Whole-Brain Modelling: Past, Present, and Future

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Abstract

Whole-Brain Modelling is a scientific field with a short history and a long past. Its various disciplinary roots and conceptual ingredients extend back to as early as the 1940s. It was not until the late 2000s, however, that a nascent paradigm emerged in roughly its current form—concurrently, and in many ways joined at the hip, with its sister field of macroconnectomics. This period saw a handful of seminal papers authored by a certain motley crew of notable theoretical and cognitive neuroscientists, which have served to define much of the landscape of whole-brain modelling as it stands at the start of the 2020s. At the same time, the field has over the past decade expanded in a dozen or more fascinating new methodological, theoretical, and clinical directions. In this chapter we offer a potted Past, Present, and Future of whole-brain modelling, noting what we take to be some of its greatest successes, hardest challenges, and most exciting opportunities.

Keywords

Connectome · Neural mass · Neural field · Mean-field · Neuroimaging

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13.1 Preliminaries

13.1.1 What Is Whole-Brain Modelling?

> **paradigm**, n.
> 4. A conceptual or methodological model underlying the theories and practices of a science or discipline at a particular time; (hence) a generally accepted world view.
>
> *OED*

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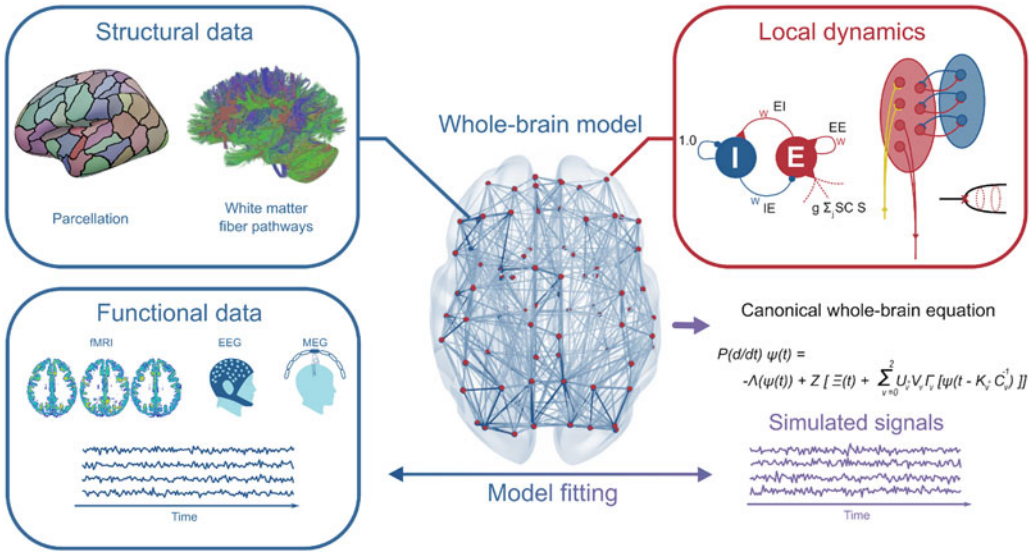


Fig. 13.1 *Schematic of the WBM approach.* 'Local' neural dynamics are described by the activity of (1) millions of point-process spiking neuron (differential) equations, aggregated by connectivity into regions; OR (2) hundreds/thousands of point-process neural mass/mean field/neural field (differential and/or integral) neural population equations—variously termed; OR (3) hundreds/thousands of point-process linear algebraic neural population equations (normally grouped into a single matrix-valued equation). Typically, all nodes in the network are described with the same local neural dynamics model and same parameters. Neural populations are coupled together based on a structural connectome, which is defined principally by noninvasive neuroimaging data, including T1-weighted MRI, diffusion-weighted MR tractography, and others. Simulated neural activity is compared against empirical measurements such as fMRI/MEEG time series or covariance structure using brute-force or parameter optimization approaches. When coupled together in the regime achieving good fits with empirical data, the collective behaviour of the system produces quasi-periodic activity whose static/dynamic functional connectivity patterns are similar to those observed for empirical data. Theoretical analysis of these models provides insight into principles and physiological details of large-scale brain organization, and can be used for in silico perturbation studies

Whole-Brain Modelling (WBM) is the subfield of computational neuroscience concerned with computational and theoretical models of approximately whole-brain neural activity. The usual objective of this approach is to study how macroscopic spatiotemporal patterns of neural activity result from the interaction of anatomical connectivity structure, intrinsic neural dynamics, and external perturbations (sensory, cognitive, pharmacological, electromagnetic, etc.). Such macroscopic phenomena, and models thereof, are of particular scientific interest because (a) they represent neural systems in a holistic and relatively intact state, and (b) they are the type of measurement that can be most readily obtained from the brains of healthy human subjects, using noninvasive neuroimaging and related methods. Simulations of *human* brain activity, in both health and disease, are therefore a principal focus of current WBM research.

The predominant research paradigm used in WBM emerged in roughly its current form at the end of the 2000s (e.g. Deco et al. 2009; Ghosh et al. 2008; Honey et al. 2007)—a development that we survey in detail in this chapter. Figure 13.1 gives a schematic summary of the approach. The basic idea is to model the brain at the macro scale as a network of interconnected regions, where the network nodes representing those regions are defined by (principally) neuroimaging-based brain parcellations, and the presence and weights of the network edges interconnecting the nodes are derived from neuroimaging- or chemical tract tracing-based anatomical connectivity measurements. We refer to whole-brain anatomical connectivity

networks and matrices of this kind as 'macro-connectomes', or just 'connectomes' for short (see Sect. 13.2.4). Most commonly, activity in this network is then studied with numerical simulations of population-level neural activity (neural masses, mean fields, neural fields; see Sect. 13.2.2), aimed at reproducing a wide range of empirical data features across multiple measurement modalities. These features include: fast oscillations in local field potential (LFP) and extracranial electromagnetic (MEG, EEG) signals; slow quasi-periodic activity fluctuations in haemodynamic (BOLD fMRI, fNIRS) signals; inter-regional synchrony/covariance (functional connectivity) and causal interactions (effective connectivity) in both fast and slow activity patterns; sensory- or electromagnetic stimulation-evoked response waveforms; graph-theoretic properties large-scale network activity; and many others.

In addition to neural population model simulations, both more complex (large-scale spiking neuron) and simpler (linear algebraic) modelling approaches are also often used. The theoretical dialogue between these three levels of description and degrees of detail—spiking neurons, neural populations, and linear systems—is a characteristic feature of WBM research, for two key reasons: First, we wish to understand, for any given empirical phenomenon observed in large-scale spatiotemporal neural activity measurements, what is the appropriate level of explanation for that phenomenon. As a rule, the most appropriate level is the most parsimonious and the simplest (i.e. Occam/Einstein/Conan Doyle 'as simple as possible, but no simpler'). Balancing this, the second reason for a multi-pronged approach in terms of spatial scale and detail is that models and theories at higher or coarser scales should aim (as far as possible) to be consistent with descriptions at finer scales, as well as with known physiological parameters. An example of this criterion in action is the practice of demonstrating, both theoretically and numerically, consistency between a given spiking neuron model and its neural population-based reductions (e.g. Deco et al. 2013a; Stefanescu and Jirsa 2008).

13.1.2 Overview of This Chapter

In this chapter we offer a survey of the Past, Present, and Future of WBM. In Sect. 13.2 we cover the historical antecedents of several foundational concepts and formalisms. Our objective in these discussions is not to undertake a rigorous historical examination per se, but rather to use the development of certain key ideas and methodologies over the years as a didactic device. We also believe that a dash of history brings a welcome dose of colour and perspective to those ideas. For our expository purposes, The Past ends and The Present begins in 2006 (for reasons explained below). Also, naturally enough, The Present ends and The Future begins at the time of writing (2021). In Sect. 13.3 we consider several key components of current WBM research, including the neural population model landscape, specification of connectivity structure, parameter estimation, and clinical applications. Finally, in Sect. 13.4 we offer thoughts on emerging themes and important future directions for the field.

13.2 The Past

13.2.1 The Long and the Short

The idea of a young scientific field having a 'short history and a long past' is a well-worn trope, but often a well-placed one. It was Ebbinghaus who first coined the aphorism in 1908, in reference to the then-nascent discipline of Experimental Psychology (Ebbinghaus, 1908). This new field had emerged some two decades earlier through the pioneering work of Wundt (the short history), out of many centuries' groundwork in natural philosophy (the long past). The situation is not dissimilar for the field of WBM in the early 2020s, which has similarly concretized in the past two decades or so, building as it does on a rich (but diffuse) legacy of ideas and formulations extending right back to as early as the 1940s. In this chapter we have opted to label the second of these two phases 'The Present' rather than the (recent) 'History' as Ebbinghaus did, but the sentiment

is otherwise the same: The late 2000s and early 2010s witnessed the birth and rapid maturation of a new WBM paradigm, which we summarized briefly in Sect. 13.1.1 and shall discuss in detail in the following pages. This maturation included both widespread use of the principal methodology (connectome-based neural population modelling), and a modest but consistent appearance of the three-word phrase 'whole brain modelling' itself in the academic literature.

The transition point from The Past to The Present in our exposition is identified as the year 2006. Of course, to identify a major scientific shift such as this with just a single year is a major oversimplification and highly artificial.[1] Acknowledging this, and allowing for a little didactic license, this characterization is we believe an informative, useful, and broadly correct one. The demarcation point of 2006 is chosen for two reasons. First, it was only a few months earlier that the macroconnectomics paradigm in neuroimaging—a necessary precondition for the subsequent development of WBM—began in earnest. Two major expressions of this were the first graph-theoretic analysis of fMRI functional connectivity matrices (Salvador et al., 2005), and scientific literature debut of the neologisms 'connectome' and 'connectomics' (Hagmann, 2005; Sporns et al., 2005). The second reason for our choice of demarcation at 2006 is that it was only a few months later that the first fully fledged examples of WBM research appeared in print (Honey et al., 2007; Sotero et al., 2007). More on both of these in Sect. 13.2.4.

Over the next few pages we examine the long Past of WBM. The timeline in Fig. 13.2 gives an overview of key scientific developments in and relating to WBM, from the 1940s to 2021. A full breakdown of this entire timeline is beyond the scope of this chapter, and so we leave it to the reader to consult the original sources and relevant secondary literatures according to their interests.[2] Three threads in this timeline do however deserve particular attention, which we spell out in the next three sections. In Sect. 13.2.2 we look at the emergence and evolution of the neural population model, and more generally the statistical mechanics-inspired approach to describing and modelling neural activity. In Sect. 13.2.3 we examine macroscopic neural field models—which were not only the first mathematical models of whole-brain neural activity but also (in a sense) the first type of macro-connectome. Finally, in Sect. 13.2.4 we discuss the emergence of macro-connectomics in neuroimaging and computational neuroscience, and how this directly and proximally contributed to the conclusion of The Past and the transition to The Present of WBM.

13.2.2 Origins of the Neural Population Model

As noted, the principal methodology used in WBM is connectome-based neural population modelling—i.e. numerical simulations with whole-brain networks of coupled neural populations. The basic atomic unit of these simulations is the neural population model—a mathematical representation of the collective activity within an ensemble of neurons. Neural population models are *mesoscopic*[3]—that is, they describe aspects of nervous system organization at spatial scales on the order of millimetres to centimetres. The main rationale for taking this

[1] Ebbinghaus (1908), for example, located the end of the 'past' in 1879 when Wundt founded the world's first psychological laboratory; but Wundt, Müller, Helmholtz, and others had been actively pursuing that research for at least 25 years before that date.

[2] Whilst there is not to our knowledge any single authoritative historical reference on the development of WBM concepts from the 1940s to the 2020s, informative discussions of some aspects of this timeline can be found in Cowan (2014), Chow and Karimipanah (2020), Sporns (2013), and Liley (2013).

[3] The lower and upper boundaries of the 'mesoscopic' regime are fuzzy, and terminological conventions vary across neuroscience sub-fields. It is therefore not uncommon to see neural populations described as microscopic or macroscopic in some contexts (although they are most commonly and properly regarded as mesoscopic). Note that these terms can also be somewhat at odds with conventions in other disciplines (in physics, for example, the mesoscale is *smaller* than the microscale, being intermediate between nano and micro).

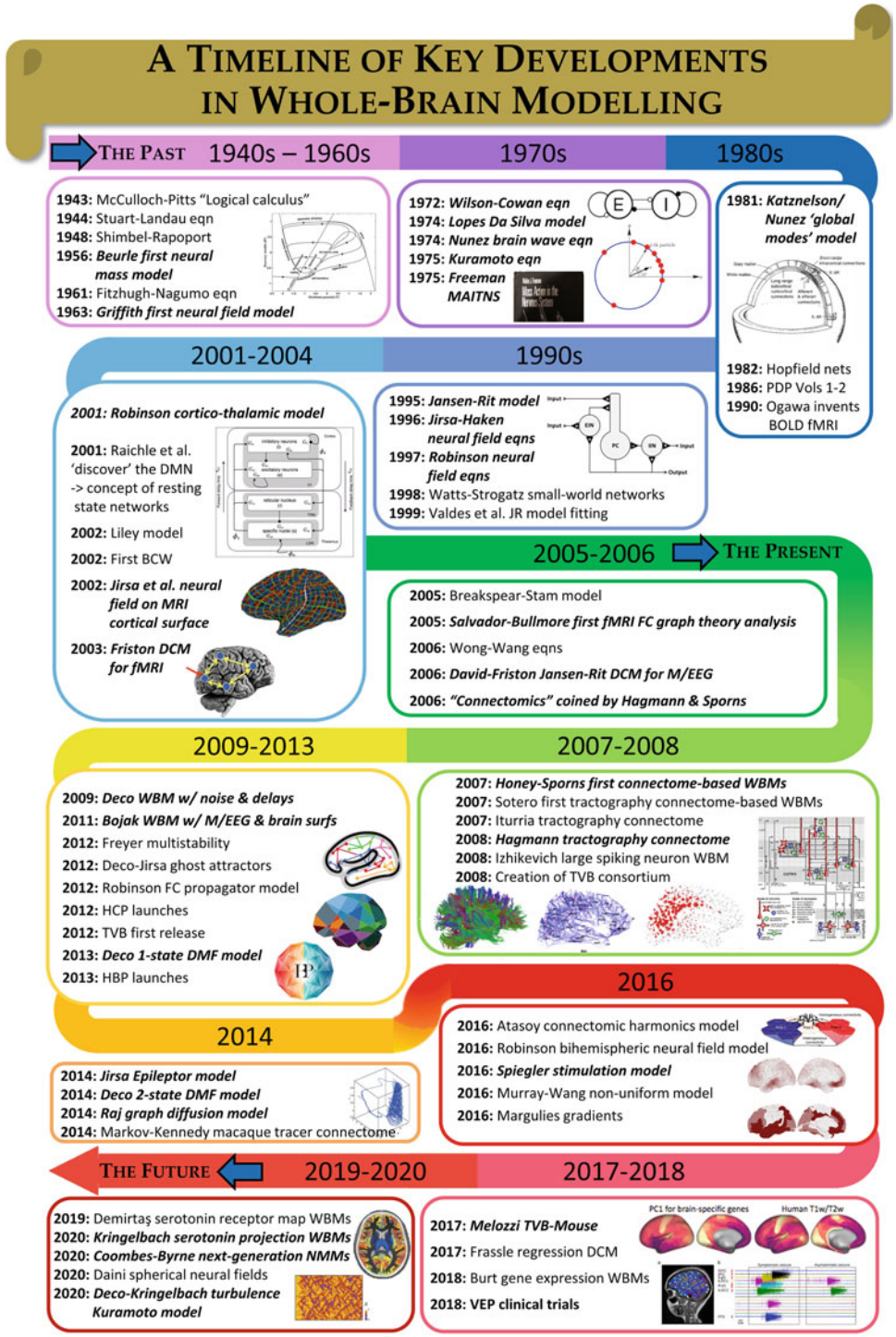


Fig. 13.2 *Timeline of major developments in and pertaining to whole-brain modelling.* Shown are a selection of key publications and events that have had a major influence on the development of WBM and adjacent fields. Particularly important entries are indicated in bold italics. The earliest neural population model formulations were outlined by Shimbel and Rapoport (1948), Beurle (1956), and Uttley (1955), building on the seminal work of McCulloch and Pitts (1943). Arguably most central in the entire timeline is the period 1970–1975, during which the key contributions of Wilson and Cowan (1972), Lopes da Silva et al. (1974), Freeman (1972); Freeman et al. (1975), and Nunez (1974) were published. In this chapter we identify The Past as the period leading up to 2006 and The Present as the period 2006–2021. See main text for full citations and discussions of the studies referenced in this figure

approach is that many (indeed, most) types of neural recording (particularly LFPs, ECoG, M/EEG, fMRI) are intrinsically population-level measurements. That is, the signals they are based on are aggregate quantities, that only reach detectable levels when contributed by at least a minimum number (tens of thousands) of simultaneously active neurons. The reasoning is, therefore, that it is both unnecessary and inefficient to attempt to model such data at the microscopic spatial scale of individual neurons, since we cannot see that level of detail in meso- or macroscopic measurements, and certainly not ones at the whole-brain scale. Better, then, to formulate the models directly at the mesoscopic, or population-level, spatial scale. A commonly used analogy here is with the properties of gases in statistical physics: Just as in thermodynamics, one does not (usually) simulate the activity of every single individual particle in a gas to track its temperature, so in neuroscience we should not be simulating the activity of all individual neurons in a patch of tissue when our main interest is tracking population-level dynamics. This reasoning depends, of course, on the availability of population-level models that can accurately summarize the particular aspects of neural ensemble activity that are of interest.

