and V_i (23), described below.

2.6. LANGEVIN EQUATIONS FOR THE SLEEPING CORTEX

Combining the ideas from Sections 2.3–2.5, the equations of motion for the sleep-cycling cortex in the homogenous, slow-neuron limit can be written as a pair of coupled Langevin equations,

$$dV_e/dt = A_e(V_e, V_i) + \Gamma_e(t) \quad (22)$$

$$dV_i/dt = A_i(V_e, V_i) + \Gamma_i(t) \quad (23)$$

where the $A_{e,i}$ are *drift* terms,

$$A_e(V_e, V_i) = [V_e^{\text{rest}} + \Delta V_e^{\text{rest}} - V_e + \lambda_{\text{ACh}} \rho_e \psi_{ee}(V_e) \Phi_{ee}(V_e) + \rho_i \psi_{ie}(V_e) \Phi_{ie}(V_i)]/\tau_e \quad (24)$$

$$A_i(V_e, V_i) = [V_i^{\text{rest}} - V_i + \lambda_{\text{ACh}} \rho_e \psi_{ei}(V_i) \Phi_{ei}(V_e) + \rho_i \psi_{ii}(V_i) \Phi_{ii}(V_i)] / \tau_i \quad (25)$$

and the $\Gamma_{e,i}$ *diffusion* terms are the Gaussian-distributed subcortical noises entering the e,i macrocolumn populations,

$$\Gamma_e(t) \equiv b_{ee} \xi_1(t) + b_{ie} \xi_2(t) \quad (26)$$

$$\Gamma_i(t) \equiv b_{ei} \xi_3(t) + b_{ii} \xi_4(t) \quad (27)$$

with b_{jk} white-noise scale factors given by

$$b_{ek}(V_k) = \lambda_{\text{ACh}} \rho_e \psi_{ek}(V_k) \sqrt{\langle \phi_{ek}^{\text{SC}} \rangle} / \tau_k \quad (28)$$

$$b_{ik}(V_k) = \rho_i \psi_{ik}(V_k) \sqrt{\langle \phi_{ik}^{\text{SC}} \rangle} / \tau_k. \quad (29)$$

The Φ_{jk} flux inputs in Eqs. (24) and (25) are homogeneous steady-state values determined from Eqs. (11–14) and (16):

$$\Phi_{ek}(V_e) = (N_{ek}^\alpha + N_{ek}^\beta) \mathcal{Q}_e(V_e) + \langle \phi_{ek}^{\text{SC}} \rangle \quad (30)$$

$$\Phi_{ik}(V_i) = N_{ik}^\beta \mathcal{Q}_i(V_i) + \langle \phi_{ik}^{\text{SC}} \rangle \quad (31)$$

Our motivation for writing down the Langevin equations for the macrocolumn is that, provided the cortex never deviates far from homogeneous equilibrium, we can write *exact* expressions for the linearised EEG fluctuation covariance, autocorrelation function, and spectral power, then compare how well these theoretical measures agree with clinical EEG recordings across the SWS→REM sleep transition.

2.7. FLUCTUATION COVARIANCE, AUTOCORRELATION AND SPECTRUM

Writing $V_{e,i}(t) = V_{e,i}^o + \delta V_{e,i}(t)$, we linearize the Langevin Eqs. (22) and (23) about $V_{e,i}^o$ steady state to obtain a two-variable *Ornstein–Uhlenbeck* (Brownian motion) description for $\delta V_{e,i}$, the small fluctuations in e,i soma voltages:

$$\frac{d}{dt} \begin{bmatrix} \delta V_e \\ \delta V_i \end{bmatrix} = -\mathbf{A} \begin{bmatrix} \delta V_e \\ \delta V_i \end{bmatrix} + \begin{bmatrix} \Gamma_e(t) \\ \Gamma_i(t) \end{bmatrix} \quad (32)$$

which we can write as

$$\frac{d}{dt} \begin{bmatrix} \delta V_e \\ \delta V_i \end{bmatrix} = -\mathbf{A} \begin{bmatrix} \delta V_e \\ \delta V_i \end{bmatrix} + \sqrt{\mathbf{D}} \begin{bmatrix} \xi_e(t) \\ \xi_i(t) \end{bmatrix} \quad (33)$$

where the elements of the *diffusion matrix* $\mathbf{D}$ are calculated from the covariances of the noise column-vector $\vec{\Gamma} = [\Gamma_e \ \Gamma_i]^T$,

$$\mathbf{D} \delta(t - t') = \langle \vec{\Gamma}(t) \vec{\Gamma}(t')^T \rangle \quad (34)$$

