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Modelling emergent properties in the brain using tissue models to investigate neurodegenerative disease

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Abstract

Here we describe emergent properties of the brain and the key challenges associated with modelling them in vitro. Modelling emergent properties of the brain will provide insights into brain function, development and disease.

Manuscript

Many properties of complex systems are *emergent*: they are the result of the collective activities of a system's components, and yet are strikingly different from any of the properties that those individual components bear (Corradini and O'Connor 2010)(McClelland 2010). In neuroscience, one obvious example of such a property is consciousness, which somehow arises from the collective activities of huge numbers of neurons and their supportive cells. As far as anyone can tell, none of the properties of individual neurons resembles consciousness, and while consciousness can be affected in predictable ways by drugs and disorders, no mechanistic explanation for it has yet been found. The problem of understanding consciousness lies in understanding how it emerges from all that underlying non-conscious activity.

Consciousness isn't the only emergent property relevant to neuroscience. As we increase in complexity moving from individual ion channels and membrane proteins to individual neurons through to circuits and tissues (Figure 1), we deal repeatedly with systems that, when brought together, exhibit properties that are new, interesting and often unexpected.

Emergence is beginning to be discussed in relation to computational models of neural systems (Turkheimer and others 2019), but not in tissue models. One recent example of emergent phenomena occurring in tissue models used human neural progenitor cells (hNPC) with amyloid precursor protein (APP) or APP and presenilin 1 (PSEN1) familial Alzheimer's disease (FAD) mutations (Choi and others 2014). When the cells were grown in 2-dimensional tissue culture, there was an increased production of amyloid- β , but only in 3-dimensional cultures were amyloid- β plaques and tau tangles formed (Figure 2). This change in protein organisation emerges from a change in tissue structure and may subsequently lead to large changes in neural networks.

Emergent phenomena can occur in ways which are very difficult to anticipate. For instance, Alzheimer's disease is investigated in various animal models (Sasaguri and others 2017). Three APP overexpressing mouse lines (APP/PSEN1, Tg2576, hAPP-J20) were assessed with high resolution serial 2-photon tomography of labelled plaques (Figure 3) (Whitesell and others 2019). The APP/PSEN1 and Tg2576 mice, displayed plaques initially in the isocortex, followed by olfactory, hippocampal, and cortical subplate regions. In hAPP-J20 mice, the plaque density was highest in the hippocampal areas, followed by the isocortex, with little to no plaques formed in the olfactory or cortical subplate areas. Overall, distinct regions were identified with high or low plaque accumulation (the lateral visual area within the isocortex of APP/PSEN1 mice had relatively higher plaque density compared to other cortical areas, while hAPP-J20 mice displayed the densest plaques in the ventral retrosplenial cortex). This work demonstrates that emergent phenomena may not be uniform throughout neural tissue, consistent with human studies (Grothe and others 2017). The spatial and temporal pattern of emergent phenomena can also vary between models, and hence the use of an appropriate model is crucial in testing the clinical relevance of emergent phenomena. For example, despite displaying emergent plaque formation, these knock-in mice do not exhibit tau pathology or neurodegeneration (Sasaguri and others 2017). While this may be due to the limited lifetime of the animal models, it indicates that although APP/PSEN1 mutations induce behavioural deficits, the emergence of plaques is not a cause of neurodegeneration in these mice.

Neural function is typically investigated through electrophysiological methods. In tissue culture, the electrophysiological behaviour may be relatively homogeneous. However the brain can display distinct patterns of electrophysiological activity. For instance, electrophysiological behaviour of grid cells in the entorhinal cortex exhibit a hexagonal topographical structure (Hafting and others 2005). It is thought that grid cells form the basis of spatiotemporal representation of places, routes, and associated experiences during behaviour and in memory (Moser and others 2008). This type of complex neural structure is being modelled computationally (Solstad and others 2006) (Tait and others 2018), but is largely unreplicated in tissue culture models because biofabrication methods have thus far not been able to create realistic neural tissue complexity.