A wide variety of mathematical forms are used to represent neural population activity, the most common of which are summarized in Sect. 13.3.2 and Fig. 13.6. All of these choices are, ultimately, motivated by the statistical physics-type rationale described above. However only a subset of commonly used neural population models attempt to incorporate cellular and local circuit organizational features of neural (usually cortical) tissue, and only a subset of those are rigorously derived in a bottom-up fashion from equations governing single neuron activity, without any arbitrarily chosen non-physiologically based components. This is sometimes reflected in binary categorizations of 'biophysical/physiological' vs. 'phenomenological' neural population model types (e.g. Sanz-Leon et al. 2015; see Sect. 13.3.2); although we would argue it is more useful to instead think about a spectrum from less to more biophysically/physiologically detailed and/or motivated.

The earliest neural population model formulations took a heavily physics-driven and bottom-up approach to deriving equations for neural ensemble activity (e.g. Beurle 1956; Griffith 1963a; Shimbel and Rapoport 1948). Interestingly however, these did not[4] draw on what are nowadays considered the definitive and canonical mathematical description of single-cell neural activity—the Hodgkin–Huxley equations (Hodgkin and Huxley, 1952). Instead, they took as their starting point the seminal work of McCulloch and Pitts (1943), who showed that networks of binary threshold elements could perform computations and thus serve as a basis for cognition. This idea laid the groundwork for a substantial slice of modern systems neuroscience, cognitive science, and artificial intelligence, including notably neural networks in machine learning—first via Rosenblatt (1958) and Grossberg (1968), and later Hinton and colleagues (e.g. Krizhevsky et al. 2017; Rumelhart et al. 1986). The development of neural population modelling has thus far proceeded largely independently from artificial neural networks in machine learning however, despite their shared ancestry. In the mid-twentieth century, theorists such as Shimbel and Rapoport in the 1940s (Shimbel and Rapoport, 1948), Uttley and Beurle in the 1950s (Beurle, 1956; Uttley, 1955), Griffith (Griffith, 1963a,b) in the 1960s, and others embraced the task of developing a statistical mechanics of collective activity in McCulloch–Pitts-like 'neural nets'. The equations for neural population activity developed by these early thinkers had three essential ingredients (Chow and Karimipanah, 2020): (1) a continuous time-dependent activity variable, (2) a linear weighted sum over these activity variables in the input, and (3) a nonlinear activation function linking input to output.

[4] For the early work of Shimbel and Rapoport, Beurle, and Uttley, this is unsurprising as their contributions either preceded or were contemporaneous with Huxley and Hodgkin's Nobel Prize-winning work. But this was also the case for the later work of Griffith, Wilson and Cowan, and others, who do not appear to have been much influenced by cellular- and membrane patch-level physiological modelling work of the time.

The most influential and well-known set of such activity equations are those introduced by Wilson and Cowan (1972). In developing this model, Jack Cowan followed fairly closely the earlier work of Beurle (1956) on the dynamics of an excitatory neural ensemble, but made the important addition of a separate inhibitory subpopulation. The inspiration for this came from the Lotka–Volterra equations for predator–prey dynamics in ecology, which were proposed to account for the well-known phenomenon of multi-year cycling in species abundances. In the Wilson–Cowan equations, the negative feedback resulting from interactions between excitatory and inhibitory neuronal subpopulations endows this relatively simple system with a level of dynamical richness (including multistability, oscillations, travelling waves, and hysteresis) that has secured them an enduring interest in theoretical neuroscience.

In the models of Wilson and Cowan, Beurle, and Griffith, the time-dependent activity variable(s) represent proportion of cells in the population that are active (i.e. firing) per unit time. Other neural population models developed at a similar time instead choose as their state variable the population-average membrane potential (Freeman, 1972; Lopes da Silva et al., 1974; Nunez, 1974). In these so-called voltage-based neural population models, the nonlinear activation function converts the membrane potential to an efferent (outgoing) population firing rate, and an additional set of equations describing axo-dendritic synaptic responses are added that convert an afferent (incoming) firing rate into membrane potential perturbations. Freeman (Freeman, 1972; Freeman et al., 1975) popularized the description and interpretation of these input/output conversions in terms of 'pulses' (firing rates) and 'waves' (membrane potentials) as 'pulse-to-wave' and 'wave-to-pulse' operators, respectively. He also coined the term 'neural mass', borrowing in part from Beurle's 'mass of cells' (Beurle, 1956), and his mentor Karl Lashley's concept of 'mass action'[5] in the neural basis of memory encoding. In computational neuroscience today, a 'neural mass model' is the most widely recognized generic term for physiologically based, point-process neural population models. Somewhat awkwardly, it is almost entirely synonymous[6] with another commonly used term, 'mean-field model', which also has the advantage of consistency with the usage of 'mean field' in other areas of science. To complicate things further, a closely related term to 'neural mass' and 'mean field' is 'neural field', which refers to a neural population model defined over some contiguous spatial domain, as opposed to neural masses/mean fields which are space-less point-processes. To be clear: the sense of 'field' in a neural field and in a (point-process) mean field is not the same.[7][8]

Two other neural population models from the mid-1970s that were highly influential for later WBM work were those of Nunez (1974) and Lopes Da Silva and Zetterberg (Lopes Da Silva et al., 1976; Lopes da Silva et al., 1974; Zetterberg et al., 1978), both of which were designed to account for the 8–12 Hz 'alpha rhythm' observed in human EEG recordings, albeit with very different hypothesized mechanisms. Nunez's contributions are discussed in Sect. 13.2.3. In their work, Lopes Da Silva and colleagues drew

[5] Freeman also made numerous other contributions to multiple neuroscience sub-fields in a career spanning seven active decades, including the idea of the 'K set' hierarchy (Freeman et al., 1975), linear system analysis of neurophysiological models (Freeman, 1972), discovery and naming of the gamma rhythm (Bressler and Freeman, 1980), pioneering the use of independent components analysis and the Hilbert transform, amongst others.

[6] Although some authors adopt a further technical distinction, where neural mass models are taken to describe only the mean of activity over a neural population, and mean-field models describe both the mean and the variance of activity (and thereby also an estimate of the full probability distribution of activity levels over the population) (Moran et al., 2013).

[7] The difference is the domain over which the field is a field over. Neural field models describe fields over space. Mean-field models describe fields over arbitrary abstract probability distributions. However in the latter case the field per se is not actually used in the model; rather it just refers to how the model is derived.

[8] ...It is this terminological bog, plus the necessity to distinguish between physiological and phenomenological model types, that leads us to prefer and use the looser term 'neural population model' in this chapter.

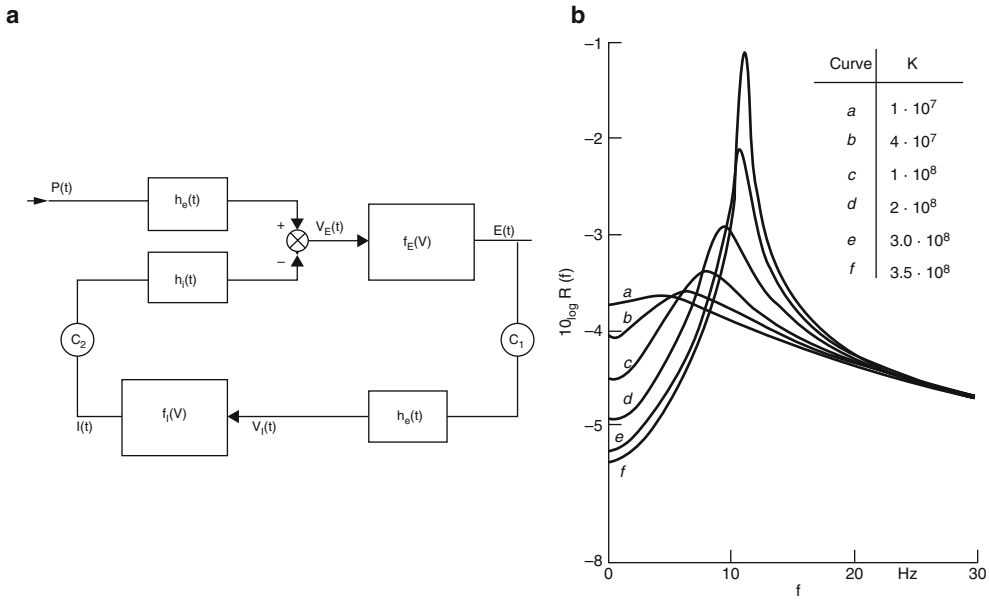


Fig. 13.3 *Lopes Da Silva–Zetterberg model*. The model by Lopes da Silva et al. (1974) designed to study corticothalamically generated EEG rhythms, was an early instance of the convolutional voltage-based neural mass model type, now regularly used in the form of the Jansen & Rit, David & Friston, and Robinson models, amongst others. *Left panel:* Equivalent current circuit of the model. *Right panel:* Analytic power spectrum. The linearization and systems analysis of the model allow calculation of the steady-state noise-driven power spectra algebraically from the parameter values. The model shows clear peaks in the alpha range, for a range of parameters. Figures taken from Lopes da Silva et al. (1974)

closely on both Wilson & Cowan's and Freeman's approaches, proposing a voltage-based neural population model with membrane potential state variables and excitatory and inhibitory cell types. They presented both numerical simulations and corresponding steady-state linear system analysis of neural power spectra that reproduced the alpha-frequency spectral peak and 1/f scaling observed in resting-state EEG data (Fig. 13.3). This model was later adapted and extended by Jansen et al. (1993) and Jansen and Rit (1995), who were able to use it to reproduce both steady-state EEG rhythms and time-locked EEG sensory-evoked responses. The so-called Jansen–Rit model, which comprises three interconnected neural subpopulations (pyramidal projection neurons, excitatory interneurons, and inhibitory interneurons forming feedback loops), is now one of the most widely studied and commonly used neural population models. A major contributor to this popularity was its adoption by David and Friston (2003), David et al. (2006a), and David et al. (2006b), as the model-of-choice for the first EEG/MEG variants of Dynamic Causal Modelling (DCM; Friston et al. 2003).

DCM is a mathematical framework for fitting neural models to neuroimaging and neurophysiological data, and testing scientific hypotheses pertaining to those models. The various model variants, technical innovations, and research questions addressed under the auspices of DCM are numerous and beyond the scope of this article to summarize even briefly (see Moran et al. (2013) for a useful summary of some of the electrophysiological DCM variants). We will therefore limit ourselves here to a few select observations. The general DCM approach was first developed in the context of task-based fMRI data analysis (Friston et al., 2003). In the original fMRI DCM model, effective connection strengths, or 'gains', between brain regions, as well as their task- or condition-dependent modulation, are estimated from time series data for small networks of <10 brain regions, using a

sophisticated Variational Bayesian model inversion scheme. The generative model of neural dynamics in this fMRI DCM model is specified by a simple, slow (i.e. with a characteristic time scale on the order of seconds), first-order linear dynamical system. Model-generated neural activity time series are then converted, through a rather complex nonlinear haemodynamic forward model, into predicted BOLD fMRI activity, to be compared against empirical measurements. In M/EEG, rather than a slow first-order linear dynamical system, the generative model used is instead a set of modified Jansen–Rit equations, with the usual pulse-to-wave and wave-to-pulse operations at the synapses (inputs) and axon hillocks (outputs). The approach of fitting activity from a voltage-based neural population model to EEG time series and spectra had been successfully demonstrated previously (Robinson et al., 2001; Valdes et al., 1999). What was notable about David and Friston's contribution was (following the model of fMRI DCMs) to extend this approach to small, distributed networks of coupled neural populations. In relation to this, they also added architectural constraints around backwards and lateral connections between neural populations, according to the observations of Felleman and Van Essen (1991).

We return to DCM at various points throughout this chapter, particularly in discussions of connectomics (Sect. 13.2.4) and parameter estimation (Sect. 13.3.3). For present purposes, a key overall point is that one of the major lasting contributions of the M/EEG DCM models (including importantly their easy-to-use implementation in the SPM software library[9]) was to introduce concepts of physiologically grounded neural population modelling to the broader (non-theoretical) human neuroimaging and neurophysiology communities.

This concludes our short survey on the origins of the neural population model as it pertains to The Past of WBM. We note that for reasons of space it has been necessary to skip over several other important developments, including the early history of the Stuart–Landau, Fitzhugh–Nagumo, Kuramoto, and other models, which will nevertheless feature prominently in later discussions. We return to neural population models specifically in Sect. 13.3.2, which summarizes the main models currently used in WBM work.

13.2.3 Macroscopic Neural Field Models

A neural field model is a neural population model defined over some contiguous spatial domain, such as a patch of cortical tissue, an entire cerebral hemisphere, or even an abstract cognitive space. This differs from neural mass and mean-field models that model local neural population dynamics as point processes—i.e. with no explicit representation of space. This inclusion of space in neural field models entails some description of the connectivity structure of the spatial domain, which in turn determines how activity propagates between locations on the field. Neural fields are therefore, in a sense, a special kind of neural population *network* model (i.e. a network of coupled neural masses), where the discrete topology and connectivity of the network are replaced by the continuous topology and connectivity of the field. Conversely, networks of neural masses can in certain cases be considered as discretizations of neural fields with equivalent connectivity structure. This parallel between network-based and field-based representations of cortical tissue has been a characteristic feature of WBM since its earliest days.

Broadly speaking, two kinds of neural field model have been studied intensely in the theoretical neuroscience literature: (a) mesoscopic and (b) macroscopic. The difference between these two is, naturally enough, the physical size of the field, and what it is intended to represent. Mesoscopic neural field models typically describe a flat two-dimensional patch of cortex with radius somewhere between a few dozen millimetres and a few centimetres. Macroscopic neural field models, in contrast, generally describe each cerebral hemisphere with a sphere, toroid, or rectangular patch, with a pole-to-pole (i.e. posterior-to-anterior) length of 10–20 centimetres. For further

[9] www.github.com/spm.

simplification, the two cerebral hemispheres are often collapsed into a single field representing the entire cerebral cortex (e.g. Daini et al. 2020; Nunez et al. 2006; Robinson et al. 1997). The majority of work on neural field models—from the early studies of Beurle (1956) and Griffith (1963a), Griffith (1963b), to the continuous version of the Wilson–Cowan model (Wilson and Cowan, 1973) and the Amari (1977) model with centre-surround inhibitory (Mexican Hat) connectivity, and most work since then—has been of the mesoscopic variety.[10] In terms of tracing the history of ideas of WBM research however, it is the macroscopic flavour of neural field models that are of particular importance. An interesting, and perhaps under-appreciated, point here is that the early macroscopic neural field models can reasonably be considered the first proto-macro-connectomes, in virtue of their (posited) connectivity structure.

