Dynamical models to evaluate structure–function relationships in network neuroscience

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In their timely Review, Váša and Mišić provide an insightful review of the range of null models available for hypothesis testing in network neuroscience (Váša, F. & Mišić, B. Null models in network neuroscience. *Nat. Rev. Neurosci.* **23**, 493–504 (2022))[1]. A central part of their Review is dedicated to generative models, understood as models for the processes that lead (brain) networks to exhibit the organization that they do. Here, we wish to draw attention to a distinct but complementary kind of generative model that can be used to embody and then test null hypotheses in network neuroscience: namely, dynamical models of mechanisms. In these models, brain network structure (and, increasingly, additional aspects such as regional heterogeneity) gives rise to the ebb and flow of brain activity and functional connectivity that unfold over time[2–4] (FIG. 1).

In a notable recent example[5], the topology of the structural connectome underlying a Kuramoto model was systematically varied, showing that a modular but not a random topology produces 'events' in the simulated time-resolved functional connectivity, analogous to those observed in empirical functional MRI signals. From the perspective of null models, this result showed that such events are attributable neither to motion and physiological artefacts nor solely to cognitive operations, as the model incorporates neither. Rather, the topology of the structural network is sufficient to determine whether such events will be observed in the functional dynamics. This work exemplifies how dynamical models can be used to arbitrate between plausible causal mechanisms for a phenomenon of interest, by explicitly building such mechanisms into the model and assessing whether the phenomenon in question emerges.

Another notable study enriched connectome-based mean-field models with PET-derived maps for the 5-HT_{2A} receptor,

