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Beyond connectionism: a neuronal dance of ephaptic and synaptic interactions – Commentary on [“The growth of cognition: Free energy minimization and the embryogenesis of cortical computation”](#) by Wright and Bourke (2020)

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In their article on the growth of cognition, Wright and Bourke (2020) present a compelling account of the emergence of cortical substructures from ante-natal network dynamics – without external inputs – and the subsequent post-natal development of these substructures as the network responds to complex visual stimuli. In order to supplement and (hopefully) strengthen their proposal, I will make one short general point and then proceed to propose specific future directions.

First, my general point. As Wright & Bourke (2020) discuss, their model dovetails nicely with the free-energy principle (FEP). Therefore, I believe their model would benefit from conceptual and technical integration with previous work in the FEP literature on morphogenesis (Friston et al., 2015; Palacios et al., 2019) and the emergence of synchrony in networks of mutually inferring neurons (Palacios et al., 2018). These have not been discussed or referenced anywhere in the target article, which I found surprising given their apparent relevance to the subject at hand.

Second, I present my own analysis of the model and sketch fruitful ways forward. The authors’ modelling choices constrain the organisation of their neural network dynamics in time and space:

1. Both the pruning of synapses and apoptosis of neurons themselves are directed by the maximisation of temporal correlations. This enforces synchronous, oscillatory firing behaviours and gives rise to bi-directional symmetry of connection weights.
2. The simulation involves two type of cells with different morphologies: alpha cells have more axons longer than length X , and beta cells have more axons shorter than length X . Signals are transmitted along these axons with conduction speed v , thus providing spatiotemporal constraints.

Different transmission lags for alpha and beta cells combined with synchronicity constraints guarantee the formation of (1) localised patches of interconnected neurons (within distance X) and (2) long-range connectivity across patches (beyond distance X). However, Wright and Bourke (2020) also note this bimodal assumption is not supported by empirical work, as real neural cells and their typical axonal lengths are much more distributed. Therefore it could be highly beneficial for this model to appeal to some other mechanism to explain such a distinction between short- and long-range connectivity. I will argue that precisely such a mechanism can be found outside of the realm of connectionism.

Various lines of research of the past decades have indicated we should move beyond connectionism and its implicit assumption that everything about the brain can be worked out in terms of synaptic coupling – most importantly: direct electrical (i.e., ephaptic) coupling between neurons (Fröhlich & McCormick, 2010; Qiu et al., 2015; Ruffini et al., 2020) and indirect neurovascular and -metabolic coupling, supported by glial-neuron interactions (Jefferys, 1995; Metea & Newman, 2006; Shu et al., 2016). Different mechanisms usually have different characteristic transmission speeds, enforcing spatiotemporal dissociations very similar to those proposed by Wright and Bourke (2020). In my view, the most promising candidate for their model would be to consider interactions between synaptic and ephaptic coupling of neural activity via the local field potentials they generate at different scales of organisation. Researchers have observed waves of synchronous activity travelling

through neural ensembles at a stable speed of 0.1m/s as compared to axonal transmission at 0.3m/s, even when synaptic connectivity was made impossible (for a review, see Qiu et al., 2015). Given that the speed of ephaptic transmission is about 3 times slower than synaptic transmission, we can visualise the spatial field of temporal cross-correlation between these fields around a signal source. For simplicity, let us assume an oscillating source generating two wavefronts, each of which can be described by an exponentially decaying periodic function:

$$I(r, t) = Ae^{-\left(\frac{r}{\lambda}\right)^\alpha} \cos\left(2\pi f\left(\frac{r}{v} + t\right)\right) \quad (\text{eq.1})$$

Here, A is the initial amplitude, r is the distance to the source, t the time, λ the spatial decay length (conductance), α the radial power-law index, f the signal frequency, v the phase velocity. Now, let us assume two of these signals: the axonal signal travelling three times faster than the ephaptic signal, the latter decaying much faster (with power-law index $\alpha = 3$; see, e.g., Ruffini et al., 2020), and both generated by the same source (i.e., zero initial phase difference). Then, it is easy to show that their temporal correlation $\rho(r)$ becomes a simple function of distance to the source:

$$\rho(r) \propto e^{-\left(\frac{r}{\lambda_{eph}}\right)^3} \cos\left(4\pi f \frac{r}{v_{eph}}\right) \quad (\text{eq.2})$$