In the mid-twentieth century, when neural field and neural population concepts were first being developed, detailed information on macroscale anatomical connectivity was not readily available, and so it was necessary to use heuristics. A prime example of this is the work of Uttley (1955) in the 1950s, who used the rather sparse available anatomical data, along with reasonable geometric and statistical assumptions, to derive mathematical formulae for the spatial structure of axonal projections and axo-dendritic connectivity. Uttley's calculations were mostly based on anatomical studies from his colleague Sholl (1953, 1956) on the dendritic systems of stellate and pyramidal neurons in the striate and motor areas of cat cortex. A key feature of these measurements was the observation, now widely recognized, that connection probability decays as an exponential function of distance. Using this relationship, and employing Freeman's concept of a neural mass, Nunez (1974) proposed the first macroscale neural field model aimed at describing neural dynamics on the scale of the entire cerebral cortex. Charismatically named the 'Brain Wave Equation' (because it is a wave equation for brain waves), this model contains an *implicit* description of whole-brain connectivity, via the isotropic, translationally invariant, and exponentially decaying connectivity kernel of the neural field. In addition to formulating the model, Nunez (1974) also emphasized that approximate analytic solutions for reasonable values of the model's parameters suggested oscillatory solutions within the frequency range of the EEG alpha rhythm. The idea here, later developed in considerable detail (Katznelson, 1981; Nunez and Cutillo, 1995; Nunez and Srinivasan, 2006; Nunez et al., 2006), and receiving some empirical support (Nunez et al., 2006; Sivakumar et al., 2016; Valdés et al., 1992), is that wave–wave interference due to boundary conditions imposed by the approximately spherical geometry and topology of the cortex results in standing waves (aka harmonics, eigenmodes) with comparable spatial and temporal characteristics to that of EEG alpha activity.[11]

Two notable extensions of the Nunez model were introduced in the 1990s and early 2000s. In 1997, Robinson and colleagues developed a partial differential equation (PDE) neural field model and studied its properties under three global topologies: an infinite 2D plane, a 2D square with periodic boundary conditions, and a sphere (with spherical boundary conditions) (Robinson et al., 1997). As these authors note, the PDE formulation is an order of magnitude more efficient to simulate than the equivalent integrodifferential equation (IDE) formulation of Wright and Liley (1996) (on which their model was directly based), and also lends itself more straightforwardly to analytic investigation of spatial properties, such as eigenmodes and inhomogeneities (later explored extensively, e.g. Connor et al. 2002). Examination of spatial damping in the model also led the authors to dispute Nunez's global standing wave

[10] A comprehensive and mathematically detailed review of this work, and of neural fields in general, is beyond the scope of this review. Excellent summaries on various aspects of neural field theory can be found in Coombes et al. (2014).

[11] It is doubtless not a coincidence that the other set of problems Nunez was working on at the time were signal processing and electromagnetic forward models for EEG, making extensive use of idealized spheres and electromagnetic field equations (Nunez et al., 2006).

theory of alpha activity, on the grounds that cortical waves are heavily spatially damped, and do not propagate rapidly and far enough to generate the interference needed for standing waves to occur (Nunez and Srinivasan, 2006; Robinson et al., 1997). Later, Robinson and colleagues augmented this neural field model with oscillatory corticothalamic loops, which they have explored extensively over the past 20 years as a candidate mechanism of EEG rhythmogenesis (Robinson et al., 2001, 2016).

In a similar line of work occurring at roughly the same time, Jirsa and Haken (1996a,b) derived a novel general neural field equation, from which they could recover both the Nunez (1974) and Wilson and Cowan (1973) systems. Building on this, Jirsa later pioneered the integration of macroscopic neural field models with structural neuroimaging data. Specifically, in 2002 Jirsa et al. (2002) were able to project and visualize dynamics modelled through a spherical neural field on to the folded cortical surface, using the then-new (now-standard) surface-based MRI registration tool Freesurfer (Fischl et al., 1999). This use of spherical or spheroidal neural fields as first-order approximations of global cortical geometry, whilst also utilizing in various ways detailed MRI-derived geodesic mesh representations for more realistic non-uniform cortical surface features, has been since developed by several other authors (e.g. Daini et al., 2020; Gabay et al., 2018; Nunez et al., 2006; Robinson et al., 2016; Visser et al., 2017; c.f. Fig. 13.4). Interestingly however, whilst it may be gaining traction, this line of work is still not widely known within either the neuroimaging or computational neuroscience communities.

The two key ingredients of Nunez's model, and most of its subsequent variants, are the two approximations: (1) exponentially decaying axonal connectivity as a function of distance, and (2) a roughly spherical cortex. In the 1970s, these approximations were both useful and necessary. During the early 2000s however, they began to be obviated by the ability (as surveyed in the next section) of modern neuroimaging and chemical tract tracing techniques to make detailed measurements of whole-brain anatomical connectivity and cortical geometry. Thus there was a palpable sense at around the start of The Present that the 'old' translationally invariant distance-based and spherical approximations would look embarrassingly far off the mark in light of the richly detailed and heterogeneous network structure of 'real' white matter anatomical connectivity and cortical geometry information coming from noninvasive imaging. Interestingly, 15 years into The Present, the picture is a little more nuanced:

First, regarding the distance-connectivity approximation: Both tractography (Betzel et al., 2016; Deco and Kringelbach, 2020; Henderson and Robinson, 2011; Roberts et al., 2016) and chemical tract tracing (Braitenberg and Schüz, 1998; Markov et al., 2014; Sholl, 1956) data show that a simple exponential distance rule in fact does a remarkably good job of characterizing distance-connectivity relationships throughout cortex. This heuristic is not perfect, for example resulting in mis-location of hub structures and under-estimation of longest-distance connection strengths (Roberts et al., 2016). It is however

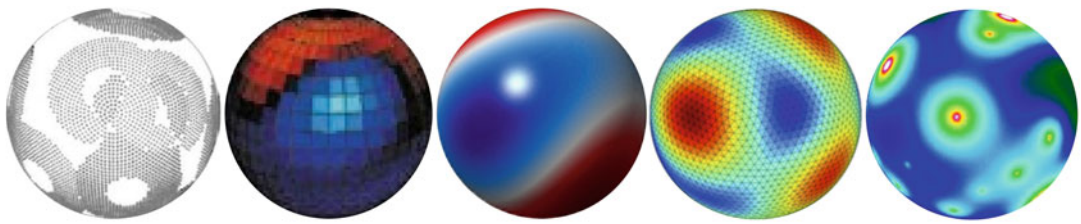


Fig. 13.4 *Spherical neural field models*. Macroscale neural field models on a spherical domain, representing endogenous or evoked activity over an entire cerebral hemisphere, have played an important role in more theoretical circles (*sic.*) of WBM, and continue to do so. From left to right (1981–2020): Katznelson (1981), Nunez et al. (2006), Jirsa et al. (2002), Gabay and Robinson (2017), Visser et al. (2017), and Daini et al. (2020)

sufficiently close to empirical measurements for distance-dependent neural field or field-like models to continue to make a valuable contribution to the theoretical landscape.

Second, regarding the spherical approximation: One interesting nod to Nunez's initial introduction of this is that spherical brains, constructed by a process of 'computationally inflating' a geodesic mesh representation of the pial and white matter surface, are now used routinely in neuroimaging for inter-subject alignment of cortical surfaces, such as with the Freesurfer library (Fischl et al., 1999). Indeed, the ubiquity of geodesic mesh representations in structural neuroimaging data analysis has facilitated a number of extensions of the spherical neural field model. These can be summarized as follows:

(1) The geodesic mesh can be directly used as the manifold on which to evaluate neural field equations (Daini et al., 2020; Robinson et al., 2016; Atasoy et al., 2016; Visser et al., 2017).
(2) The Laplace–Beltrami operator, computed numerically for the surface mesh, can replace the spherical Laplacian operator in neural field equations that use spatial partial derivatives (Robinson et al., 2016).
(3) The eigenvectors of the cortical surface Laplace–Beltrami operator turn out, in practice, to be highly similar to the eigenvectors of the Laplacian operator for a sphere (i.e., the spherical harmonics), for at least the first 5 or so modes (Gabay and Robinson, 2017; Gabay et al., 2018; Robinson et al., 2016). Thus, a large amount of the low-order spatial mode structure in a folded cortical surface (i.e. the real brain) is similar to that for a more mathematically idealized spherical cortex.
(4) Relating to the point noted above regarding connectivity: The implied Laplacian connectivity structure of a cortical surface geometry incorporates within it the exponentially decaying distance-connectivity profile already discussed to be empirically observed in fibre tracking data. So, the geometry and connectivity statistics of spherical cortex neural field models are actually fairly consistent with the dominant characteristics of experimental connectivity measurements.

13.2.4 Macro-Connectomics and the Emergence of the WBM Paradigm

By the mid-2000s, many of the key ingredients of the modern WBM approach were in place. Most of the mathematical formalisms for neuron and neuron population activity used today were available and well understood by the computational neuroscience community. The notion of using physiologically based models to describe emergent large-scale activity dynamics, such as EEG rhythms and evoked potentials, was well established (David and Friston, 2003; Jansen and Rit, 1995; Robinson et al., 2001; Valdes et al., 1999). Networks of coupled neural population models had been used to model activity in delimited small-scale systems (David et al., 2006a; Friston et al., 2003); but whole-brain connectivity, and models of whole-brain activity dynamics, had at that point only really been conceptualized and tackled through the somewhat boutique lens of macroscale neural fields. Questions about whole-brain structural and functional organization were of particular interest to an established and rapidly growing human neuroimaging community—working primarily on questions in clinical and cognitive neuroscience, but increasingly drawing on and integrating with systems and computational neuroscience. The 'mass univariate' approach that had dominated fMRI since its invention in the early 1990s gave a particular perspective on task-evoked whole-brain activity patterns, made possible by treating activity in all brain areas (all voxel time series) as dependent variables and as independent of each other. Coupled with the Dondersian doctrine of cognitive subtraction, this mass univariate, general linear model-based paradigm for design and analysis of neuroimaging experiments was (and continues to be) especially well-suited to identifying differentially 'activated' regions on various cognitive tasks (affectionately

referred to in the community as 'blobs' in virtue of their colourful visual presentation). This early focus in neuroimaging on functional specialization of brain regions (an idea also developed earlier, over many decades from neuropsychological lesion studies) is also often understood as an emphasis on ideas of 'functionally segregation'—and thereby contrasted with ideas about 'functional integration', such as inter-regional communication, connectivity, and network structure (Friston, 1994; Tononi et al., 1994). By the turn of the twentieth century functional segregation-based research questions in neuroimaging were becoming balanced (and arguably, eventually superseded) by questions about functional integration. These connectivity-based investigations were largely not whole-brain however,[12] but rather focused on pairwise or global covariance patterns amongst small sets of brain regions.[13] The scene, then, was set for the final part of the picture on the way to modern WBM: the emergence of network science and (shortly afterwards) connectomics.

Network science is an academic discipline that studies network phenomena, both from first principles and as they occur in nature and human activity, across an extremely broad range of empirical domains. Its two principal tools are algebraic graph theory and dynamical systems. Network science developed as a highly prominent autonomous field in the early 2000s, following key theoretical developments on the mathematical properties of various graph topologies (e.g. Barabási and Albert 1999; Watts and Strogatz 1998), and other enabling conditions such as the rapid growth of data on extremely large internet-based communication and social networks. Particularly influential in the early years of network science was the concept of a 'small-world network', introduced by Watts and Strogatz (1998), who studied some simple but compelling demonstrations of the computational and dynamic properties of graphs with small numbers of randomly introduced long-range edges.

The principal emphasis in network science has been on topological features of (typically) large networks, such as small-worldness, community structure, modularity, communication, and connectedness. These approaches to network characterization are often highly 'statistical' in nature, involving things like counts and distributions of node degrees, connection weights, and path lengths. This differed somewhat from the typical approach in neuroscience, which tended to be more interested in specific well-defined, and functionally characterized brain systems and anatomical pathways, rather than spatially non-specific topological properties of an entire network per se. Graph-theoretic investigations did nevertheless gain some traction in neuroscience in the 1990s and early 2000s, notably through the contributions of Olaf Sporns, with early collaborators Gerald Edelman, Giulio Tononi, Rolf Kotter, and Karl Friston (Sporns and Kötter, 2004; Sporns et al., 2000; Tononi et al., 1994). In neuroimaging, however, it was only in the mid-2000s that the power of graph- and network-theoretic approaches began to be realized and embraced.

It was the group of Ed Bullmore and colleagues (Achard et al., 2006; Salvador et al., 2005) who pioneered the methodology in fMRI (following earlier work in sensor-level EEG by Stam (2004)) of taking representative time series from a brain parcellation, calculating correlations between each parcellation time series, treating this correlation matrix as an adjacency matrix and as a complex network, and studying graph-theoretic topological metrics. The corresponding analysis methodology in structural neuroimaging, also using grey matter parcels to define nodes, but now using diffusion-weighted MRI tractography streamline densities as a measure of anatomical connection strengths, was developed at roughly the same time (Hagmann, 2005; Hagmann et al., 2008; Iturria-Medina et al., 2007). Figure 13.5 shows an example of such tractography-based anatomical connectomes at multiple parcellation scales (Daducci et al., 2012), which are now a regular object of study in neuroimaging, macro-connectomics, and WBM.

[12] Notable exceptions to this being eigenimage analysis and early spatial ICA.

[13] A prime example of this being DCM, as discussed earlier.

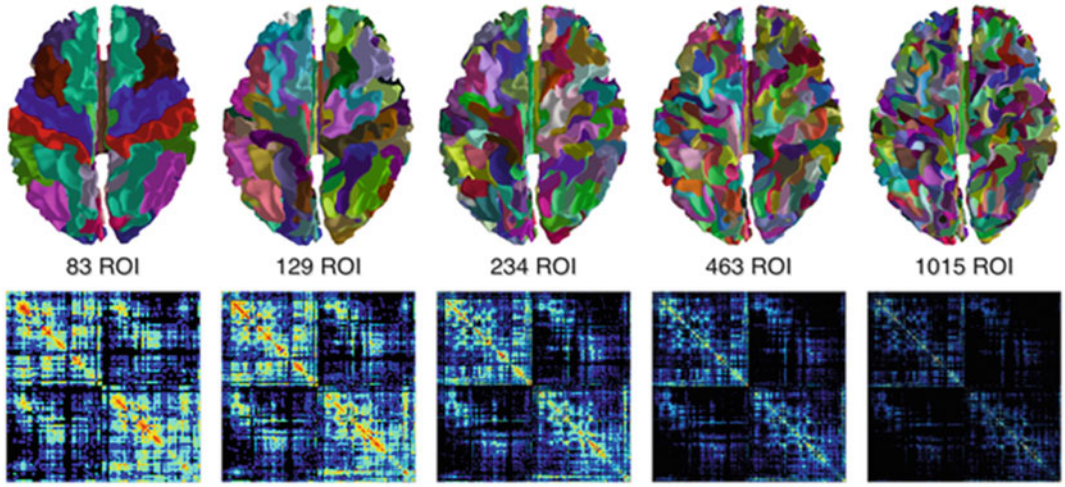


Fig. 13.5 *Multiscale macro-connectomes*. *Upper row:* Regions of interest (ROIs), aka parcels, shown on cortical surface meshes for five different scales of the 'Lausanne2008' parcellation (Hagmann et al., 2008). The parcellation scales are increasingly fine-grained from left to right, with 83 parcels in the smallest scale, and 1015 parcels in the largest scale. *Lower row:* Adjacency or connectivity matrices, consisting of diffusion-weighted MRI tractography-derived connection strengths (streamline counts) for every ROI pair. Exactly the same information is used to construct each connectivity matrix, with the only difference being the level of spatial granularity at which network nodes (matrix rows/columns) are defined. The final anatomical connectivity matrix, or 'anatomical connectome' in the lower right of the figure is 1015 rows × 1015 columns. From Daducci et al. (2012)

Also at this time, Sporns et al. (2005) and Hagmann (2005) independently coined the term 'connectome' for the notion of a comprehensive map of the brain's connections, by analogy with the map of the genes successfully developed within genomics. The idea of the 'connectome' and of 'connectomics' is caught on in a big way in the broader neuroscience community—and, interestingly, particularly so in two quite different sub-fields: human neuroimaging and non-human light and electron microscopy. It is therefore useful to distinguish between *macro*-connectomics—concerned with whole-brain connectivity structure at relatively coarse (macroscopic) spatial resolution, and *micro*-connectomics—concerned with (for example) reconstructing and mapping every individual synapse and axo-dendritic connection within an isolated, excised, cubic-millimetre patch of mouse cortex.[14] In the intervening years, macro-connectomics methodologies and ideas have consistently enjoyed an ascendancy in neuroimaging research.