Recognising the role of emergence in neural phenomena is crucial for developing a better understanding of the function of healthy brains and the ways in which brain function can be affected by disease. Such diseases are often associated with changes that could disrupt healthy emergent properties and behaviours, introduce new, harmful ones or display emergent symptoms. These changes can include the loss of cell types, the degradation of neural networks and the build-up of aggregated proteins, such as amyloid plaques or Lewy bodies. Investigating these possibilities requires an understanding of the variety of types of emergent properties and behaviours that can be found in the brain.

Healthy neural function and disease are often investigated through different tissue models. These include 2-dimensional and more recently 3-dimensional cell cultures, organoids, tissue slices, live animal models and finally human clinical trials. There are limitations in each of these models (Wellbourne-Wood and Chatton 2018). Cell cultures are often composed of a single immortalised or primary cell type, although co-cultures of multiple cell types are possible. Immortalised cell lines and different animal models allow investigation of biological mechanisms, but differences in genetic sequence lead to vast differences in structure, composition and signalling, and thus may have a poor relevance to human disease

(Götz and others 2018). Human tissue from normal and diseased people can be used to form cell cultures and organoids, providing more relevant data on biological mechanisms (Choi and others 2014)(Raja and others 2016)(Amin and Paşca 2018). However, the developmental stage of these tissues is not the same as in an adult living being, so the level of neural networks and development of aged disease phenotypes in the model are not equivalent to those in the target system. Finally, tissue slices are only feasible after a patient has deceased, while the amount of invasive testing allowed during clinical trials is limited for ethical reasons. As a result, a lot of extrapolation is required between different tissue models to determine the causes and progression of diseases.

Successfully extrapolating across different models is possible when those models accurately capture the relevant features of individual components. In the simplest cases, the properties of individual cells 'add up' to the whole brain structure and function. In those cases, extrapolations from a simple tissue model are relatively straightforward: the properties we study in the tissue model simply have to be magnified to give an appropriate prediction concerning the brain. Complete understanding requires tissue models that are complex enough to display similar emergent behaviours themselves: we need to generate the emergent properties in the tissue model in order to understand it in the target system. Only then can we be confident that our tissue models have captured the relevant underlying features.

Tissue models involve a wide variety of simplifications compared to real brains, including simplifications in cellular structure, network connectivity, morphology, neural function, cell type, sensory input and output, and chemical input (Wellbourne-Wood and Chatton 2018). Neurons in a tissue model may display certain axon and dendrite structure with various ion channels and synapses, but in the whole brain a wider variety of cell types and structures are found. In a tissue model, a limited number of connections are made across the neurons present, while in the whole brain, larger neural networks can form, and they can cross different brain regions. Tissue models are often a 2-dimensional network, in the brain 3-dimensional structures form, and in primates and humans, cortical folds provide a very high surface area. Tissue models show limited coordinated function, whereas the brain shows distinct regions that are able to perform functions such as retaining memory. Tissue models are often composed of limited cell types, in the brain, multiple cell types are present which will alter neural behaviour. Tissue models have limited sensory input and output, while in the brain, connections with other organs such as the eye and to muscles leads to formation of new types of connections and feedback mechanisms. Tissue models have limited chemical input, while in the brain, hormones and other drugs can affect neural behaviour. In all of these cases, simple tissue models omit features that could be most relevant for producing the emergent phenomena they are supposed to help us understand.

Tissue models aren't the only method for investigating the brain. Computer models are also used to understand cellular and network behaviour. These models balance complexity with cost and speed of computation, implementing different mathematical representations of cellular or network function. While these models can create some emergent phenomena, they are limited by the choice of neural features being modelled (Markram and others 2015). For instance, a model of electrophysiological response in neural networks often does not provide mechanistic biochemical information. Emergent phenomena generated by interactions between these features would not arise in such a model. Extrapolation from the model to the

target system would be hampered by the fact that the model has not captured the relevant underlying features.

The challenge of studying emergence is in anticipating which underlying features are relevant, and which simplifications in a model are allowable (Gan and others 2018). Emergent phenomena may arise at many different scales, involving interactions of molecules, cells, brain regions, organs or organisms. They may be the result of the number of components interacting together (e.g. large numbers of molecules, cells, connections), the specific type of components present (e.g. certain types of cells), or their arrangement (e.g. within a neural network) (Figure 4). For instance, in determining the impact of amyloid- β plaques and tau tangles in Alzheimer's disease, and to develop effective treatments, the effect of tissue structure must be investigated.