Here, λ_{eph} is the ephaptic decay length and v_{eph} is the ephaptic wave velocity – both can be frequency-dependent without changing the form of equation 2. Figure 1 shows this function as a 2D surface for the case where the decay length is slightly larger than the ephaptic wavelength. The first peak is visible after a full period has passed ($r \sim v_{eph}/2f$; red circle), which means the limiting case of $r \leq \lambda_{eph}$ provides us with the minimum signal frequency required for a given decay length:

$$f \geq \frac{v_{eph}}{2\lambda_{eph}} \quad (\text{eq.3})$$

If we now apply this equation to an anatomical structure of about 1-2mm (such as summarised by Wright & Bourke, 2020) with $v_{eph} = 0.1\text{m/s}$ (Qiu et al., 2015), we obtain f_{min} of 50Hz and 25Hz respectively, which is strikingly consistent with the Gamma band (20-125Hz). Furthermore, if we place additional signal sources on this ring, we obtain a morphology (Figure 1, right panel) very similar to the one obtained by Wright and Bourke (2020), without invoking different alpha or beta cell types (Section 3.1 of the target article). This type of analysis can be applied to any number of signal types emitted by the same source, allowing us to incorporate even much slower effects such as the diffusion of nerve growth factors, which is known to be crucial in development (see, e.g., Biane, Conner, & Tuszynski, 2014). Generally speaking, an additional benefit of appealing to non-synaptic mechanisms is that they tend to be inherently bi-directionally symmetric and do not require pruning (Sections 3.2-3.4 of the target article).

In sum, a neuronal dance of ephaptic and synaptic interactions can be enough to explain the emergence of patches in cortical morphogenesis – without appealing to different cell types. Furthermore, it guarantees and supports bi-directional symmetry of connectivity without relying directly on synaptic pruning. My analysis therefore suggests that moving beyond connectionism transmission will be a fruitful direction for the development of Wright and Bourke's model of cortical morphogenesis.

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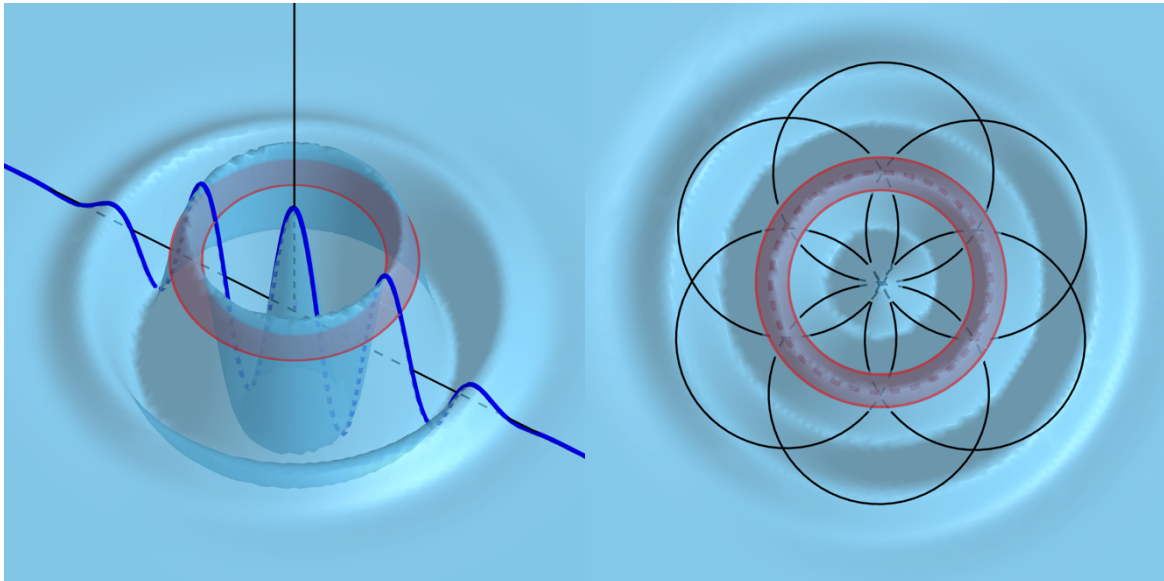


Figure 1. A depth view (left panel) and bird's eye view (right panel) of the cross-correlation surface between two periodic signals (blue line, cyan surface) emitted by a source (peak at middle point). Due to their different transmission speeds, a stable circular ring of cross-correlation (red circle) emerges around the source. In the right panel, 6 black circles indicate the stable configuration of 6 additional sources embedded in this field, creating similar patterns as shown in Figure 2 from the target article by Wright & Bourke (2020).

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