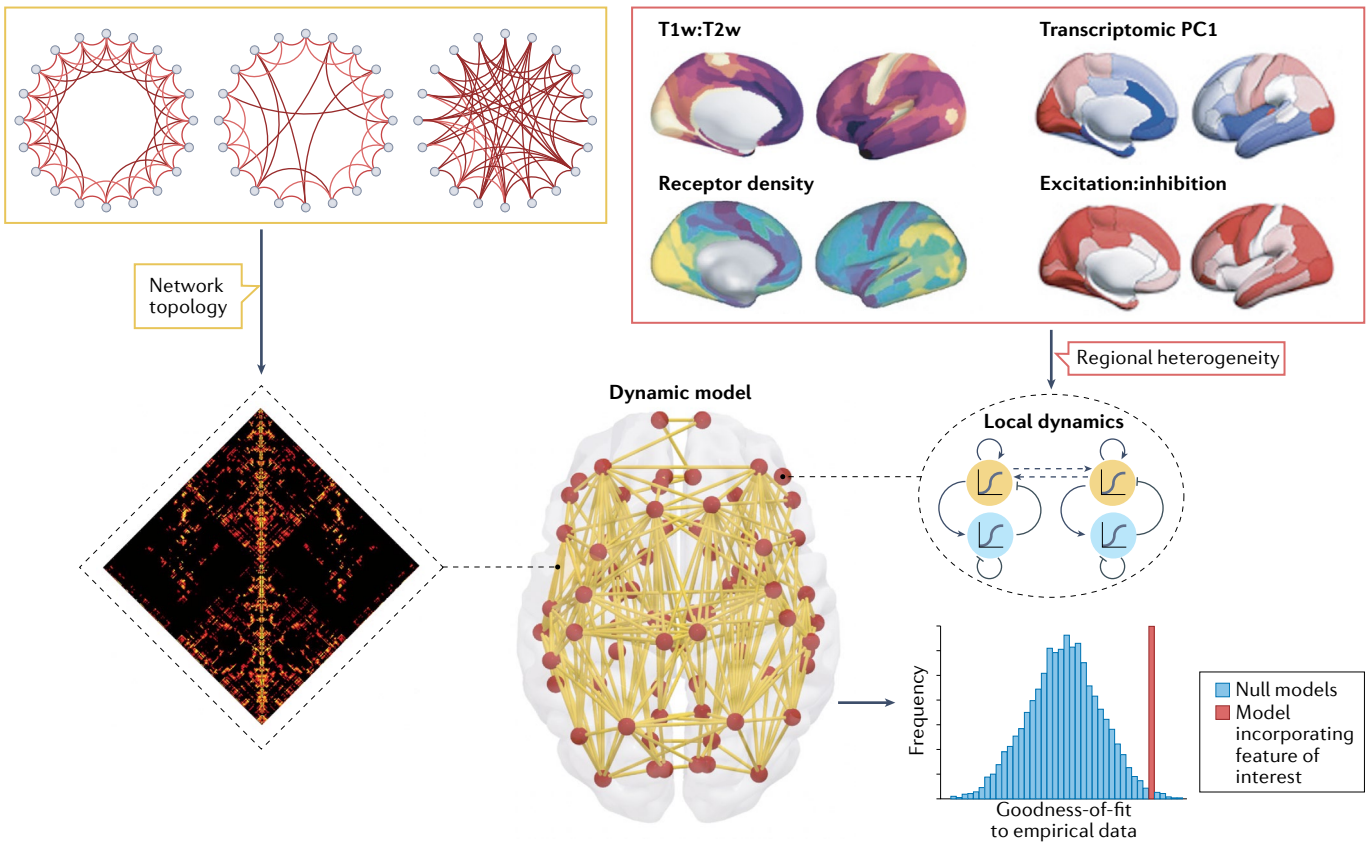

Fig. 1 | **Use of whole-brain dynamical models to test null hypotheses about the relationship among brain network structure, regional heterogeneity and brain activity.** Dynamical whole-brain models simulate the emergence of brain activity and functional connectivity in silico, combining a model of local dynamics (red), with varying degrees of biological realism, and global connectivity (yellow), typically obtained from diffusion MRI tractography in humans or tract-tracing in animals. The role of regionally heterogeneous features of neurobiology in shaping brain function can be evaluated by modulating local dynamics according to empirical maps, such as T1w:T2w ratio, receptor density from PET or transcriptomics, the principal component of gene expression (PC1), or excitation:inhibition ratio (among others). The heterogeneous model's goodness-of-fit to empirical functional data is then compared against a distribution of models enriched with null maps. The contribution of specific features of structural network topology to brain function can be evaluated by comparing the model's goodness-of-fit to empirical data against a distribution of null models, rewired to remove the network feature, or features, of interest. Figure adapted with permission from REF.[7], Elife; REF.[8], Elsevier; and REF.[9], AAAS.

recapitulating blood oxygen level-dependent dynamics under the effects of the serotonergic psychedelic lysergic acid diethylamide (LSD)[6]. Null models enriched with alternative 5-HT receptors, or with uniform or scrambled 5-HT_{2A} maps, allowed the authors to embody and then reject alternative hypotheses whereby the spatial distribution of the 5-HT_{2A} receptor does not contribute to the dynamics of LSD. A subsequent transcriptomics-enriched model evaluated non-5-HT receptors and the role of spatial autocorrelation[7], highlighting the synergy between different facets of null hypothesis testing in network neuroscience. Increasingly, dynamical models are being enriched with other aspects of neurobiology, such as T1w:T2w ratio[8], excitatory:inhibitory ratio[9], the principal component of gene expression[9], or feedback versus feedforward connectivity[10] (to name just a few in a fast-growing literature), representing additional avenues with which to embody and test hypotheses about annotated brain networks.

Overall, generative models of brain dynamics represent a powerful recent addition to the hypothesis-testing toolset of network neuroscientists. They provide an avenue to embody and assess mechanistic hypotheses, not only of how the organization of structural brain networks came to be, but also of how in turn it interacts with regional dynamics to shape the temporal unfolding of brain activity. We hope that explicit recognition of this flexible framework for testing mechanistic hypotheses will facilitate the emerging research on the interrelationships of brain network structure, dynamics and neuromodulation, bringing additional aspects of neurobiology into consideration for the study of both structural and functional brain networks.

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Competing interests
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