In order to understand brain diseases and develop effective treatments, we need to develop a range of models, covering different cellular, network and cognitive functions (Bassett and others 2018). This is the best way to ensure that the relevant features underlying emergent phenomena are captured in our models. Animal models may display similar neural function, however variations in genes may have a large impact on the mechanisms behind this behaviour (Götz and others 2018)(Dawson and others 2018). Cell cultures may show cellular structure and the development of synapses, but without other cell types, such as oligodendrocytes and microglia, myelination won't occur and the impact of the immune response is omitted (Madhavan and others 2018). A human derived organoid can display some neural structure involving several cell types, but the developmental stage limits cell maturation and lack of vasculature limits organoid size, preventing development of large neural networks and complex structure (Choi and others 2014)(Amin and Paşca 2018). Only by integrating a range of models can we hope to capture the relevant features of a disease process (Bassett and others 2018).

Mapping the degradation in cognitive function with disease progression can provide clues to the relevant components underlying emergent phenomena, but it doesn't eliminate the possibility that a more complex mechanism is occurring. By having a range of models, the relevant emergent phenomena promotes understanding of normal brain function and for developing treatments for disease (Bassett and others 2018). One approach is to develop new, more complex models that display different emergent phenomena than currently available in cell culture. This will involve controlling the cell number, types and their arrangement to determine these effects on emergent properties in neural function and disease. This may be achieved by further development of tissue engineering methods such as 3D bioprinting (Figure 5) (Zhuang and others 2018). It will also define the limitations of simpler models currently in use. The outcome will be to incorporate the concepts of emergence into tissue modelling in order to understand neural function and neurodegenerative disease.

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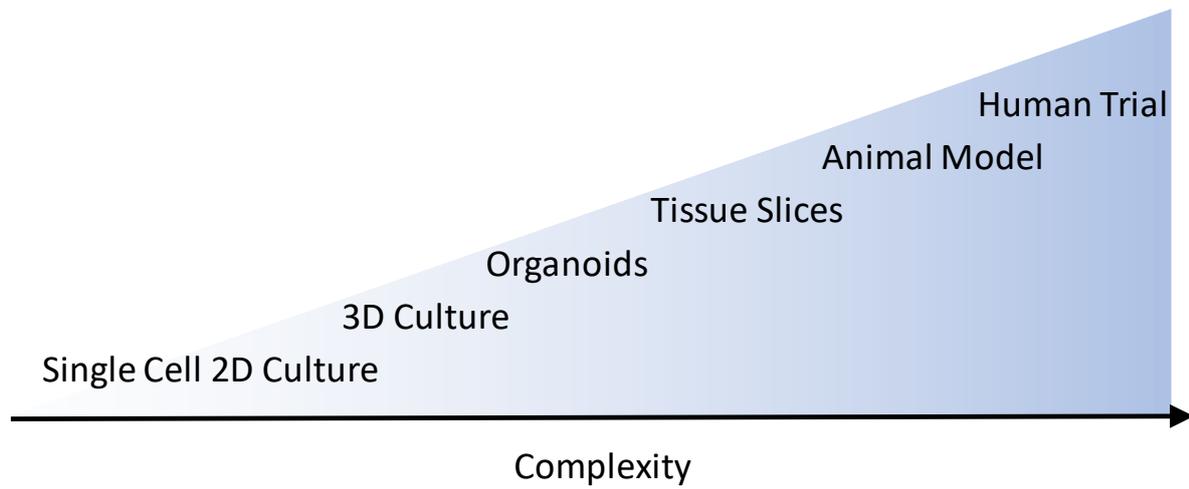


Figure 1: The complexity of tissue increases across different models. Low complexity models allow investigation of cellular behaviour, but may not capture sufficient information or be sufficiently accurate to explain more complex tissue relevant to the human brain and neurodegenerative disease.