The natural conclusion of our historical survey is to summarize the emergence of the WBM paradigm in full, which occurred through a few seminal papers in the first few years of The Present. One of the catalysts for these, and for many of the developments listed above and in later sections, was the founding by Rolf Kötter and others of a regular, small-scale scientific meeting called the Brain Connectivity Workshop (BCW).[15] The BCWs provide a discussion forum for researchers thinking and working at the intersection of the neuroimaging, systems, and computational neuroscience communities. The event has an explicitly encoded culture of short talks with most time reserved for productive interactive discussions. In an effort to further rally the BCW community into focused collaborative projects, Randy McIntosh—a prominent advocate of connectivity-based

[14] In addition, we could also define 'meso-connectomics' for the (less common) efforts at characterizing connectivity at spatial scales intermediate between micro and meso (e.g. Oh et al. 2014).

[15] https://www.brain-connectivity-workshop.org.

thinking and methodologies in neuroimaging and cognitive neuroscience (McIntosh, 2000; Mclntosh and Gonzalez-Lima, 1994)—founded in 2005 an international consortium called the Brain Network Recovery Group (NRG).[16] As part of this, in 2006 he spent a sabbatical in Dusseldorf working with Kötter on translating his macaque brain CoCoMac database into corresponding human brain anatomy, to make it more easily interoperable with human structural and functional neuroimaging data. In parallel with this, one of Viktor Jirsa's conclusions from his earlier spherical neural field work discussed in Section 2.3 (Jirsa et al., 2002), communicated and discussed intensely at BCW meetings, was that inhomogeneous and non-translationally invariant connectivity structure and time delays were essential for a faithful modelling of human large-scale brain dynamics. The natural replacement of the spherical cortex was therefore the anatomical connectome, now available from chemical tracing data thanks to the efforts of Kötter and McIntosh, and shortly after from tractography data from Hagmann et al. (2008), Iturria-Medina et al. (2007), and others.

These various behind-the-scenes activities began to be felt in the scientific literature through a series of publications starting in 2007, when both Honey et al. (2007) and Sotero et al. (2007) investigated emergent dynamics in whole-brain networks. The model of Sotero used diffusion-weighted MRI tractography to define the anatomical connectome, and Jansen–Rit equations for the activity at each network node, focusing on large-scale patterns in EEG activity. Also that year, Honey et al. (2007) published the first of several excellent WBM studies exploring various aspects of large-scale brain organization, using models based on non-human primate connectivity from the CoCoMac database (Kötter, 2004). More fully in the connectomics vein (as would be expected given the authors), this study focused on the relationship between anatomical connectivity and simulated BOLD fMRI functional connectivity patterns, as characterized using graph-theoretic metrics such as node degree distributions and hub structure. In a follow-up paper, Honey and Sporns (2008) studied the effects of lesions on graph properties of simulated functional connectivity in whole-brain networks. This study used the Kuramoto phase oscillator model to describe neural population activity, as opposed to the (more unwieldy) coupled chaotic oscillators they used earlier in Honey et al. (2007). Shortly after, Deco et al. (2009) (using the standard CoCoMac connectivity), Ghosh et al. (2008) (using McIntosh's human-modified CoCoMac connectivity), Bojak et al. (2011) (using a different human-modified CoCoMac connectivity), and Knock et al. (2009) (directly comparing the CoCoMac and tractography-derived connectivities) examined the contribution of noise and time delays to large-scale network dynamics.

The methodology and questions from these briefly surveyed studies have largely laid the pattern for the past 10 years of WBM research. One prominent manifestation of the research program that grew out of these activities was the evolution in 2010 of the NRG into The Virtual Brain Consortium, which further focused the group's attentions on the development of a new neuroinformatics and brain simulation platform called The Virtual Brain (TVB), which was first released in 2012. Since then, TVB has facilitated a large amount of research activity in WBM,[17] including some of its most significant achievements, which we discuss in the next section.

13.3 The Present

Thus far we have outlined the historical trajectory and neurobiological rationale behind the use of WBMs in studying large-scale brain dynamics and organization. The previous Part concluded with a summary of some early examples of the mature WBM paradigm in action. Whilst the subsequent decade has seen many exciting develop-

[16] https://brain-nrg.squarespace.com/.

[17] Another notable achievement of the TVB platform was to be 'drafted in' as the poster-child human brain simulator within the activities of the European Human Brain Project.

ments, there have been no major qualitative shifts in the methodological approach used now and that used ten years ago. In this Part on The Present we therefore turn our attention to current technical and conceptual issues in the field, and key recent successes (of which there are many) in scientific and clinical applications. We first discuss three important technical areas: (1) the canonical WBM equations, (2) physiological parameter estimation and inference, and (3) anatomical connectivity. We then offer highlights and general comments on the extensive and rapidly growing WBM clinical applications literature.

13.3.1 The Canonical WBM Equations

Figure 13.1 gave a schematic of how WBMs are built and used to simulate large-scale neural activity patterns. As we have indicated in this figure and elsewhere, a satisfactorily inclusive definition of WBM should include three different modelling flavours: spiking neural models, neural population models, and algebraic models. The second of these is however by far the most commonly used, and so in this section and the next we discuss briefly some technical considerations on connectome-based modelling of neural population activity.

The most generic and comprehensive mathematical summary to date of neural population models and their deployment in WBM can be found in Sanz-Leon et al. (2015). These authors provide detailed equations for a wide range of physiological and phenomenological neural population models, as well as various types of neural population coupling function, forward models, neural field kernel variants, numerical integration schemes, and more. It is beyond the scope of the current chapter to cover this material at a detailed technical level. We will however give some comments on the overall approach.

A generic or canonical formulation for connectome-based neural population models is given by the following stochastic delay integrodifferential equation (ref. Sanz-Leon et al. 2015, eq. 2.4):

$$\mathbf{P}(d/dt)\mathbf{\Psi}(t) = -\mathbf{\Lambda}\big(\mathbf{\Psi}(t)\big) + \mathbf{Z}\Big[\mathbf{\Xi}(t) + \sum_{\nu=0}^{2} \mathbf{U}_\nu \circ \mathbf{V}_\nu \mathbf{\Gamma}_\nu\big[\mathbf{\Psi}(t - \mathbf{K}_\nu \circ C_\nu^{-1})\big]\Big]$$

Here, the neural population state variables are contained in the vector $\mathbf{\Psi}$ and are mapped on to their derivatives by the temporal differential operator $\mathbf{P}$. The state variables may be, for example, population-average membrane potentials (as in Jansen–Rit) proportions of active cells (as in Wilson–Cowan), or something as minimal as the population-level phase (as in the Kuramoto model). The operator $\mathbf{\Lambda}$ in the first term on the RHS represents the component of this update that is a function of current activity within each state variable, sometimes called the 'local nonlinearity'. The lengthy expression in the second term on the RHS describes how each state variable responds to synaptic inputs from other states in the system—which are first summed and then passed through the coupling function $\mathbf{Z}$, which typically takes a sigmoidal shape. The first term within the large square brackets, $\mathbf{\Xi}$, injects external inputs to one or more state variables, which may include random noise (if the system is stochastic), and/or other direct perturbations such as electromagnetic stimulation. The second term within the large square brackets aggregates synaptic inputs to $\mathbf{\Psi}$ across three hierarchical levels, denoted by the subscript ν: inputs from other state variables within a neural population (ν=0), inputs from spatially nearby populations (ν=1), and inputs from spatially distant populations (ν=2). The first and third of the levels in this hierarchy are universal components of all WBM models. The second level is based on the approach first introduced by Spiegler and Jirsa (2013), incorporating lateral interactions in mesoscopic neural fields into

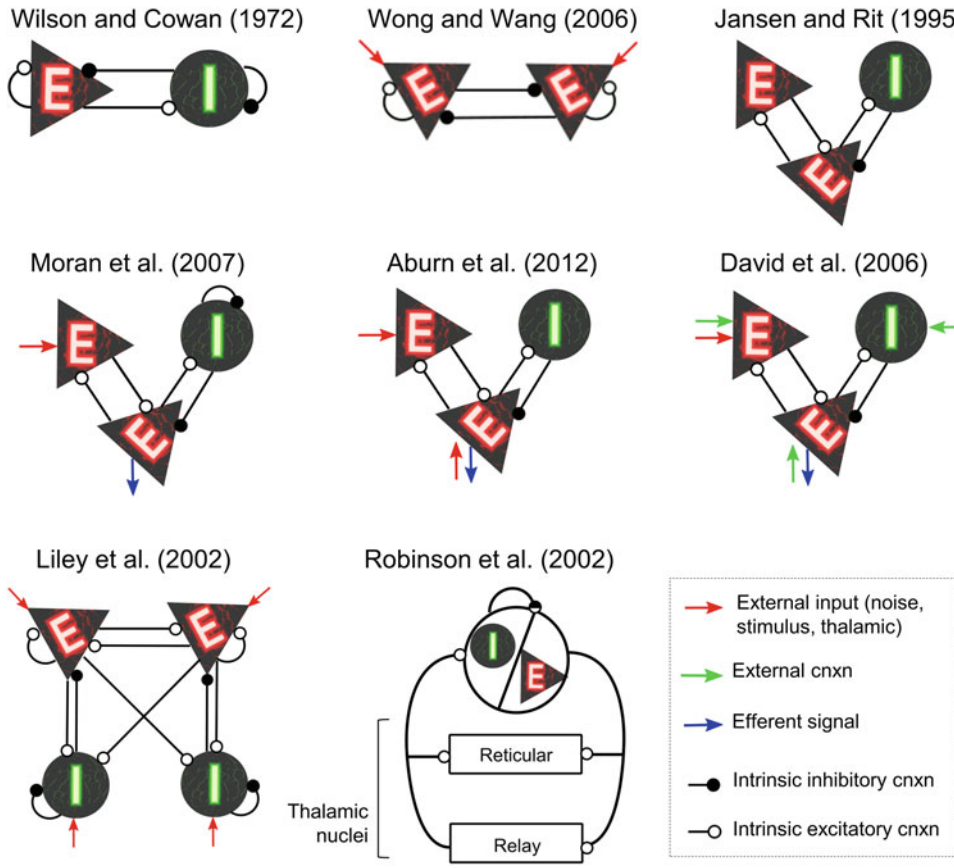


Fig. 13.6 *Neural population model topologies.* The vast majority of neural population models used in the literature consist of small motifs of 2–4 neuron excitatory and inhibitory subpopulations within a cortical or corticothalamic circuit. This figure shows a non-exhaustive set of examples of model topologies that differ, often subtly, in their wiring and specification of afferent/efferent input signals. Note that these motifs are independent of the exact equations governing the dynamics used, which also differ across models

WBMs through a discretized local network of neural masses defined over vertices of a cortical surface geodesic mesh. This approach is less commonly used in the field, in part because it leads to orders of magnitude more numerically intensive simulations due to the large number of neural mass populations in the discretized local networks.

Within the sum, the matrix $\mathbf{V}$ specifies the connectivity topology. At ν=0, this is the interaction between states within a neural mass (c.f. Fig. 13.6). At ν=1, V represents the topology of lateral connectivity within a cortical surface patch given by the local neural field kernel. At ν=2, $\mathbf{V}$ is the large-scale anatomical connectivity matrix (the anatomical macro-connectome), as obtained for example from DWI tractography (see Fig. 13.5). The function $\mathbf{\Gamma}$ applies (if necessary) a rescaling operation. Finally, the term $\mathbf{\Psi}(t - \mathbf{K} \circ C^{-1})$ indexes the previous values of Ψ at a delay that is a function of the per-connection distance or tract length $\mathbf{K}$ and axonal conduction velocity C. C may be scalar-valued (for a single global conduction velocity) or matrix-valued (for a different conduction velocity per connection). At ν=0 and ν=1 these delays are conventionally set to zero, and the only non-negligible delays are assumed to come in at ν=2 due to the large spatial distances and finite conduction velocities of long-range inter-regional communication.

The notation above is useful in that it encompasses all connectome-based neural mass model variants that are formulated in terms of ordinary or stochastic integrodifferential equations.[18] However because of its generality, models are not commonly seen written (in articles and code) in exactly this way. More usually, the $v = 0$ and $v = 2$ terms within the sum, reflecting intra-neural population and long-range inter-neural population interactions, respectively, are written out explicitly as separate terms (e.g. Griffiths and Lefebvre 2019; Griffiths et al. 2020). Note also that we have said nothing here about the actual form of the neural population dynamics—i.e. the equations defining the operator $\mathbf{\Lambda}$. We turn to this next.

13.3.2 Neural Population Models

In Sect. 13.2.1 we traced the development of the idea of using dynamic models at the level of neural populations to represent and track the collective activity of a patch of neural tissue. To complete this picture, in this section we provide some brief summaries of the major neural population models that have been used in WBM work during The Present. Due to space restrictions we do not go into formal mathematical details—for a more technical presentation of most of these models we refer the reader again to Sanz-Leon et al. (2015), and to the original and exemplary studies cited below.

As noted earlier, one of the key distinctions made in the field is between 'phenomenological' and 'physiological' (or sometimes 'biophysical') model types[19] (Sanz-Leon et al., 2015; Sanz Leon et al., 2013). The early neural mass and field models discussed in Sect. 13.2.1 were all of the 'physiological' type. Physiological models attempt to describe, parsimoniously but accurately, relevant aspects of the physiology of neural tissue that determine dynamics at the population scale. This includes the state variables and parameters that represent physiological quantities like firing rates, synaptic strengths, rate constants, synaptic kinetics, and conduction delays. Phenomenological models, in contrast, adopt the 'spirit' of the neural population activity idea outlined in Sect. 13.2.1, but typically do not attempt to ground the equations used in biological concepts and mechanisms. Beginning with the second of these first:

13.3.2.1 Phenomenological Models

Linear Diffusion The linear diffusion (LD) model (also linear time-invariant system, linear dynamical system, linear graph diffusion model), has been used extensively in WBM, in several variants. The basic model takes the form $\dot{\mathbf{\Psi}} = \mathbf{V}\mathbf{\Psi} + \mathbf{\Xi}$, where (as in the previous section) $\mathbf{\Psi}$, $\mathbf{V}$, and $\mathbf{\Xi}$ represent neural activity, large-scale connectivity, and additive noise, respectively. This is the simplest possible linear dynamical system, and when $\mathbf{V}$ is a graph Laplacian ($\mathbf{V} = \mathbf{D} - \mathbf{A}$, i.e. the diagonalized node degree matrix $\mathbf{D}$ minus the adjacency matrix $\mathbf{A}$; see also Sect. 13.3.4), this gives the standard equation for linear diffusion on a graph. Whilst the LD model is best thought of as a phenomenological neural population model type, we note these or similar equations have been arrived from consistent and reasonably well-motivated reductions and simplifications of more physiologically detailed neural mass models (Deco et al., 2013a, 2014; Galán, 2008).[20]

[18] The notation does not cover alternative expressions using partial differential equations (e.g. Sanz-Leon et al. 2018), but those have not been widely used for WBM to date.

[19] As argued earlier, the categorical distinction sometimes made between 'phenomenological' and 'physiological' model types is, in our opinion, not a particularly helpful one. The reason for this is that, in a nutshell, some physiological models are 'more physiological' than others. For example, the Jansen–Rit and Robinson models, despite including several neural subpopulations and aspects of their physiology, are ultimately based on a set of equations (Freeman et al., 1975; Lopes da Silva et al., 1974) that were chosen to accurately reproduce characteristics of neural activity recordings, but not actually derived in a mathematically consistent way from physiological description of single neurons, as was done for example with the Wilson–Cowan (Wilson and Cowan, 1972) and Dynamic Mean-Field (Deco et al., 2013a) models.