Applying the delta-correlation property (19), we obtain a constant 2×2 diagonal diffusion matrix,

$$\mathbf{D} = \begin{bmatrix} b_{ee}^2 + b_{ie}^2 & 0 \\ 0 & b_{ei}^2 + b_{ii}^2 \end{bmatrix}_{\text{eq.}} \quad (35)$$

with the “eq.” subscript indicating that the matrix elements are to be evaluated at equilibrium. The 2×2 *drift matrix* $\mathbf{A}$ is the *negative* of the Jacobian whose elements are formed by computing the partial derivatives of the (24) and (25) $A_{e,i}$ drifts,

$$A_{jk} = - \left. \frac{\partial A_j}{\partial V_k} \right|_{\text{eq.}} \quad (36)$$

Now that the macrocolumn fluctuations have been expressed in linearized constant-matrix form, we can make use of some well-established stochastic calculus results (e.g., p.109 of [5]) to write down exact expressions for (i) the stationary *covariance matrix* Σ :

$$\Sigma = \frac{\det(\mathbf{A})\mathbf{D} + [(\mathbf{A}) - \text{tr}(\mathbf{A})\mathbf{I}] \mathbf{D} [(\mathbf{A}) - \text{tr}(\mathbf{A})\mathbf{I}]^T}{2 \text{tr}(\mathbf{A}) \det(\mathbf{A})} \quad (37)$$

where $\mathbf{I}$ is the 2×2 identity matrix, $\det(\cdot)$ and $\text{tr}(\cdot)$ are determinant and trace operators respectively; (ii) the *autocorrelation matrix* $\mathbf{G}(\tau)$

$$\mathbf{G}(\tau) = \exp[-\mathbf{A} \tau] \Sigma, \quad \tau \geq 0 \quad (38)$$

from which we can compute the generalized *correlation time* T for the δV_e fluctuations

$$T = \frac{1}{\Sigma_{11}} \int_0^\infty \mathbf{G}(\tau) d\tau = \frac{1}{\Sigma_{11}} [\mathbf{A}^{-1} \Sigma]_{11} \quad (39)$$

where Σ_{11} is the δV_e variance (i.e., the 1, 1 element of the Σ covariance matrix (37); and (iii) the *spectral density matrix* $\mathbf{S}(\omega)$, obtained by Fourier transforming the autocorrelation matrix (Wiener–Khinchin theorem):

$$\begin{aligned} \mathbf{S}(\omega) &= \frac{1}{2\pi} \int_{-\infty}^\infty \mathbf{G}(\tau) e^{-i\omega\tau} d\tau \\ &= \frac{1}{2\pi} (\mathbf{A} + i\omega\mathbf{I})^{-1} \mathbf{D} (\mathbf{A}^T - i\omega\mathbf{I})^{-1}. \end{aligned} \quad (40)$$

Extracting the 1,1 element of the $\mathbf{S}(\omega)$ matrix gives us an explicit expression for the spectral density of the δV_e fluctuations,

$$S_{11}(\omega) = \frac{1}{2\pi} \frac{A_{12}^2 D_{22} + A_{22}^2 D_{11} + D_{11} \omega^2}{(\det(\mathbf{A}) - \omega^2)^2 + \text{tr}(\mathbf{A})^2 \omega^2}. \quad (41)$$