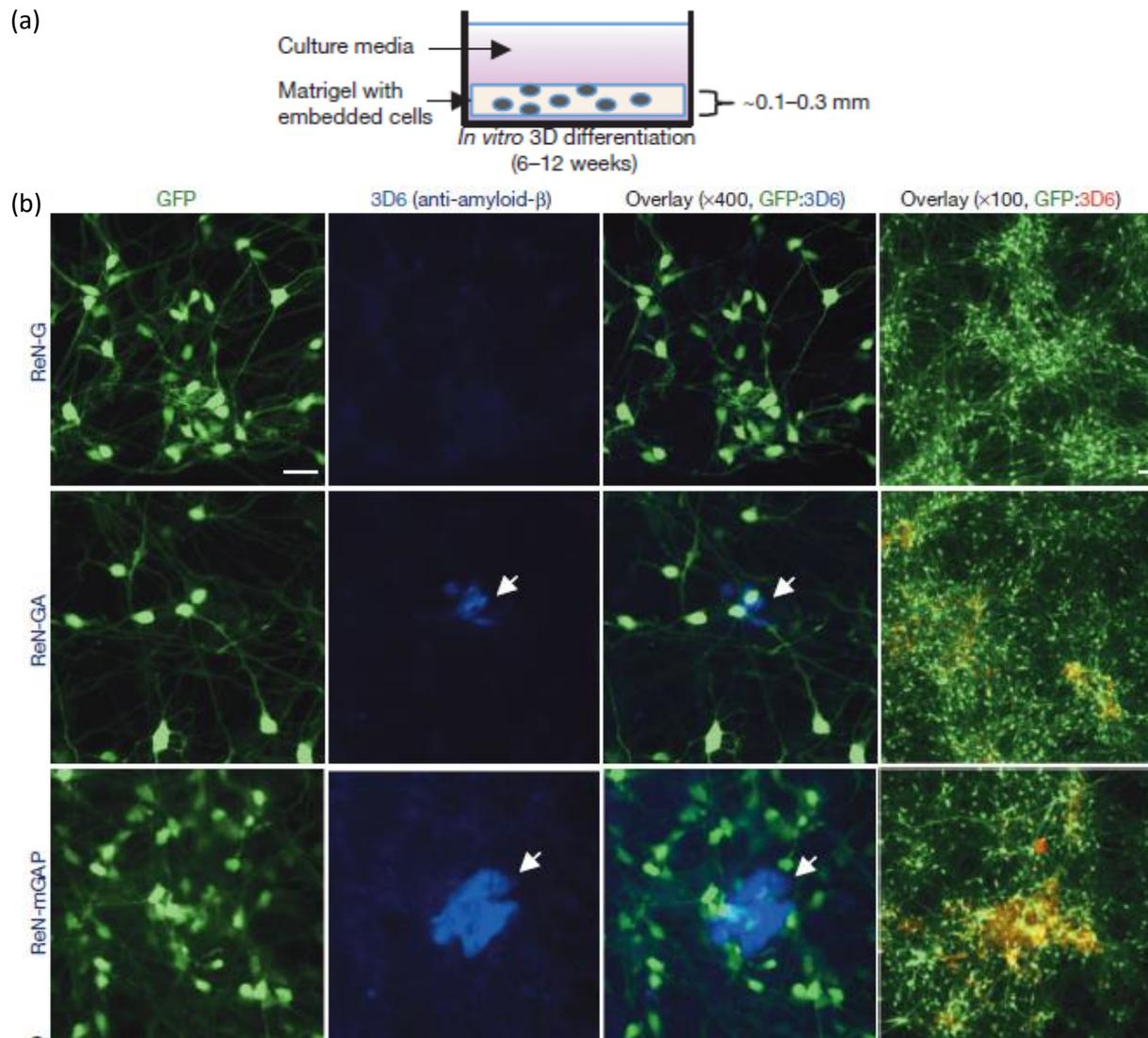


Figure 2: Formation of amyloid- β plaques in 3D culture using differentiated hNPCs with FAD mutations. (a) 3D culture protocol, (b) amyloid- β deposits in 6-week differentiated control (ReN-G), APP (ReN-GA) or APP/PSEN1 (ReN-mGAP) cells (green, GFP; blue, 3D6; scale = 25 μ m; arrowheads, extracellular amyloid- β deposits; right-most panels, 3D6 staining was pseudo-coloured to red). Adapted with permission from: (Choi and others 2014)