[20] As noted, earlier the above equation is also the same as used in the original generative model for fMRI DCMs (Friston et al., 2003) (assuming zero values in the DCM 'B' and 'C' matrices), and features heavily in the more recently

The LD model plays a special role in neural population model simulations, as it represents a null model for hypotheses proposing that physiologically detailed and nonlinear dynamics are needed to produce a given simulated data feature. The main data feature that has been studied in this context is temporal covariance structure (aka functional connectivity), and for this the LD model has usually been found to perform at least as well as more complex nonlinear models (Abdelnour et al., 2014; Deco et al., 2013a; Honey et al., 2009). Furthermore, due to its simplicity the LD model allows questions around functional connectivity patterns to be explored analytically, through algebraic calculations of steady-state covariance structure (i.e. time-domain functional connectivity), power spectra, and complex cross-spectra (i.e. frequency-domain functional connectivity). In particular, a closed-form expression for the standard Pearson cross-correlation functional connectivity matrix can be easily obtained from the LD model in terms of the eigenvectors and eigenvalues of the anatomical connectivity matrix (Abdelnour et al., 2018; Galán, 2008; Honey et al., 2009; Robinson, 2012). We return to the relationship between anatomical and functional connectivity and implications of these LD model results later.

Kuramoto Like the LD model, the Kuramoto model (Breakspear et al., 2010; Kuramoto, 1984) gives a highly simplified description of neural population activity, using only a single state variable per neural population or network node, without differentiating neuronal subpopulation types. The distinguishing feature of Kuramoto model is that this state variable is the phase of a limit cycle oscillator, giving a direct but quite abstract representation of rhythmic neural activity. WBMs employing the Kuramoto model aim to describe large-scale neural activity in terms of the synchronization dynamics of multiple phase oscillations, coupled weakly according to the underlying anatomical skeleton (Breakspear et al., 2010; Cabral et al., 2011). These oscillators may spontaneously lock to a common frequency despite having differences in their natural frequencies (Strogatz, 2000). Assumptions of the Kuramoto model as applied in WBM include the existence of weak coupling between oscillators and the dependency of interactions on the sine of phase differences between pairs of brain regions. Indeed, applying more abstracted models not only enhances analytical tractability but also better explains common fundamental mechanisms that may underpin a variety of diverse anatomical and physiological processes. Despite being highly abstract, the Kuramoto model and its different variants (e.g., including delays and complex coupling structures) have proven to be capable of reproducing many of the non-trivial collective dynamics and complex emergent synchronization behaviours observed in empirical neuroimaging data (Breakspear et al., 2010; Cabral et al., 2011). Notably, Kuramoto also introduced the complex order parameter, by averaging the complex numbers representing the phases of coupled phase oscillators, to capture the level of macroscopic (whole-network) synchrony of the collection. The magnitude of the order parameter describes the global phase coherence of the whole system at each time point. Usually, the global dynamic behaviour of a network of coupled oscillators is described by the mean and standard deviation of the magnitude of the order parameter across all time-points, respectively called the global synchrony and global metastability of the system (Breakspear et al., 2010; Kaboodvand et al., 2019; Strogatz, 2000).

Stuart–Landau The Stuart–Landau (SL) model, originally derived and studied by John Trevor Stuart, Lev Landau, and others as a model of turbulence in hydrodynamics, is a two-state nonlinear dynamical system that gives the canonical model (normal form) for an Andronov–Hopf bifurcation (the switch from a quiescent equilibrium state to a self-sustained limit cycle). The SL model has been used extensively in the WBM literature (Deco et al., 2017; Freyer et al., 2012; Kaboodvand et al., 2019), particularly in the context of research questions on criticality and bifurcations. It is capable of expressing both

developed spectral fMRI DCMs (Friston et al., 2014), which have also recently been extended to connectome-scale networks (Razi et al., 2017).

noisy asynchronous dynamics and oscillatory behaviours. Notably, recent studies using coupled SL oscillators to model resting-state dynamics in fMRI data found that the best fit of this model to neuroimaging data occurs at the brink of the bifurcation (transition from fixed point to oscillating behaviour), where both steady-state solutions and periodic oscillations co-exist (Deco et al., 2017; Kaboodvand et al., 2019). In addition to multistability, this model also captures another key feature of healthy brain dynamics: high metastability. Metastability refers to the simultaneous realization of two competing tendencies to synchronize and desynchronize, achieved by spontaneous shifting between unstable states or transient attractor-like states (Scott Kelso, 2012). Models exhibiting a Hopf bifurcation are particularly well-suited for simulating the effects of external manipulation (including perturbation and neurostimulation, e.g. (Spiegler et al., 2016, 2019), and grey matter lesions (Kaboodvand et al., 2019)). Relatedly, introducing frequency dynamics into the system of coupled Stuart–Landau oscillators has been shown to improve performance of WBM fits to empirical data, by yielding temporally richer dynamics (Kaboodvand et al., 2019).

Fitzhugh–Nagumo The Fitzhugh–Nagumo (FHN) model is a planar oscillator that is well-known within computational neuroscience as a 2-dimensional reduction of the 4-dimensional Hodgkin–Huxley equations, that retains their essential qualitative dynamical behaviour. It has been used extensively (Ghosh et al., 2008; Sanz Leon et al., 2013; Spiegler et al., 2016) in the WBM literature as a simple model of oscillatory neural population activity. Like the SL model, the FHN model is easily moved via variation of its parameters through a Hopf bifurcation, where it switches from quiescent to self-sustained limit cycle oscillations. In WBM studies using FHN model, the natural frequency is usually set to either alpha or gamma.

13.3.2.2 Physiological Models

A number of different physiological neural population models are currently used in WBM research. These differ along two primary dimensions: (a) the local circuit motif (number of neuronal subpopulations, and how they are connected), and (b) the dynamics—i.e. the equations used to describe activity in each subpopulation. Speaking to the first of these, Fig. 13.6 shows the local circuit motifs for a number of commonly used physiological neural population models.

Wilson–Cowan As described earlier in Sect. 13.2.1 The Wilson–Cowan model (Chow and Karimipanah, 2020; Cowan, 2014; Wilson and Cowan, 1972) features two interacting excitatory and inhibitory subpopulations, with coupled first-order nonlinear ordinary differential equations describing activity level (proportion of active cells per unit time) in the population. Whilst this is the most widely known neural population model in computational neuroscience, it has actually not been used extensively in WBM, compared to other alternatives. The Wilson–Cowan model has however provided the inspiration for many of the more commonly used models discussed in this chapter.

Jansen–Rit Also described at length in Sect. 13.2.1, the Jansen–Rit model (Jansen and Rit, 1995) features one inhibitory and two excitatory neural subpopulations, with second-order differential equations describing population-average membrane potential dynamics. Widely known in part due to its use in DCM for M/EEG (David and Friston, 2003; David et al., 2006a), the Jansen–Rit model has been employed in WBM studies to study neurostimulation (Kunze et al., 2016; Spiegler et al., 2011) and brain rhythms (Stefanovski et al., 2019).

Dynamic Mean Field The dynamic mean field (DMF) model, also known as the 'Reduced Wong–Wang' or 'Wong–Wang–Deco' model, was derived by Deco et al. (2013a) from the equations of a (leaky integrate-and-fire) spiking network. A key part of the model's derivation included ignoring fast glutamatergic (AMPA receptor-mediated) and GABAergic activity, and only tracking the slow glutamatergic (NMDA

receptor-mediated) activity within a neural population. For this reason it is particularly suited to modelling slow neural fluctuations seen in haemodynamic signals such as fMRI (Deco et al., 2013a; Hansen et al., 2015). In the following year, the 1-state DMF model was extended to include a second inhibitory neural population, resulting in a two-state system very similar to the classic Wilson–Cowan equations, with negative feedback that is capable of generating oscillatory activity. This 2-state DMF model has been principally use to study resting-state fMRI (static and dynamic) functional connectivity data (Deco et al., 2014; Murray et al., 2018; Zimmermann et al., 2018).

Robinson The Robinson model (Robinson et al., 2001) is a neural field model that includes a rhythm-generating corticothalamic circuit with nonzero conduction delay. The dynamics of membrane potential fluctuations in each cortical and thalamic subpopulation are second-order in time, with many mathematical similarities to the Lopes Da Silva and Jansen–Rit equations. As shown in Fig. 13.6, the corticothalamic circuit includes excitatory and inhibitory subpopulations in the cortex, as well as excitatory (relay) and inhibitory (reticular) thalamic nuclei. The circuit has been studied extensively as a model of EEG alpha rhythms (Robinson et al., 2001), as well as in relation to sleep (Abeysuriya et al., 2015), Parkinson's (Müller et al., 2017), and TMS plasticity (Wilson et al., 2016, 2018). In addition to the corticothalamic circuit dynamics, the whole-brain aspect of this model relates to the cortical compartment, which is an extended neural field representing all of cortex (or, in more recent versions, separated into left and right hemispheres (Gabay and Robinson, 2017; Robinson et al., 2016)). A recent focus on the spatial structure of neural activity eigenmodes in this model (Gabay and Robinson, 2017; Gabay et al., 2018; Robinson et al., 2016) is following similar ideas to Nunez (1974), Nunez and Cutillo (1995), and Nunez and Srinivasan (2006).

Others Honorary mentions in this expedited neural population model survey go to *Liley*—whose model (Liley et al., 2002) gives an alternative account to Robinson's of EEG alpha oscillations and has been developed with a focus on EEG phenomena during anaesthesia; *AdEx*—the adaptive exponential integrate-and-fire neural population model, one of a new breed of mean-field reductions that have a more consistent relationship to single-cell behaviour (see also Montbrió et al. 2015; Zerlaut et al. 2018).

13.3.3 Parameter Estimation

A central component of all mathematical modelling is the tuning of parameters of a model to match experimental observations. In parameter estimation (aka parameter optimization, model fitting, model inversion; we treat these terms as synonymous here) the features of interest in those experimental observations are encoded in an objective function, and various algorithms are used to efficiently (or inefficiently!) find the optimal parameter values that minimize/maximize the objective function by best replicating the experimentally observed features, after taking into account any other (regularization) constraints. Identifying these optimal parameters is useful in at least three ways: First, one might be interested in the actual numeric value of the parameter. This applies in particular to parameters that represent concrete, meaningful physiological quantities, such as axonal conduction delays Van Albada et al. 2010, effective connection strengths David et al. 2006a, and excitation–inhibition ratios (Murray et al., 2014; Zimmermann et al., 2018). For other commonly explored but less physiologically interpretable parameters such as global coupling, the Kuramoto order parameter, or the FHN self-recurrence control parameter, the absolute numerical value may not be as useful. Second, one might be interested not in the parameter values per se, but in the dynamical properties of the modelled system when the parameters are set to their optimal values. Third, WBM parameter estimates can be treated 'blindly' (i.e., without specific concern to their physiological interpretation) as additional data features for biomarker discovery efforts (Iravani et al., 2021).

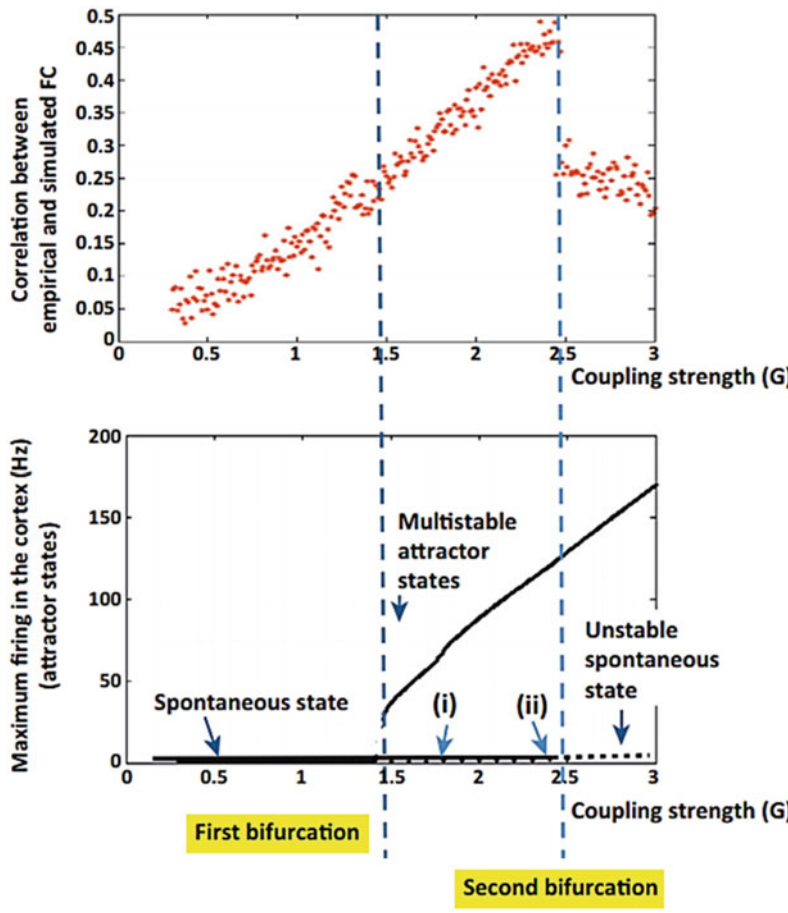


Fig. 13.7 *WBM FC fit is maximized in the vicinity of a bifurcation point.* In brute-force 1-D optimization of the global connectivity scaling parameter g, Deco et al. (2013a) found that the fit of simulated to empirical functional connectivity matrices (*upper panel*) is maximized at the (second) bifurcation point where the network's behaviour (pattern of firing rates) changes qualitatively from multistability to instability (*lower panel*). Modified from Deco et al. (2013a)

In WBM research, the data features of interest have typically been one or more of (1) functional connectivity (static or time-varying), (2) power spectra, and (3) evoked response waveforms, in fMRI, MEG, EEG, ECoG, or SEEG recordings. Within fMRI WBMs, the most common objective function used to date is based on the Pearson correlation between the vectorized upper triangles of simulated and empirical functional connectivity matrices (e.g. Deco et al. 2013a; Honey et al. 2009), although several recent studies have highlighted the importance of dynamic connectivity patterns as well (Deco et al., 2017; Kaboodvand et al., 2019). It has been suggested that maximizing similarity of global dynamic behaviour of the ensemble of oscillators (captured by global synchrony and global metastability) and minimizing the distance between distributions of instantaneous phase synchrony patterns can significantly improve the model fit to empirical data. In a now-classic study, Deco et al. (2013a) computed this objective function for a series of BOLD-fMRI simulations using the DMF neural population model. This was done across a range of values for a global coupling parameter g, which linearly scaled connectivity weights. The authors found (Fig. 13.7) that the optimal value of g (the one that maximized correlation with empirical functional connectivity) was also in the vicinity of a bifurcation to multistability in the neural dynamics. Proximity to specific bifurcations confers certain important properties on dynamical systems, including criticality and pattern formation, and is believed to be important for optimal brain functioning (Deco et al., 2013b). This work is an excellent example of a scenario where the qualitative system behaviour (the bifurcation) is of principal interest, not the final estimated values

of g, which have no direct physiological interpretation (Deco et al., 2013a).

The global coupling scaling parameter g is one of the most sensitive and important components of a WBM, and its tuning is a standard part of almost all WBM studies. This is also seen in Fig. 13.8, which summarizes key results from Abeysuriya et al. (2018), who used the Wilson–Cowan model to study the fast-timescale whole-brain dynamics seen in source-space MEG data. The model fitting approach here varied g (as in Fig. 13.7), and in addition simultaneously varied a global axonal conduction velocity parameter v. The optimum values of g and v (red dot in Fig. 13.8a) were determined by the best fit between simulated and empirical MEG functional connectivity, as defined by bandpass-filtered, alpha-frequency range amplitude envelope correlations (AECs; Fig. 13.8b,c).