We briefly foreshadow a surprising prediction arising from these linearized equations. Note that the denominator of the covariance matrix (37) is directly proportional to the determinant of the 2×2 drift matrix $\mathbf{A}$. But since the determinant of any matrix can always be expressed as the product of its eigenvalues (e.g., see p. 88 of [21]), we can write $\det(\mathbf{A}) = \lambda_1 \lambda_2$, where $\lambda_{1,2}$ are the two eigenvalues of $\mathbf{A}$. The dominant eigenvalue of the pair characterises the rate of decay (or growth) of small perturbations towards (or away from) steady state, and therefore determines state stability. We find that in the vicinity of a phase-change for the macrocolumn, such as the point of abrupt transition from a low- to a high-firing state (or vice versa), the dominant eigenvalue approaches zero, and becomes *precisely zero* at the point of phase transition. Therefore linear theory predicts that the variance of the noise-driven fluctuations will grow strongly near the transition, diverging to infinity at the transition. The spectral density equation (41) tells us that this divergence will be “coloured” – the spectral power will be increasingly biased towards dc, and will diverge to infinity at zero frequency: $S_{11}(\omega) \propto 1/\omega^2$. This means that as the macrocolumn approaches a phase jump, very low frequency fluctuations will grow without limit, with the fluctuations becoming infinitely slow at the jump. This is the *critical slowing down* phenomenon that is characteristic of many thermodynamic phase transitions in physics. Our sleep model asserts that the growth – followed by abrupt collapse – in correlated low-frequency power in the cortex of the sleeping cat in Figure 1 (and in a sleeping human: see Figure 10) can be described in terms of a first-order phase transition from SWS into REM.

3. Theoretical Predictions and Clinical Results

3.1. SLEEP STATES ON AN EQUILIBRIUM MANIFOLD

In order to locate the steady states for the cortical model, we set all time- and space-derivatives in Eqs. (9–14) and (16) to zero, and set the four noises $\xi(t)$ in Eq. (17) to zero also, then solve numerically to find the stationary values $V_{e,i}^o$ as a function of the sleep-domain parameters ΔV_e^{rest} and λ_{ACh} . The resulting 3-D manifold of steady states is displayed in Figure 5.

Although most of the manifold displays a single equilibrium value V_e^o , for $\Delta V_e^{\text{rest}} < +1$ mV there is an S-shaped “fold” that contains *three* steady states. A linear stability analysis predicts that within this multi-root region, the mid-branch root will be *unstable* with respect to small perturbations, while the top and bottom branches will be stable.

Draped over the Figure 5 manifold we impose an elliptical tour (see Figure 6) whose orientation and shape are designed to be qualitatively consistent with our picture of the cortical changes experienced by a sleeper who cycles from SWS to REM and back. The location marked “+” is at a hyperpolarised, low-firing position on the bottom branch, presumed to be SWS. As adenosine levels diminish, the resting voltage will rise slightly, causing the tour to encounter the bottom-branch turning point, forcing an immediate jump transition into a cortically-activated state, presumed to be REM, marked “⊙” on the high-firing top branch. Acetylcholine (ACh) levels rapidly increase in REM, leading to simultaneous reduction in λ_{ACh} (i.e., reduction in synaptic efficiency) and increase in V_e^{rest} . At some point, ACh production ceases and the hyperpolarising influence of the residual adenosine pushes the tour back into deepening stages of SWS, allowing the cycle to repeat. (Although our proposed tour forms a *closed* elliptical cycle, in fact we would expect the progressive decreases in adenosine to cause the tour to drift to the right, transforming the ellipse into a 2-D “corkscrew” or epicycle. Here we choose to ignore this complication.)

3.2. STOCHASTIC SIMULATIONS

Figure 7 shows the result of a 3-second numerical simulation of the nonlinear Langevin equations (22) and (23) for a macrocolumn started in a low-firing (hyperpolarised) equilibrium state close to the critical point. The continuous white-noise buffeting of the macrocolumn causes the excitatory soma voltage to fluctuate about the $V_e^{\text{o,Bot}} \approx -64.4$ mV steady-state value that corresponds to an excitatory firing rate of $Q_e^{\text{o,Bot}} \approx 1.8$ spikes/s. After about 2 s, the fluctuations are of sufficient magnitude to cause the macrocolumn to spontaneously and rapidly switch to the high-firing state $V_e^{\text{o,Top}} \approx -53.9$ mV, $Q_e^{\text{o,Top}} \approx 26.6$ s⁻¹.

