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Whole-brain modelling: an essential tool for understanding brain dynamics

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Whole-brain modelling is an essential tool that provides relevant insights for neuroscientists as they work to discover the fundamental principles of healthy brain function.

Over the past few decades, there has been very slow progress in the understanding and diagnosis of neuropsychiatric disorders, mainly due to a lack of causal insight into their biological mechanisms. This has been further compounded by the numerous statistically significant yet minimally distinguishing findings in neuropsychiatric disorders. Reliable animal models are rare, and the problems with current treatments indicate that new research strategies are needed to treat neuropsychiatric disorders. Whole-brain modelling is an excellent tool for moving beyond these limitations. In silico whole-brain models are designed using neuroimaging data of patients' brains used to identify pathologies and appropriate interventions. For example, sometimes patients suddenly and unexpectedly wake up after years of coma; individualized in silico whole-brain models could be used to find the awakening force that may then be applied in other cases. In silico whole-brain models must balance complexity and realism to describe the most important functional features of the brain in vivo[1].

Successful whole-brain computational models have taken their lead from statistical physics where the synergetics theory of Haken and others explains the formation and self-organization of patterns and structures in open systems far from thermodynamic equilibrium[2]. This provides precise tools for understanding the self-organization of any complex macroscopic system consisting of many non-linear interacting subsystems. This has demonstrated that macroscopic physical systems obey laws that are independent of their mesoscopic constituents. Each node typically consists of a suitable approximation of the local neuronal dynamics, which can be expressed as a spiking neuronal network, mean field model or mesoscopic models[3,4]. The fundamental principle is to link anatomical structure with functional dynamics (Fig. 1). The anatomy can be represented in many ways, ideally through large-scale tract tracing providing directional anatomical connectivity. This information requires invasive tract tracing, which is not ethical to obtain in humans, so instead researchers have measured non-directional connectivity using in vivo diffusion MRI combined with probabilistic tractography.

These tractography measures are not without problems, given that fibre tracking is complex and involves many steps inherently subjected to potential errors. Despite this, they are still able to link anatomical structures with functional dynamics. Anatomical fibre tracking is done at the level of a parcellation of the brain based on structural and functional information, typically on the order of 80–1,000 nodes, which further reduces the complexity of modelling. Overall, in the whole-brain model, the functional global dynamics emerge from the mutual interactions of local node dynamics coupled through the underlying empirical anatomical connectivity. This functional activity can be captured with whole-brain neuroimaging, typically functional MRI, magnetoencephalography and electroencephalography. These measures capture different time scales of brain activity. Typically, these models fit the empirical data by optimizing parameters, including heterogeneity in conductivity[5].

The whole-brain modelling framework has been successful in explaining the patterns of spontaneous inter-regional functional activity correlations, forming the resting-state networks captured by functional MRI[6]. There are many static and spatiotemporal measures of brain activity that the whole-brain model can be fitted to. These include static functional connectivity but also dynamical measurements like the temporal structure of the activity fluctuations such as functional connectivity dynamics. Whole-brain models can also be used to explain brain activity on faster timescales of milliseconds, but many challenges remain to unify the different timescales. Crucially, it has also been demonstrated that whole-brain models can bridge the gap between different timescales from milliseconds to tens of seconds, offering unparalleled mechanistic insights into the multiscale nature of whole-brain activity.

These personalized whole-brain models can be further augmented to produce a digital twin[7]. There are different levels of precision in this model and care should be taken not to create unrealistic expectations of exact fidelity. Still, there is already successful research, for example the Virtual Epileptic Patient using neuroimaging data to inform the in silico modelling of the brain of a patient with epilepsy, supporting diagnostic and therapeutic interventions, clinical decision-making and prediction of consequences[8]. This has shown that the network-level observation of epileptic seizures is due to an emergent hypersynchronous and high-amplitude rhythmic state of the network of neurons or neural populations, which in turn offers potential avenues for personalized treatment.

Similarly, there is now ongoing research in identifying the best stimulation targets for forcing the awakening of patients post coma. A proof of principle was provided using sleep data in healthy human participants and investigating accurate ways to promote the transition from one brain state to another, and in particular finding ways to awaken the brain from deep sleep to wakefulness and vice versa[9]. This was demonstrated using a framework that provides a deep understanding and quantitative definition of what constitutes a brain state and what can drive the transitions between brain states.

This framework has great clinical promise, where structural neuroimaging can be obtained from a patient post coma with damaged connectivity. This connectivity can then be used in the personalized whole-brain model, which is fitted to the functional post-comatose brain dynamics. The whole-brain model is then systematically probed to find an awakening to healthy brain dynamics. Subsequently, the successful stimulation candidate for awakening can use external stimulation like deep brain, multifocal transcranial direct current or