Searching across all parameter values within a specified range and displaying some high-level (usually scalar-valued) feature of each model run, as is done in both Figs. 13.7 and 13.8, is known as 'parameter space exploration' (PSE). The point of these low-dimensional PSEs is usually to visualize the pattern of changes in qualitative system behaviour over the parameter space. In a model fitting context, this is also known as 'brute-force' parameter optimization.[21] This brute-force approach has been the primary model fitting methodology used this far in WBM. It works particularly well in 1D and 2D (i.e. when one or two parameters are varied simultaneously), in which case the results can be easily visualized with scatter plots and heatmaps, as in Figs. 13.7 and 13.8. The down side of brute-force search is that the number of simulation runs required grows exponentially with the number of parameters varied. For WBMs—particularly of fMRI data—depending on the implementations used and the type of data being simulated, single run times may vary from a minute or less to several hours or days. Brute-force search therefore becomes infeasible for parameter spaces of around 5 dimensions or higher (depending naturally on the granularity of sampling within the ranges for each parameter). At this point, if essential parameters cannot be fixed or otherwise ignored, it becomes necessary to employ more sophisticated optimization approaches.

Several authors have proposed sampling-based approaches (e.g. Abeysuriya and Robinson 2016) and evolutionary algorithms (e.g. Cona et al. 2011) for neural mass model parameter estimation. Both of these work well for relatively simple models (e.g. of algebraic power spectra Abeysuriya and Robinson 2016) that are quick to evaluate, and therefore allow for large numbers of samples. For more complex models however, it is necessary to employ some form of gradient-based approach to achieve workable scaling and speeds. The pre-eminent example of gradient-based parameter optimization in the brain modelling space is DCM, which employs several variants of gradient descent on the log model evidence (a complexity-penalized goodness-of-fit metric), using variational techniques to guarantee convergence. Generalizing these implementations from small-scale networks to whole-brain models presents two challenges, however. First, a 'trick' employed in most DCM M/EEG model types is to employ a re-formulation of the original David–Friston neural mass model equations that yields an analytic Jacobian, and absorbs the delay operator into the Jacobian. The analytic Jacobian dramatically facilitates gradient-based methods (because it allows the calculation of the gradients). Unfortunately however, it is not possible to write the majority of neural population models (particularly those with explicit and variable conduction delays) in this way. An emerging alternative to only using models admitting of an analytic Jacobian comes from modern tools developed principally in the machine learning community (such as Tensorflow, PyTorch, STAN, and Jax) that employ algorithmic or automatic differentiation (commonly known as 'autodiff'). Automatic differentiation allows gradients to be computed directly from numerical code, without the need for extra mathematical work (which is anyway unfeasible in the general case)

[21] Although from an algorithmic point of view brute-force search is so simple and computationally inefficient as to barely warrant the name 'model fitting'.

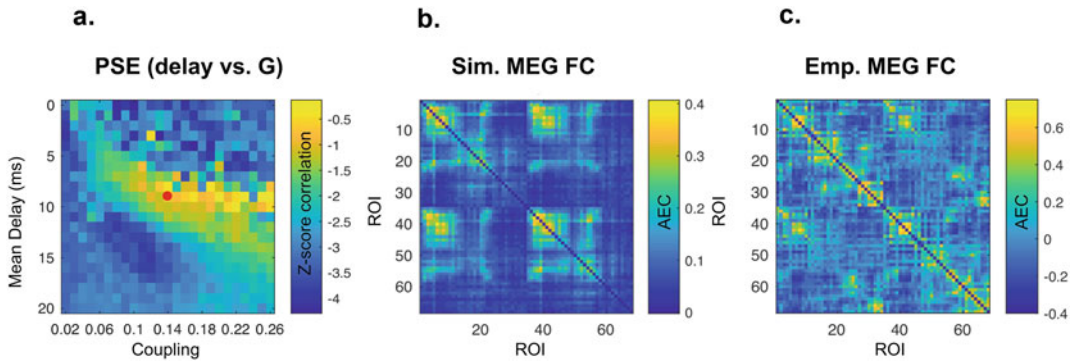


Fig. 13.8 *Fitting MEG Functional Connectivity.* Shown are (2-D brute force) model fitting results from Abeysuriya et al. (2018). These authors used modified Wilson–Cowan equations to model MEG power spectra and functional connectivity. (**a**) Model fit is shown for all values of the global connectivity scaling parameter g and global axonal conduction velocity (converted into a mean delay over connections for ease of interpretation). The zone of best fit is a diagonal manifold within the 2D parameter space, and the best-fitting parameter combination is indicated in the figure with a red dot. (**b**) Best-fitting simulated alpha-band MEG amplitude enveloped correlation (AEC) functional connectivity, (**c**) Empirical MEG AEC

(Baydin et al., 2018). The version of this type of optimization employed by STAN is known as ADVI (Automatic Differentiation-based Variational Inference Kucukelbir et al. 2017). Recent WBM work on personalized epilepsy treatments, also discussed in Sect. 13.3.5, has successfully employed a hybrid global (MCMC sampling) and local (STAN ADVI) inference approach (Hashemi et al., 2020). Given the importance of robust and meaningful parameter estimation in WBM, further technical work in this area is a high priority for the field.

13.3.4 Connectivity

As we have seen, definition of the network structure subtended by long-range white matter fibres (i.e. the anatomical macro-connectome) has a quintessential and critical role in WBM. One of the great promises of WBM is the possibility of using noninvasive brain imaging to incorporate individual subjects' and patients' unique connectivity fingerprints, potentially perturbed by various disease processes into 'personalized' WBMs. Whilst the general approach for building such models is now fairly well established, there are a number of attendant technical details that vary considerably across published work and need to be properly understood by researchers. In addition, normative atlases of human and non-human connectivity structure, at various levels of resolution, have a key role to play in refining the use of connectivity in WBMs. In the following paragraphs we offer some commentary on these issues.

13.3.4.1 Scaling of Connection Weights

In tractography-based analysis pipelines for reconstruction of inter-regional anatomical connectivity, the chief end-result is usually a matrix containing the number or 'count' of tractography streamlines interconnecting a given pair of regions in a parcellation. The analysis steps leading up to this matrix are extensive and include the specifics of diffusion-weighted MRI data acquisition, preprocessing, local tissue model and tractography algorithm used, and tractography post-processing (e.g. application of lower and upper thresholds on streamline lengths, streamline filtering with e.g. SIFT or LiFE). It is beyond the scope of this chapter to summarize all of these options, which are in any case not specific to WBM per se, and well covered in the diffusion MRI macro-connectomics methods literature (e.g. Jeurissen et al. 2019; Sotiropoulos and Zalesky 2019). We therefore focus the discussion here on transforms one might apply to the raw

streamline count matrix to prepare it for WBM simulations.

First, it is essential to appreciate that streamline counts are not direct measurements of the actual quantity of interest—which is, broadly speaking, number of axons. Fortunately, comparisons against chemical tract tracing studies in non-human primates have at least shown proportionality between axonal count estimates and tractography streamline counts and densities (Donahue et al., 2016), although the degree of correlation leaves a lot to be desired. Tractography-based connectivity estimation is nevertheless well-known to suffer from substantial numbers of false positives (in the case of probabilistic algorithms) and false negatives (in the case of deterministic algorithms) (Maier-Hein et al., 2017). One common source of false positives is the large number of locations in white matter that contain crossing fibres, at which points tractography streamlines are liable to 'skip' from one white matter tract to another, thereby yielding an erroneous 'composite' connection. A common source of false negatives is the bias against long connections, resulting from the fact that the larger number of steps required to track a long fibre leads to a higher probability of termination due to local signal noise at some point along the fibre's trajectory (Jeurissen et al., 2019; Zalesky and Fornito, 2009). Countering this, tractography is also known to have a positive bias towards long connections when the streamline initiation points are set randomly throughout white matter, because fibres that are long are also large, and so take up proportionally more of that volume, making them more likely to be seeded at Hagmann et al. (2008) and Jeurissen et al. (2019). Due to the latter consideration, a distance correction is often applied, dividing the tractography-estimated connection weight between two regions by the average streamline length (Adhikari et al., 2015; Hagmann et al., 2008; Roberts et al., 2016). This correction is also however sometimes erroneously applied following analysis pipelines when streamlines are initiated at the grey–white matter interface rather than deep white matter. A further correction sometimes used is to normalize streamline counts by the total size of the two connecting ROIs, or by the combined total volume of their surfaces receiving tractography projections, resulting in a per unit volume connection density (Adhikari et al., 2015; Hagmann et al., 2008; Schirner et al., 2015; Van Den Heuvel and Sporns, 2011). In chemical tract tracing studies, the distribution of connection strengths (density of axons per unit area) is logarithmic and very wide, spanning six orders of magnitude (Markov et al., 2014). The distribution of streamline weights in tractography is also logarithmically distributed, although it is unclear to what extent this is due to the real anatomical features seen in the ground-truth data, versus the biases noted above (Donahue et al., 2016; Sotiropoulos and Zalesky, 2019). It has been suggested (without much justification) by Honey et al. (2009) that 'effective' connection strengths in the brain likely do not span several orders of magnitude. These authors' proposed solution to this 'issue' was to resample the highly skewed tractography weights matrix to a unit-normalized Gaussian distribution. Other authors simply apply a log transform to the connection strengths (Abeysuriya et al., 2018; Griffiths et al., 2020). It is certainly true that, whether well biologically justified or not, in connectome-based neural population model simulations, logarithmically distributed connectivity weights will likely lead to a small number of areas having disproportionately high influence on the activity.

After these explicit adjustments to the connection strength distribution, it is usually necessary to rescale so that the values lie within some desired range (e.g. 0 and 1). Most commonly this is done at a global level, for example by dividing all values in the matrix by the maximum value (Abeysuriya et al., 2018), or by the Frobenius norm (Mehta-Pandejee et al., 2017). Alternatively, rescaling is sometimes done at the row (i.e. node) level (Demirtaş et al., 2019; Spiegler et al., 2016). Again, rows can be unit-normalized by dividing each row by the maximum value of that row. More standard in other areas of science (particularly graph theory) is to compute the network or graph Laplacian, by subtracting a diagonal matrix of node degrees (i.e. row sums) from the orig-

inal adjacency (in this case, rescaled streamline density) matrix. The effect of both these latter two operations—normalizing row-wise and taking the Laplacian[22]—is to make the row sum (i.e. total incoming connection weights for each node) take a uniform value over regions (value of 1 in the first case, value of 0 in the second). Neither of these approaches are advisable if the aim is to maintain clear biological interpretability of connection weights in the WBM, however. The reason for this is that the implicit assumption that all brain regions receive identical net input, and differ only in the distribution of input strengths over network nodes, is highly questionable. Moreover, the heterogeneity of approaches for tractography streamline and connectivity weights matrix adjustment and rescaling is somewhat problematic for the field. The resultant differences in connectivity matrix structure are likely to have a major impact on the generalizability and reproducibility of modelling studies. We return to this issue, with some proposals, in Sect. 13.4.2.

13.3.4.2 Atlases and Exemplar Datasets

In WBM studies where tractography-derived subject-specific anatomical connectivity is not a key component, it is useful to have a go-to dataset that serves as the default option for a critical mass of researchers. There are two datasets that have served this role in WBM over the past decade: the CoCoMac database (and its derivatives) and the connectivity matrices first described in 2008 by Hagmann et al. (2008) and Daducci et al. (2012) (see Fig. 13.5). The 'Hagmann Connectivity' Hagmann et al. (2008) has been used by dozens if not hundreds of research studies on brain connectivity, including many using WBM. Despite being over 15 years old, the Hagmann diffusion-weighted MRI dataset is actually still a relatively high quality one by current standards. Nevertheless, the Hagmann Connectivity's role as one of the WBM and neuroimaging macro-connectomics community's primary exemplar connectivities has now been all-but relinquished[23] to tractography reconstructions from the (original, 'phase 1')[24] WashU-Minnesota Human Connectome Project (HCP) dataset—a rich, multimodal neuroimaging and neurocognitive assessment resource, with a large sample size ($N > 1000$) of healthy subjects.[25]

As described in Sect. 13.2.4, several early WBM studies were based on CoCoMac connectivity (Deco et al., 2009; Ghosh et al., 2008; Honey et al., 2007), which at the time was the only real source of approximately human whole-brain connectivity before macro-connectomics neuroimaging took off in the late 2000s. CoCoMac has the distinct advantage of representing 'gold-standard', 'ground-truth' information on anatomical projections; something that cannot be said for tractography-based estimates, whose relationship to anatomical ground truth remains somewhat unclear. The main disadvantages of CoCoMac are that (a) it is based on macaque rather than human tracer studies, and (b) its connectivity weights have a somewhat limited range of values (0, 1, 2, or 3). The first of these has been addressed somewhat by mapping (as discussed in Sect. 13.2.4) of the CoCoMac brain regions CoCoMac on to the human brain. This human-mapped CoCoMac

[22] Note that moving from the original adjacency to the Laplacian only involves a change in the diagonal values of the matrix—specifically it adds a strong negative self-connection on the diagonal equal to the number or weighted sum of positive incoming connections. Whether it makes sense to use the Laplacian in a WBM, and what the implications of that choice are, depends on whether the model of interest (and its software implementation) does actually use the matrix diagonals. When they are used, diagonal entries denote self-connections within a node, but WBM modelling software often ignores the diagonals because nodal self-connections are encoded separately within the neural population model equations. In the TVB software, for example, matrix diagonals are ignored for this reason; in the DCM software, however, matrix diagonals are used for parameterization of self-connections. Naturally, diagonal values play a profound role in the behaviour of linear algebraic WBM models.

[23] Gradually asymptoting to 'every man and his dog has played with HCP'.

[24] (there are now over a dozen ongoing HCP follow-up studies).

[25] Curiously, however, at the time of writing the Human Connectome Project is still after 10 years yet to release a Human (anatomical) Connectome.

connectivity was studied by Ghosh et al. (2008) and Knock et al. (2009), eventually grew into the 'default' connectivity matrix distributed in and used extensively by the TVB simulator library. Here it serves very much as the go-to dataset for WBM in the way described above. Recent work has developed a procedure for fusing CoCoMac and tractography data (Bezgin et al., 2017), which importantly also includes a detailed and high-resolution map of intra- and extra- thalamic connectivity (Bezgin et al., 2017; Spiegler et al., 2016), which cannot be easily obtained from tractography. The limitation in the weights range of CoCoMac has also been addressed somewhat by the more recent availability of high-quality macaque tract-tracing data—which spans several orders of magnitude in weights (Markov et al., 2014). Shen et al. (2019) have found that probabilistic tractography, when using the best parameters, achieves good correspondence with tracer injection data.

Looking beyond primate species, a relatively new and extremely powerful addition to the WBM space is the Allen Mouse Brain Atlas.[26] Featuring an extremely detailed microscopy-based, cellular-level resolution map of mouse brain connectivity, as well as richly characterized cell type, gene expression, and physiology information, the Allen Mouse Brain Atlas is widely recognized as the most comprehensive and useful neuroinformatics resource in the field of neuroscience today. Recent work has adapted the connectivity and cortical surface data from the Allen Atlas for use within the TVB platform (Melozzi et al., 2017; Spiegler et al., 2019), and this joint resource ('The Virtual Mouse Brain'; TVMB) is likely to be an important vehicle for discovery and innovation for WBM research the coming years.

13.3.5 Clinical Applications

Applications of WBM to questions in clinical neuroscience has been a central focus in the field from its inception, as indeed it has been in other fields that employ neural population models, macro-connectomics, and neuroimaging. The specific and unique contributions of WBM to these efforts relate to:

1. *Mechanisms*—studying how physiological processes underlying various pathologies manifest at the whole-brain level.
2. *Personalization*—the development of patient-personalized WBMs for diagnosis, prognosis, and treatment design.
3. *Virtual Therapies*—the in silico testing of multiple alternative treatment options, and use of this information in clinical decision support.

As we shall see in the following pages, the majority of work done on clinical applications of WBM to date has been concerned with the first of these. This is entirely proper because the second two are contingent on the availability of appropriate WBMs that incorporate and express solid biological understanding.