We focus attention on the fluctuations $\delta V_e(t)$ by subtracting off the equilibrium voltage, and in Figure 7(b) we see the remarkable change in the amplitude and spectral distribution of the fluctuation energy: prior to transition the voltage excursions are typically slow, correlated, and of large amplitude; but after transition the fluctuations have lost their low-frequency correlated character, showing more rapid excursions of much smaller amplitude. These “before” and “after” descriptions are a good qualitative match to what is seen in EEG recordings for a sleeper (cat or human) that moves from slow-wave sleep to REM sleep.

How well does the linearised Ornstein–Uhlenbeck (OU) theory (Eqs. (37–41)) predict the behaviour of the coupled nonlinear Langevin Equations (22–23)? Figure 8a provides a specific test of the OU prediction (37) for the standard deviation for the δV_e fluctuations about equilibrium, $\sigma_{11} = \sqrt{\Sigma_{11}}$, for a slow clockwise journey through the first one-eighth of the Figure 6 ellipse. The journey started on the bottom (low-firing) branch at the position marked “+” in Figures 5 and 6. The black curves in Figure 8(a) give the theoretical $\pm 2\sigma_{11}$ limits, and display a flaring “cornucopia” (trumpet shape) that diverges at 0.097 cycle (ellipse angle $\theta \approx 35.08^\circ$) – this is the theoretical jump point into REM, the instant at which the

Figure 7. Stochastic simulation of the nonlinear Langevin Eqs. (22) and (23) for a macrocolumn sitting on the bottom (Bot) branch at ellipse angle $\theta = 34^\circ$ (measured clockwise from the + starting point shown in Figure 6), close to the cusp at $\theta_\odot \approx 35.08^\circ$. After about 2 sec, the excitatory soma voltage crosses the unstable mid-branch and rapidly converges towards the top branch. Note the dramatic loss of low-frequency fluctuation energy after transition. (a) Soma voltage V_e vs time. (b) Soma fluctuations δV_e versus time. This ac signal is computed from the dc trend in (a) by forming the differences $V_e - V_e^{o, \text{Bot}}$ (before transition) and $V_e^{o, \text{Top}} - V_e$ (after transition), thus giving a rough approximation of what might be seen on an accoupled chart-recorder. *Simulation details:* Semi-implicit predictor-corrector (Euler-trapezium) vector algorithm (p. 502 of [9]); time-step $\Delta t = 1$ ms; driven by four independent subcortical white-noise sources with Eq. (17) scale-factor $s_{jk} = 0.5N_{jk}^{\text{sc}}$ for synaptic connectivity $N_{jk}^{\text{sc}} = 50$.

dominant eigenvalue λ_1 of the drift-matrix Jacobian goes to zero (see Figure 8b). Superimposed in grey verticals are the results of a series of simulation runs of the stochastic DEs (22–23) at 2251 finely-spaced positions on the ellipse between 0 and 0.125 cycle. Each simulation ran for 5 s, with a time resolution of $\Delta t = 1$ ms; the grey vertical lines show the maximum extent of fluctuation excursions registered during each run. As one might hope, we see that linearised theory gives an excellent match with numerical experiment – provided the fluctuations remain small. However, as we approach the critical point at 0.097 cycle, the macrocolumn becomes exquisitely sensitive to perturbations, and is increasingly likely to “jump early”. This is the source of the extremely large excursions seen near the horn of the cornucopia.