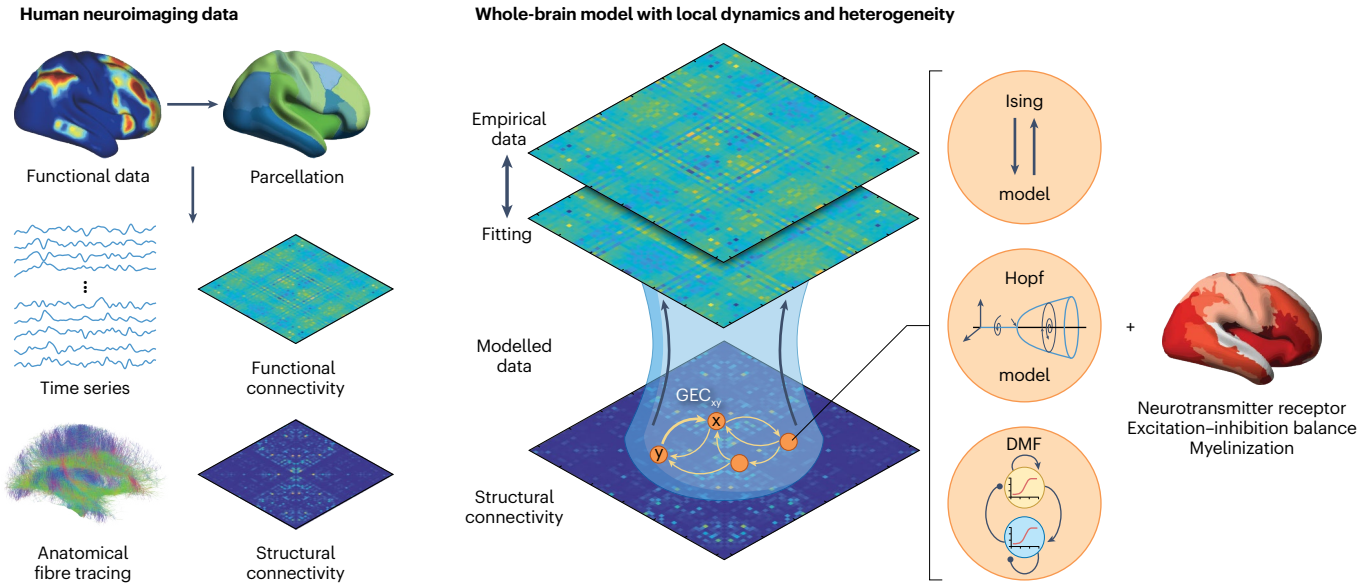

Fig. 1 | Principles of whole-brain modelling. Human neuroimaging data are used in the whole-brain model to link structural anatomy to function. The whole-brain model uses a population model that describes the behaviour of that region. Some examples are the Ising model, which works on a binarized representation of the brain activity and is often used to study phase transitions; the Stuart–Landau oscillator, often called the Hopf model because it represents the normal form of a supercritical Hopf bifurcation, which is a simple model exhibiting a parameter-dependent bifurcation between a fixed attractor and oscillations and that is usually used to study activity transfer between regions; and the dynamic mean field (DMF) model, a biologically inspired model often used to find mechanistic explanations of the regional influence of heterogeneous region-based measures mentioned above.

transmagnetic stimulations. Given the existing success of digital twins in, for example, epilepsy, multiple sclerosis and Parkinson disease, the prospect of real awakenings would appear to be within our grasp[7].

The Virtual Brain is the most widely used framework for whole-brain modelling. It incorporates a diverse array of neuronal models and dynamics into its brain simulator. This integration seamlessly merges computational modelling with multimodal neuroimaging tools, facilitating the simulation, analysis and inference of neurophysiological mechanisms across various brain scales. Notably, The Virtual Brain enables the creation of personalized virtual brains and facilitates the exploration of intricate multi-scale neural mechanisms. Recent enhancements include its integration with cloud services via the European platform EBRAINS.

Overall, whole-brain modelling stands out for its capacity to formulate explanatory mechanistic models, enabling a much deeper understanding of healthy brain mechanisms through non-invasive measurements. This capability, previously associated predominantly with disciplines such as physics and chemistry, would mark a substantial evolutionary jump towards deeper insights and comprehension of the unresolved understanding of human cognition. Recent research has even started to show how the physical principles of thermodynamics and turbulence combined with whole-brain models can substantially advance our understanding[10]. Thus, computational neuroscience has arrived at the maturity point where it can provide tools to finally grasp the fundamental principles of brain function in health and disease.

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References

1. Breakspear, M. Dynamic models of large-scale brain activity. *Nat. Neurosci.* **20**, 340–352 (2017).
2. Haken, H. (ed.) *Information and Self-Organization: A Macroscopic Approach to Complex Systems* [Springer Series in Synergetics] (Springer, 1988).
3. Kringelbach, M. L. & Deco, G. Brain states and transitions: insights from computational neuroscience. *Cell Rep.* **32**, 108128 (2020).
4. Deco, G. & Kringelbach, M. L. Great expectations: using whole-brain computational connectomics for understanding neuropsychiatric disorders. *Neuron* **84**, 892–905 (2014).
5. Deco, G. et al. Dynamical consequences of regional heterogeneity in the brain's transcriptional landscape. *Sci. Adv.* **7**, eabf4752 (2021).
6. Biswal, B. B. et al. Toward discovery science of human brain function. *Proc. Natl Acad. Sci. USA* **107**, 4734–4739 (2010).
7. Wang, H. E. et al. Virtual brain twins: from basic neuroscience to clinical use. *Natl Sci. Rev.* **11**, nwae079 (2024).
8. Jirsa, V. et al. Personalised virtual brain models in epilepsy. *Lancet Neurol.* **22**, 443–454 (2023).
9. Deco, G. et al. Awakening: predicting external stimulation to force transitions between different brain states. *Proc. Natl Acad. Sci. USA* **116**, 18088–18097 (2019).
10. Kringelbach, M. L., Sanz Perl, Y. & Deco, G. The thermodynamics of mind. *Trends Cogn. Sci.* **28**, 568–581 (2024).

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Author contributions

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Competing interests

The authors declare no competing interests.