We have already discussed in previous sections personalization of WBMs in a non-clinical context, through their connectivity structure. However it is in the clinical setting that personalization of WBMs really comes into its own. This is because inter-subject variability in disease progression, and how that interacts with the individuating characteristics of a given patient's brain, undoubtedly leads to many subject-specific aspects of clinical conditions that warrant a personalized, patient-level characterization. The idea here is therefore to develop for each patient a model that is specific to *their* pathology in *their* brain, based on information from neuroimaging and other sources.

The third dimension of clinical application work—development of Virtual Therapies—is something that draws strongly on understanding of mechanisms, and (although not strictly necessary) would benefit heavily from patient-level personalization. The aim here is to use WBMs to assess, on mechanistic neurobiologically based (and well-validated) grounds, the expected outcome of a given clinical intervention. With this in place it is then in principle a simple (embarrassingly parallel) matter of software

[26] https://mouse.brain-map.org/.

engineering to assess the expected outcome of thousands or millions of alternative simulated intervention variations, and find the optimal choice under the relevant practical constraints.

In the following pages we discuss applications of WBM in work on epilepsy, traumatic injury, stroke, neurodegeneration, neuropsychiatry, and brain stimulation. It is impossible in the space available to do justice to the breadth of work in any of these domains, and so we do not aim here to be either comprehensive or systematic. Instead, we restrict ourselves to summarizing a few notable examples, and in addition offer some high-level comments on general themes and considerations.

13.3.5.1 The General Approach

The general approach in clinical WBM work can be summarized as follows: changes due to pathophysiology or pharmacological interventions may be (a) specified a priori (using e.g. regional brain pathologies detectable on structural MRI scans), (b) estimated from functional (fMRI/MEG/EEG) data through parameter optimization, or (c) some combination of the two.

For the second of these—changes estimated from functional data—the starting point is a homogeneous model with uniform parameters, for all brain regions and all subjects. Fitting is then performed—iteratively comparing the simulated and empirical data for the brain activity feature of interest, and updating model parameters to maximize the (penalized) goodness-of-fit. The resultant parameter estimates may then be used at the single-subject level as diagnostic evaluations of current brain state, or in second-level (group or condition comparison) analyses.

In the case of a priori (or 'bottom-up') modelling of disease-related changes: these changes may—depending on the pathology in question—be modelled either as disrupted anatomical connectivity or as disrupted regional neural dynamics. The two principal ways of modelling anatomical connectivity pathologies a priori are to modify (usually weaken) connection strengths or change (usually decrease) conduction delays between region pairs. Removal of all edges connecting a node constitutes removal of that node. Pathological changes in node dynamics may be expressed either through a novel dynamical model, or (more often) an off-the-shelf model, with modified parameters reflecting the hypothesized changes. These changes may be global or (more commonly) region-specific, reflecting such things as lesions, pathophysiological tissue, spatial maps of neurotransmitter efficacy, or brain stimulation therapy. The end-result in this case is a prognosis or prediction about how the hypothesized disease process will influence brain dynamics, at either the group- or individual patient-level.

13.3.5.2 Epilepsy

Epilepsy is a severe neurological condition with high prevalence (~5–8%) in the general population worldwide. It is characterized by spontaneous recurrence of seizures—sudden bursts of uncontrolled synchronous neural activity—causing neurological, cognitive, psychological, and social disturbances (Muhigwa et al., 2020). Neurophysiological modelling of epileptiform activity is a veritable cottage industry in computational neuroscience (e.g. Breakspear et al. 2006; Jirsa et al. 2014; Kameneva et al. 2017; Taylor et al. 2014). The reasons for this are likely twofold: First, epilepsy is by its very nature a dynamical disease, and for this reason is an inherently attractive research area to scientists of both a mathematical and computational bent. Second, seizure-like (high-amplitude, fast-bursting) activity is a relatively easy-to-induce regime in many computational models of neurons and neural populations; and so epilepsy presents itself as a natural topic of study for scientists already working on and exploring those systems. Similarly, for scientists working on and interested in network dynamics, the phenomenon of seizure spreading 'infectiously' throughout a network, in ways that are influenced by the network's topology, is an inherently interesting phenomenon. Clinical questions in WBM work on epilepsy relate to the physiological mechanisms of seizure initiation and spread, and to interventions aimed at controlling or minimizing seizures through therapeutic drugs, stimulation, and neurosurgery.

Somewhat uniquely in neural population modelling, models of epileptic activity are often specific to that application, not general-purpose descriptions of neural activity. There are roughly two flavours: (1) models that describe seizure generation through bistability mechanisms, and (2) models where seizures are generated via parameter-induced bifurcations—where a (slowly varying) model parameter moves the system into and out of a regime where seizure is the only stable state.

In an early example of epilepsy modelling with WBMs, Taylor et al. (2014) developed one of the first personalized connectome-based neural population models of epileptic activity.[27] The population model used was an Amari-type neural field with centre-surround inhibition, placed in a parameter regime able to spontaneously generate seizure-like activity. Subsequently Taylor et al. (2015), these authors used a modified version of this model to derive an optimal stimulation control algorithm, that could be used to abate seizures through implanted neurostimulators. There is much interest currently in the development of physiological model-based technological devices of this sort, although to our knowledge a working prototype has yet to be demonstrated in practice.

Whilst neurostimulation is an area of active study, the usual treatment option for the ~20–40% of epilepsy patients who are unresponsive to drugs is surgical resection of the epileptogenic tissue. Importantly, there is room for improvement in the efficacy of epilepsy surgery, principally by improved identification of the epileptogenic zone or other nearby resection targets. The epileptogenic zone also usually spans multiple brain regions, often including areas of Eloquent cortex, whose removal increases the risk of serious neurological complications. In those cases, alternative resection targets that decrease seizure frequency with negligible impact on neurocognitive function are needed. In response to this, major WBM research efforts have been directed towards the mathematical analysis of seizure dynamics, with the aim of identifying universal rules governing the initiation and termination of seizures, and establishing a taxonomy of seizures, to aid in surgical interventions.

In addition to neurostimulation, Taylor and colleagues also pioneered the use of patient-personalized brain network models to study the effects of surgical resection (Sinha et al., 2014). However, the most influential work in this area in recent years has come from the group of Viktor Jirsa and colleagues in Marseille. In 2014, they (Jirsa et al., 2014) developed a generic neural population model, termed the 'epileptor', that characterizes dynamics governing seizure onset and offset in terms of well-defined mathematical events.

The Epileptor model comprises five state variables described by a system of integrodifferential equations acting on three different time scales. Two variables operate on the fastest time scale, and are responsible for generating the rapid discharges (fast oscillations) during the seizure. At the intermediate time scale, a further two state variables act to determine the so-called spike and wave events. On the slowest time scale, a so-called permittivity variable governs transitions between interictal and ictal states, where seizure onset and offset are respectively associated with saddle-node and homoclinic bifurcations. Importantly, the authors showed that although a wide array of possible biophysical parameters/mechanisms (representing specific experimental conditions) can push the system towards seizure, the dynamical system theory-based properties of the system remain invariant (Jirsa et al., 2014). Subsequently, Jirsa and colleagues focused on using the Epileptor model to characterize seizure propagation in patient-specific connectome-based neural population models, with the aim of improving surgical resection strategies. In this so-called Virtual Epileptic Patient (VEP) approach (see also Sects. 13.3.3 and 13.4.4), Epileptors describing individual brain regions were coupled according to the patient's structural connectome (An et al., 2019; Jirsa et al., 2017), resulting in a WBM that accurately reproduced epileptic seizure dynamics recorded by implanted stereotactic EEG (sEEG)

[27] See Wang et al. Wang et al. (2019) for an excellent review on the history and successes of personalized brain network modelling in epilepsy.

electrodes. A graph theory-based community detection algorithm was then employed to identify candidate areas for resection, as brain regions and fibre tracts involved in seizure propagation. 'Virtual' resection of those areas in the VEP model was confirmed to result in suppression of seizure propagation in simulations. As discussed further later, the VEP is fairly unique amongst clinical applications of WBM, in that a clear route to positively influencing patient treatment has been identified, with clinical trials well underway.

13.3.5.3 Stroke and Neurodegeneration

Several early WBM studies investigated the impact of focal brain lesions on large-scale brain dynamics by 'lesioning' the connectivity matrix, usually by removing or reducing the strength of specific connections, or by removing specific network nodes (Alstott et al., 2009; Cabral et al., 2011; Honey and Sporns, 2008; Váša et al., 2015). Following implementation of a hypothesized lesion within the anatomical connectivity, these authors have tended to focus chiefly on characterizing observed shifts in hub regions and other graph-theoretic properties of simulated (fMRI) functional connectivity. One issue with these lesion-based studies, however, is that they made only limited direct comparisons with empirical imaging data in actual patients with brain lesions, such as stroke survivors. There have however not, to our knowledge, been any WBM studies demonstrating that patient-specific, empirically derived changes in WBM connectivity structure result in modified fMRI functional connectivity patterns seen in those same subjects.

Falcon et al. (2015) conducted parameter space explorations with WBMs built from individual stroke patients' connectivity matrices. They found that stroke-related white matter changes led to changes in excitation–inhibition balance. Falcon et al. also conducted a 'virtual intervention', in which they were able to accurately predict improvement in motor performance in recovering stroke patients using simulation parameter estimates. Building on this, in a recent study on brain tumours, Aerts et al. (2018) also studied excitation–inhibition balance, via local model parameters, using empirical structural connectivity to specify connectivity (encoding tumour presence via both the tumour's impact on the tractography-derived weights matrix, and also via model fits to fMRI data to estimate local model parameters). Kaboodvand et al. (2019) also studied the effect of malfunction or lesions by changing each brain region's local dynamics—in this case to evoke noisy behaviour, rather than removing nodes/links from the underlying structural connectome. These authors introduced *vulnerability* as a measure of each region (or connection)'s hypo-/hyper-connectivity risk in the face of malfunction in other areas. Along with this, they proposed a 'hazard' map predicting the level of brain network deterioration inflicted by each region's malfunction, and provided evidence of lower tolerance to lesions in the central hub regions compared with random lesions.

A major growth area for clinical WBM at present is Alzheimer's and dementia. One of the first WBM studies exploring this area was that of Zimmermann et al. (2018), who used the DMF model to analyse fMRI data from patients and control subjects, observing a reduction in E/I balance in Alzheimer's patients. More recently, Stefanovski et al. (2019) used the Jansen–Rit model to study changes in EEG in Alzheimer's (Stefanovski et al., 2019). In an interesting and methodologically novel model design, these authors introduced PET-derived spatial maps of plaque-related amyloid beta load as a regionally varying modulation of the ratio of excitatory and inhibitory neural population time constants. This spatially varying 'perturbation' was found to account well for EEG results showing a characteristic pattern of changes in Alzheimer's patients—namely spectral slowing in EEG oscillatory activity. Stefanovski et al. also studied a 'virtual' intervention in their WBM, mimicking the influence of cognitive enhancing drug prescribed for mild cognitive impairment, and found that this successfully re-normalized the spectra—paving the way for new hypothesis-driven WBM-based pharmacological investigations for dementia and related conditions.

13.3.5.4 Neuropsychiatry and Neuromodulation

Investigation of large-scale brain changes using neuroimaging-informed WBM has become a prominent arm of the multi-disciplinary field of computational psychiatry (see Deco and Kringelbach 2014; Murray et al. 2018 for excellent reviews on this topic), which explores both neurophysiological and neurocognitive models of psychiatric pathologies. One of the key ideas in computational psychiatry is the proposal that schizophrenia may constitute a form of 'disconnection syndrome' (Friston and Frith, 1995; Friston et al., 2016). Unlike the relatively focal (or at least contiguous) lesions seen in stroke and tumour patients, however, disconnectivity in schizophrenia is considered to be relatively more global and diffuse. In a classic study, Cabral et al. (2011) investigated this using a WBM with Kuramoto dynamics. These authors report that decreased connectivity strengths in the model led to altered graph-theoretic properties in simulated fMRI functional connectivity, including decreased small-worldness and clustering—replicating qualitatively observed changes in patient recordings. Others have explored the idea that functional disconnectivity patterns in schizophrenic brains may result from disrupted local dynamics, rather than anatomical connectivity disruptions per se. For example, using a WBM with two-state DMF dynamics, Yang et al. (2016) and Krystal et al. (2017) found that implementing a spatial hierarchy of altered E-I balance accounted parsimoniously for the emergence of inhomogeneous fMRI disconnectivity profiles in schizophrenic patients.

Two of the principal treatment types used in psychiatry are (a) drugs and (b) electrical/magnetic brain stimulation. One of the areas where WBM can make an important contribution is in helping to better understand the macro-physiology of brain responses to novel pharmacological interventions, such as LSD, psilocybin, ketamine, etc. A new and fast-developing line of WBM work in this area has been lead by the groups of Gustavo Deco, John Murray, and others. In a 2018 study, Deco et al. (2018) investigated the impact of LSD on brain dynamics using WBM with the DMF model. In particular, they modified their computational model using regional variations in 5-HT_{2A} (serotonin type 2A) receptor binding, obtained from PET (similar to the use of PET amyloid beta maps by Stefanowski described above (Stefanovski et al., 2019)). Addition of this spatial serotonergic receptor expression information improved the fit to fMRI data recordings in human subjects on LSD, consistent to its known mechanism of action. More recently, these authors continued in this line of research by incorporating spatial serotonergic connectivity (as opposed to receptor expression) information into a WBM, using the targets of ascending serotonergic projections from the raphe nucleus, and again modelling the influence of neuromodulation through the steepness of the coupling function (Kringelbach et al., 2020). They similarly found that adding these neurotransmitter systems into WBMs improved fits to empirical fMRI data. This work stands out as exemplary for the future, as it builds in a level of richness of brain organization—modification of ongoing neural activity via spatially structured pre- and post-synaptic neuromodulatory systems—that has been largely absent from WBM studies to date (for a recent review of physiological and mathematical concepts related to this, see Shine et al. 2021).

The other neuromodulatory therapy type is brain stimulation. Electroconvulsive therapy, deep brain stimulation, transcranial magnetic and electrical stimulation are all now regularly used in many countries for treatment of major depressive disorder. There have not to our knowledge been any WBM studies of brain stimulation in a direct clinical context, and this remains a relatively unexplored area with many opportunities. Comprehensive work from Spiegler and colleagues used the FHN model to explore how canonical brain networks may be selectively activated given targeted sensory, cognitive, or electromagnetic perturbation (Spiegler et al., 2016). More recently, the same authors have deployed a similar FHN model within TVMB to study stimulus-evoked

responses in mouse brains, as measured with wide-field dorsal view calcium imaging (Spiegler et al., 2019). The combination of WBM with the high temporal resolution, large-scale (albeit not quite whole-brain), invasive, and highly manipulable experimental preparations possible in the mouse will be critical for further refinement of models and understanding of macro-scale responses to stimulation perturbations.

In models of noninvasive brain stimulation in humans, the two principal modalities are transcranial (electrical) current stimulation (TCS) and transcranial magnetic stimulation (TMS), each of which in turn have two principal variants: transcranial direct vs. alternating electrical current stimulation (TDCS/TACS), and single pulse vs. repetitive magnetic stimulation (spTMS/rTMS). spTMS, combined with concurrent EEG, has shown some utility as an index of brain excitability in different states (wake vs. sleep) and in patient groups with disorders of consciousness (Massimini et al., 2005, 2012). Fascinating recent work by Wendling and colleagues has developed the first WBM capable of reproducing both resting-state spectral changes from wake to slow-wave sleep in whole-head EEG recordings, as well as the broad spatiotemporal pattern of EEG-measured TMS-evoked potentials (Bensaid et al., 2019).