Figure 8. Fluctuation amplitude and eigenvalues for SWS $\rightarrow$ REM transition. The x -axis gives the location on the Figure 6 ellipse for a tour from $\theta = 0$ to $\theta = 45^\circ$ (i.e., cycle = 0 to 0.125). The critical angle $\theta_\odot$ is at ~ 0.097 cycle $\approx 35.08^\circ$. (a) The black curves show $\pm 2\sigma_{11}$ limits for δV_e , the voltage fluctuations about equilibrium, as predicted by *linearised* (Ornstein–Uhlenbeck) theory, with $\sigma_{11} = \sqrt{\Sigma_{11}}$ where variance Σ_{11} is the 1,1 element of the covariance matrix (37). (b) The surge in fluctuation amplitude arises because λ_1 , the dominant eigenvalue of the system Jacobian, tends to zero on approach to the critical point at ~ 0.097 cycle. The grey vertical lines in (a) are the results of 2251 separate 5-sec simulation runs of the *non-linearised* Langevin Eqs. (22) and (23). The first run was started on the bottom branch at ellipse angle $\theta = 0$; subsequent runs were positioned at $\theta = 0.02^\circ, 0.04^\circ, \dots, 45.0^\circ$. For each run, the largest positive and largest negative voltage excursions were recorded, then plotted as a vertical line joining the extrema. The very large excursions near the horn of the cornucopia occur when the macrocolumn jumps “early”, as happened in Figure 7. Note that the abrupt change in fluctuation activity is suggestive of the cat SWS $\rightarrow$ REM transition shown in Figure 1.

3.3. PREDICTIONS FOR EEG VARIANCE, CORRELATION TIME, SPECTRUM

Figure 9 shows the OU predictions for the changes in EEG fluctuation characteristics over the complete elliptical tour that serves as our idealised sleep cycle. The theoretical “EEG power” is the variance of the excitatory fluctuations given by Σ_{11} (Eq. (37)); the correlation time is computed from (39); and the spectral power fractions, computed using (41), were designed to match the frequency bands used by Destexhe’s group in their cat analysis of Figure 1 (apart from the high-band: we chose to use 47 Hz as the upper limit to allow comparison with the human sleeper

Figure 9. Predicted changes in EEG fluctuation characteristics for the phase-transition model of the sleep cycle: (a) variance of EEG signal, (b) correlation time, (c) fraction of EEG power within the 15–47-Hz band, and (d) within the 0.1–4-Hz band. Horizontal axis indicates position on the closed elliptical tour that starts (cycle = 0) and ends (cycle = 1) at the (+) label of Figures 5 and 6.

results shown in Figure 10). The high- and low-band power fractions are defined

$$F_{\text{hi}} = \int_{15}^{47} S_{11}(f) df / P_{\text{tot}} \quad (42)$$

$$F_{\text{lo}} = \int_{0.1}^4 S_{11}(f) df / P_{\text{tot}} \quad (43)$$

with $P_{\text{tot}} = \int_{0.1}^{47} S_{11}(f) df$.

The Figure 9 graphs make *four* testable predictions: (1) There will be a pronounced surge in total power and correlation time during the time leading up to the SWS→REM transition (graphs a,b: transition occurs at cycle ≈ 0.1); (2) this

Figure 10. Analysis of an EEG signal recorded from a human subject resting overnight in a sleep laboratory. (a) Fluctuation power, (b) correlation time, and (c) low- and high-band power fractions, all plotted as a function of elapsed time in hours. Sleep staging in (d) was done manually according to the classification rules of [12]. Key: +1 = REM; 0 = wake; (−1, −2) = light sleep; (−3, −4) = deep sleep (SWS). The power surge in SWS corresponds to maximally correlated fluctuations in time (here) and space (see Figure 1: “space constant”). Correlated activity is much reduced in REM sleep.

power surge will be dominated by low-frequency activity (graph d); (3) the high- and low-band power fractions will tend to vary in anti-phase throughout the sleeping cycle (compare c, d); (4) there will be a second, but less pronounced, power surge as the sleeper crosses the steepest part of the Figure 5 manifold, putatively exiting REM (at cycle ≈ 0.42) and cycling back into SWS.

Reviewing the Figure 1 cat record, we see encouraging confirmations of these qualitative predictions: the power surge prior to REM is primarily of a

low-frequency character, the low- and high-band power fractions vary in anti-phase, and the correlation *length*, which is expected to be a fair proxy for correlation *time*, is large in SWS and much reduced in REM sleep.