An important development of the past 5–10 years in noninvasive brain stimulation, that has excellent potential for integration with WBMs, has been the refinement and increasingly widespread adoption of the so-called biophysical E-field models (see also Sect. 13.4.1). These models aim to characterize the *physics* (as opposed to the *physiology*) of brain stimulation modalities such as TMS and TCS. They use Maxwell's electromagnetic field equations, combined with detailed tissue conductivity and tissue boundary location information from structural MRI scans, to estimate the spatial pattern of stimulation induced for a given set of stimulation parameters (location, orientation, and intensity for TMS; those plus anode/cathode source-sink channel arrangements for TCS). An early attempt at integrating E-field models with WBMs is the study of Kunze et al. (2016). These authors proposed an approach to injecting a distributed E-field current distribution as inputs into multiple nodes of a WBM, and studied the effects on oscillatory brain activity and connectivity using the JR model. In related work, Dagar et al. proposed a WBM-based framework for electrical stimulation with TDCS to renormalize disrupted E/I balance (with a particular focus on stroke), incorporating E-Field inputs and combined simulations of EEG and fNIRS signals (Dagar et al., 2016).

Finally, a question of substantial clinical relevance is how best to model and understand the effects of therapeutic rTMS. Cona et al. (2011), in an approach similar to that of Kunze et al. above, found that fitting a Wilson–Cowing-based neural mass model to rTMS spectral responses within a small network was able to capture successfully differential frequency effects of rTMS in different brain regions. In a different line of work, Fung, Robinson, Wilson, and colleagues have studied in mathematical detail the synaptic and sub-cellular mechanisms of potentiating and depressive synaptic responses to rTMS (Fung et al., 2013; Wilson et al., 2016, 2018). An important frontier for WBMs is to build on the above work by integrating the spatiotemporal characteristics of TMS/TCS perturbation patterns with their hypothesized longer-term plasticity-related effects, and determine how best to use these models as tools to help improve clinical outcomes.

13.4 The Future

Over the past two Parts in our surveys of The Past and The Present, we have outlined most of the ideas, tools, techniques, and areas of application at play in current WBM research. Now we look to The Future. Naturally, the actual future trajectories taken by the field will be driven in large part by new empirical discoveries and measurement techniques. A prime example of this is the 'discovery' of resting-state brain dynamics in the early 2000s (Biswal et al., 1995; Raichle et al., 2001), which has dominated neuroimaging and, by association, WBM research for the past 15 years. Qualitatively new scientific ideas such as

this are of course difficult to predict, and we do not attempt to do so here, beyond acknowledging their influence. Developments in various technical domains are a little easier to forecast however, and we mainly restrict our attention to these in the following pages.

13.4.1 Multiscale

Multiscale modelling is an approach, now taken in several scientific fields, of using two or more interlinked models with different levels of resolution and complexity to study a single system (Weinan and Lu, 2011). The motivation is to strike a balance between accuracy (favouring more detailed microscale models) and feasibility (favouring less detailed meso/macroscale models). In physics, the canonical levels that may be linked through multiscale approaches are those of quantum mechanics, molecular dynamics, kinetic theory, and continuum mechanics. In computational neuroscience, the usual levels of physiological description are (1) morphological neuron models (transmembrane ion fluxes and passive current flow within and between small sub-cellular compartments), (2) spiking neuron models (point-process, single-cell level), and (3) neural population models. In addition to these, important phenomena also occur at the level of biophysics (e.g. using Maxwell's field equations for electrical stimulation), biochemistry (e.g. sub-cellular reaction–diffusion equations), biomechanics (e.g. accounting for effects or trauma or vascular pulsatility), and cognition/information processing (e.g. predictive coding) (Lytton et al., 2017). Multiscale modelling approaches.[28] combine two (or more) of these levels of description in a single simulation.[29] We can furthermore distinguish 'weak' and 'strong' multiscale variants, depending respectively on whether information is passed between levels in a uni-directional or bi-directional manner. The bi-directional case carries with it considerable additional technical challenges in terms of numerical stability and biological accuracy.

Weinan and Lu (2011) distinguish two types of question that may be addressed by multiscale modelling, which they term *Type A* and *Type B* problems. Type A problems are where some interesting events (complex chemical reactions, material defects, singularities) occur at some precise spatial location and require a microscale model to describe them in adequate detail, but otherwise macroscale models can be used for the rest of the system. Problems are of Type B when the macroscale model does not include some important constitutive information, and as a result coupling with a microscale model is required in order to supply this missing information.

In the context of WBM, an example of a Type A problem would be to replace the neural population model at one node in a connectome network with a detailed spiking neuron-based network (the localized microscale model), and use neural population equations for the rest of the network (the macroscale model). An application area where this type of approach will be of particular interest is the modelling of simultaneously recorded macro-scale neuroimaging and microscale stimulation and/or activity measurements from various neural implant devices. These are being increasingly used to treat patient populations with ailments ranging from Parkinson's, paralysis, depression, obesity, blindness, deafness, and epilepsy. Major recent

[28] It is worth noting that we are using a strong technical definition here. The term 'multiscale' is also commonly used throughout neuroscience, indicating the more general notion of spanning scales in one or other aspect.

[29] Note that the three hierarchical levels outlined in Sect. 13.3.1—namely the coupling between neural mass subpopulations, local lateral interactions, and long-range interactions—would not be multiscale (in the strong sense of the term), even though they together span several orders of magnitude in spatial scale. This is because the defining characteristic of multiscale models is the use of multiple *different* theoretical formulations of system behaviour—appropriately *interlinked* but having different variable types, units, and governing principles.

efforts in this particular multiscale modelling direction have centred around integrating the respective neural population-level and spiking neuron-level simulation capabilities of the TVB and NEST platforms (Meier et al., 2021).[30]

An example of a Type B problem would be to combine a WBM of ongoing activity with a biophysical model of electrical stimulation entering multiple brain regions. Unlike the previous example, where (in principle) the macroscale behaviour of the spiking neuron model is well-approximated by the neural population-level model, in this case the electromagnetic physics of the E-field model are nowhere to be found in the theoretical framework of neural activity dynamics. An interface is therefore needed to link the two levels of description, translating the physical, spatiotemporal electrical field pattern into a neural population activity input. In an excellent example of this approach (also noted above), Kunze et al. (2016) used a biophysical E-Field model to estimate the current amplitude and orientation received by all nodes in a WBM, using Jansen–Rit population dynamics. The pulse-to-wave transformation function was used to calculate the firing rate input to the stimulated areas during TDCS.

An interesting (albeit considerably more complex) alternative to the approach of Kunze et al., which combines both Type A and Type B problems, could be to merge both of the above examples: use Maxwell's equations to calculate the E-field strengths, model stimulated areas with detailed neuron models, and describe the rest of the brain with neural populations. Interestingly, in this case the best choice for the type of detailed model to couple to a neural population model may in fact be morphological neurons, rather than (as might be expected) spiking neurons (Seo and Jun, 2017). This is because the shape and orientation of neurons impact considerably the influence of electrical currents and magnetic fields on their activity, and so the formulation of morphological compartmental models is better-suited than (non-spatial) point-process spiking neurons to capture this physical interaction. In our opinion, the goal of developing effective multiscale WBMs—and using them to study these and many other fascinating and challenging neuroscientific phenomena—is likely to be a defining characteristic of the next decade of computational neuroscience.

[30] https://github.com/the-virtual-brain/tvb-multiscale. For a different approach, coupling TVB simulations to *cognitive*-level brain simulations, see Ulloa and Horwitz (2016).

13.4.2 Standardized, Hybrid, Model Construction

We have discussed in Parts 13.1 and 13.2 of this chapter how various kinds of large-scale anatomical connectivity information from diffusion-weighted MR tractography, chemical tract tracing in rodents and non-human primates, and geometric statistical considerations, are currently being used in the process of building WBMs. Many variants in connectivity matrix construction have been and continue to be explored, as the state of the art in experimental techniques progresses. However, heterogeneity across the WBM literature in certain critical procedures such as the definition and rescaling of edge weights have a major impact on the generalizability and replicability of reported results. Standardization of the model construction process (particularly the connectivity part) is therefore an important future direction for the field of WBM. One approach to dealing with this issue is to introduce a neuroanatomically grounded parameterization of large-scale connectivity structure—which is separate from, but can be heavily informed by, empirical information like tractography streamline densities. These 'connectivity models' would be specified in biologically meaningful units, such as number or per-unit-area density of axons, and be constrained to exhibit certain statistical properties known from gold-standard tracer studies in non-human primates, such as exponential fall-off with distance and multiple orders of magnitude in weights. Personalized connectivity information from tractography reconstructions in individual subjects would be introduced into these models through a (yet to be determined) *modulation* of

the basic structure, in such a way that allows flexibility but retains the desired overall spatial and graph-theoretic statistical properties the network. Contrast this with the current situation, where connectivity edge weights are more-or-less defined as simply the direct output numbers from the latest tractography algorithm, applied to data from the currently available scanner, running the current best available MR sequence, and using an often rather arbitrarily chosen selection of transformations and rescalings. The issue with this is that tractography algorithm outputs such as 'streamline densities' are highly artificial constructs that are not expressed in physically, physiologically, or anatomically meaningful quantities. WBMs built around these numbers are therefore at danger of producing results that are liable to be as transient and temporary as the currently *en vogue* algorithms, software packages, and scanner sequences they are constructed from.

A version of the 'normative parameterization' approach outlined above was taken by Stephan et al. (2009), in their work on tractography-based priors for fMRI DCMs. These authors examined several functional forms (quantified through hyperpriors) for how to map (probabilistic) tractography streamline densities on to the parameters (mean and variance) of prior distributions for DCM effective connectivity strengths.[31] Posterior distributions for those connectivity strengths were subsequently estimated from fMRI data in the usual way. This work gives some indication of the type of statistical framework that a WBM standardized connectivity model could use to integrate individualized data measurements. In addition to individual edge-wise priors, as was the focus of Stephan et al. (2009), it may be desirable to also parameterize network-level characteristics, such as graph-theoretic and spatial statistics (see e.g. Betzel et al. 2016; Roberts et al. 2016).

A second reason for moving towards a convention where connectivity matrices for WBMs are not fully defined from tractography data alone is that this would facilitate the incorporation of important connectivity information that is not currently resolvable by conventional DWI methods. This is particularly the case for subcortical structures, such as thalamic and basal ganglia nuclei, that undoubtedly have a profound influence on neural and cognitive function, but are largely ignored in most current WBM efforts. Some limited progress in this direction has already been made: Spiegler et al. (2016) studied responses to stimulation in a WBM using a connectivity consisting of 82 cortical regions (the standard CoCoMac regional map parcellation connectivity matrix) and, in addition, 116 thalamic regions.[32] The thalamic regional parcellation and connectivity used here, which was compiled from macaque tracer study databases, has far greater detail than that achievable using just tractography in humans for thalamic connectivity mapping. More generally, the contribution of subcortical structures to cortical activity, and brain function in general, has been largely under-appreciated in WBM to date. Hybrid connectivity models of this kind would provide some of the tools to enable further development in this area.

13.4.3 Cross-Species

As noted from the outset, the core application and interest area of WBM to date has been understanding the human brain in health and disease. A key source of progress over the next decade however is likely to come from extension of the methodology to non-human primate and rodent brains. The principal reason for this is that as a rule, developments in neuroscience recording technology move faster in animal than human fields. EEG, MEG, and fMRI, for example, have not enjoyed substantial improvements in spatiotemporal resolution or SNR (except in some niche areas) for over twenty years. At the same time, in other areas of neuroscience, a major focus of technical development has been increas-

[31] Effective connectivity strengths in DCMs are the same as connectivity weights usually given by anatomical connectivity in connectome-based WBMs.

[32] This combined corticothalamic connectivity matrix is distributed with the TVB software library ('connectivity_192').

ing the total area of brain covered and number of channels per unit area in invasive electrophysiology and optical imaging experiments, and extent and resolution of connectivity tracing techniques. Examples of these trends include the stated priorities of the US 'BRAIN Initiative' funding program (namely, improvement of neural recording hardware), the industrial-scale functional, anatomical, cellular, and genetic mapping of the mouse brain by the Allen Institute, and the miniaturization and 'un-tethering' (wireless data transfer, wireless charging) achievements of the new Silicon Valley neurotechnology outfit Neuralink. As these invasive techniques continue to 'scale up' in this way, they begin to approach the kind of whole-brain coverage only currently available from noninvasive methods, but with an order of magnitude or more improvement in spatial resolution.

The three non-human animal species where these improvements are likely to be most clearly seen are the mouse, rat, and marmoset. The macaque continues to be the gold-standard for comparative non-human neuroanatomy and neurophysiology, but is likely to remain a niche research area for both economic and ethical reasons. For the normative 'connectivity model' proposed in the previous section, careful tracer injections and structural neuroimaging in macaques shall be essential. Marmoset and rodent anatomical connectivity information is of substantially less relevance in that domain. The critical contributions of these other species will be in the area of interventional physiological experiments, and large-scale brain dynamics in general. Excellent progress has already been made in WBMs for resting-state and stimulus-evoked activity in the mouse, building on the high-quality connectivity information from the Allen Mouse Brain Atlas, and integrating with experimental data from other sources (Melozzi et al., 2017; Spiegler et al., 2019).

13.4.4 Translation

As we saw in Sect. 13.3.5 and elsewhere, a substantial amount of WBM work has been aimed at clinical applications across the spectrum of neurology and psychiatry. Most of this work has been concerned with modelling or inferring potential disease mechanisms of various kinds. Some of it however, such as Jirsa and colleagues' VEP work (Jirsa et al., 2017), are explicitly and directly trying to improve clinical care itself using WBMs. The success of these and related efforts over the next few years will be a major litmus test for WBM.

A reasonable question here might be 'what would successful clinical translation of WBMs look like?'. There are several options, most of which are untried and untested. Ultimately, successful translation means making a positive impact on the lives of patients. In practice, this means either a) the development of a new and better form of therapy or b) providing more and better information to clinicians, with which to select the best of available options. Realistically, development of fundamentally new therapies and therapeutic technologies is unlikely to come purely from WBM work, at least at its present and near-future state of maturity. The more likely route to impact in the short and medium term is by assisting with and improving decision making and therapy design within established medical paradigms. A general term for this is a 'clinical decision support tool'.

Within this space, once a promising approach has been identified, the next question is what strategy to take with respect to regulatory approval. The conventional option is to undertake extensive clinical trials, to demonstrate comprehensively that the actions taken under recommendations from a WBM-based decision support tool are superior to those without it. This is the route currently underway with the VEP. The aim is to show that surgical resection decisions have better outcomes (according to standard metrics) when factoring in (alongside the standard surgical planning process) recommendations from patient-personalized Epileptor-based WBMs.

The process of obtaining regulatory approval for novel medical techniques and technologies is a long and expensive haul, and rightly so. In many countries, including notably the USA, the real target for companies developing new

medical technologies is not regulatory approval per se, but health insurance 'billing codes'. In countries with insurance-based health systems, billing codes (which do nevertheless depend on regulatory approval) are the route to reimbursement and sales, which in turn open the door for viable business models. A more modest and more expedited route to impact is to develop tools that can be classified as assistive devices. Two examples that are somewhat adjacent to WBM and useful to consider here are neuronavigation and electromagnetic field modelling for noninvasive brain stimulation. Both of these are computational methods that improve the accuracy of brain stimulation therapies.[33] Neither have undergone major clinical trials themselves, but they are increasingly considered important tools for the accurate quantification and delivery of FDA-approved brain stimulation therapies. In a similar vein, one can imagine a useful line of future WBMs that supply robust, validated, physiologically meaningful, and fast (ideally real-time, at the point of administration) predictions/reports about the expected outcomes/other characteristics of brain stimulation, pharmacological, or other therapeutic interventions.

13.5 Conclusions

In this chapter we have sought to provide the reader with a perspective on the intellectual history, current major issues, and possible futures of the new scientific discipline of whole-brain modelling. One thing that has stood out clearly in conducting this survey is that as the field continues to grow, the rate of innovation and of major progress in new research directions also increases at a rapid pace. The volume and quality of new WBM research ideas and discoveries can be daunting, in fact. Yet, we are sure most would agree that even the most well-developed lines of enquiry have barely begun to scratch the surface of what—hopefully—can be achieved with WBM techniques. The future is, we believe, a bright one, and there is plenty of work to do!

[33] Actually E-field modelling and neuronavigation are two very similar variants of one general method—solving Maxwell's equations for brain stimulation. Neuronavigation is usually more 'coarse-grained' than E-field modelling, and—critically—operates in real-time.

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