3.4. COMPARISON WITH CLINICAL RESULTS

For a final test of theory against experiment, we examine the EEG record of a human sleeper resting overnight in a sleep laboratory. The EEG was recorded from an electrode pair placed at C₄, F_{pz} scalp coordinates (International 10–20 system), sampled at 256 samples/s, and filtered to restrict the signal frequency range to 0.1–47 Hz. The time-series was analysed in 5-s epochs, and later smoothed, for display purposes, with a centred, sliding rectangular window of width 31 epochs (i.e., 155 s). Correlation time was determined by computing the autocorrelation function for each 5-s epoch, and measuring the time-lag required for the autocorrelation to decay to $1/e$ of its zero-lag maximum. The record was staged (classified) by a sleep technician who had access to EMG (electromyogram) and EOG (eye-movement) somnograph channels (not shown here), adhering to the standard rulebook of Rechtschaffen and Kales [12]. The staging is shown in Figure 10(d).

The first three sleep cycles are well-resolved. Focusing attention on the second cycle that commences in the second hour of sleep, we see both total power (a) and correlation time (b) steadily rise to a peak, then subside dramatically at the point of REM onset. The power surge is primarily at low frequencies (top trace of c), and occurs at the expense of high-frequency activity. In contrast, the REM state is characterised by reduced power, reduced correlation time, and higher-frequency EEG. All of these observations are consistent with our model predictions. The claim of a *second* power surge at REM offset remains untested however – there is insufficient resolution here to make a determination.

4. Discussion and Conclusions

In order to make some headway towards the grand challenge of understanding the structure and purpose of sleep, we have assumed that it is sufficient to model just two of the myriad sleep modulation effects: the waxing and waning of acetylcholine concentration that occurs during each 90-min sleep cycle, and the much slower ebbing and flowing of the “somnogen” (fatigue agent) adenosine that accumulates during wake and dissipates during recovery sleep. We model these effects as slow changes in synaptic efficiency and neuron resting voltage. We incorporated these sleep modulations into a pre-existing mean-field framework that has been developed over many years by members of the cortical modelling community, a modified version of which we have adopted previously to develop a phase-transition theory for the effect on the cortex of general anaesthetic agents.

There is strong evidence that the cortex requires a continuous wash of input noise in order to function normally; this motivated our introduction of stochastic

driving into the cortex. After making the “adiabatic” approximation that assumes that, relative to the neuron soma voltage, dendritic input events are fast and rapidly equilibrating, we were able to simplify the cortical equations for the excitatory and inhibitory soma voltage to a coupled Langevin pair. By linearising about steady state, we transformed these to a 2-D Ornstein-Uhlenbeck (OU) representation whose fluctuation statistics can be written down exactly. The statistics of interest are the fluctuation variance, correlation time, and power spectrum. We remarked (see discussion following Eq. (41)) that in the vicinity of a jump transition in the manifold of steady states, the theory predicts a divergence in both fluctuation variance and zero-frequency spectral energy (“critical slowing down”). Combining this fact with the observation that SWS sleepers (cat and human) show increasing low-frequency EEG patterns near the point of transition persuaded us that the SWS→REM change of cortical state might plausibly be modelled as a first-order phase transition from a low-firing state to an activated state.

We tested the OU predictions by running numerical simulations. We then compared the theoretical predictions against clinical recordings. We find that the phase-transition theory provides natural explanations for the following sleep phenomena: the high-firing state (REM) has *lower* fluctuation energy, albeit of higher frequency, than the inactivated state (SWS); SWS has fluctuations of higher amplitude and greater correlation than does REM; these correlations and amplitudes grow strongly on approach to REM, then collapse abruptly upon transition. The theory also predicts a more subtle effect that remains to be verified: namely, a smaller power surge as the cortex transits out of REM back into SWS.

While these are very pleasing results, our theory is a very preliminary “static” description of sleep cycles, and many questions remain. For example: Is it possible to locate the wake state somewhere on the manifold of steady states? How do we model the process of “falling asleep”? We are currently investigating the significance of the cortical *dynamics* that were deliberately suppressed in the present equilibrium-focused model, and the results of these investigations will be reported elsewhere [22].

Acknowledgements

The authors gratefully acknowledge the support of the New Zealand Marsden Fund, contract UOW307.

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