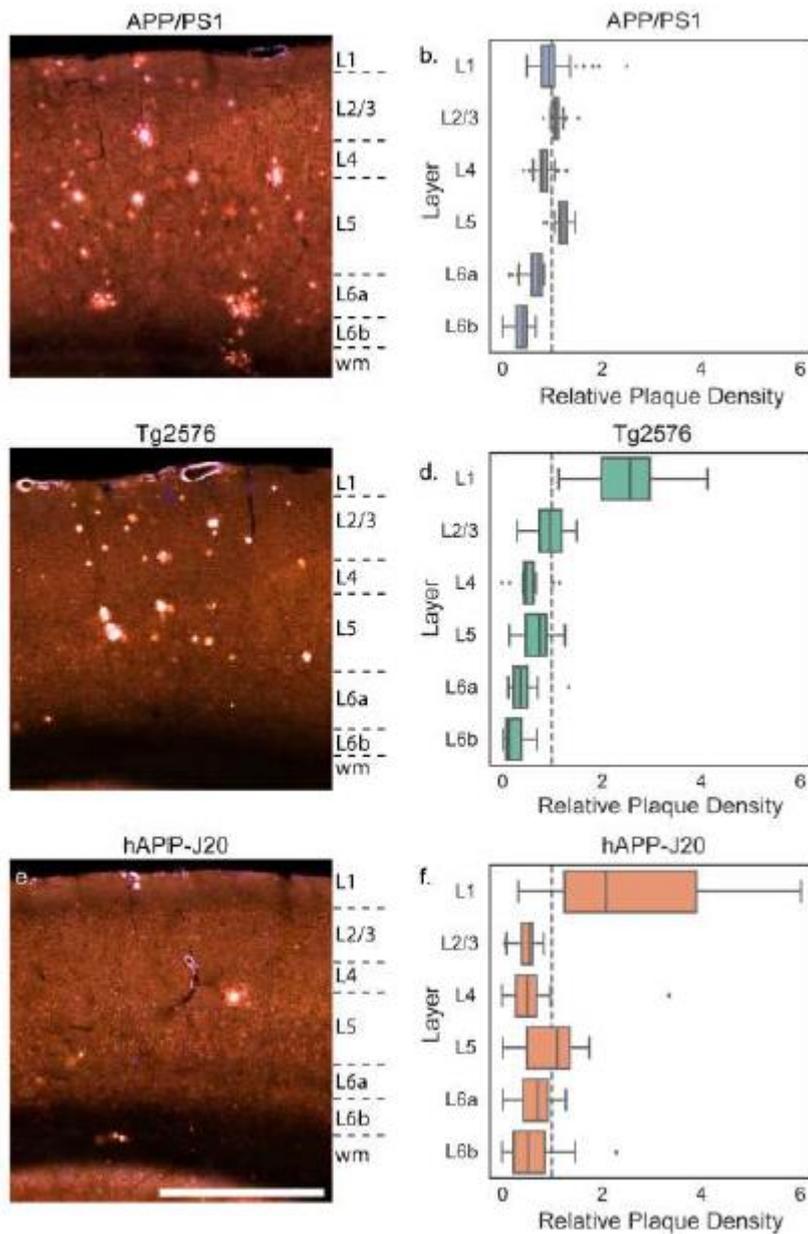


Figure 3: Plaque distribution across cortical layers differs between mouse models. Images showing plaques in the parietal cortex of 19-month-old (a) APP/PSEN1, (c) Tg2576, and (e) hAPP-J20 mice. Approximate layer boundaries are indicated in text to the right of each image (wm = white matter). Scale = 500 μ m. The relative plaque density in each cortical layer across the entire isocortex is plotted separately for (b) APP/PS1, (d) Tg2576, and (f) hAPP-J20 mouse lines. Box plots show median and IQR with whiskers extending up to 1.5 times the IQR. Outliers are plotted as individual points. Adapted with permission from: (Whitesell and others 2019)

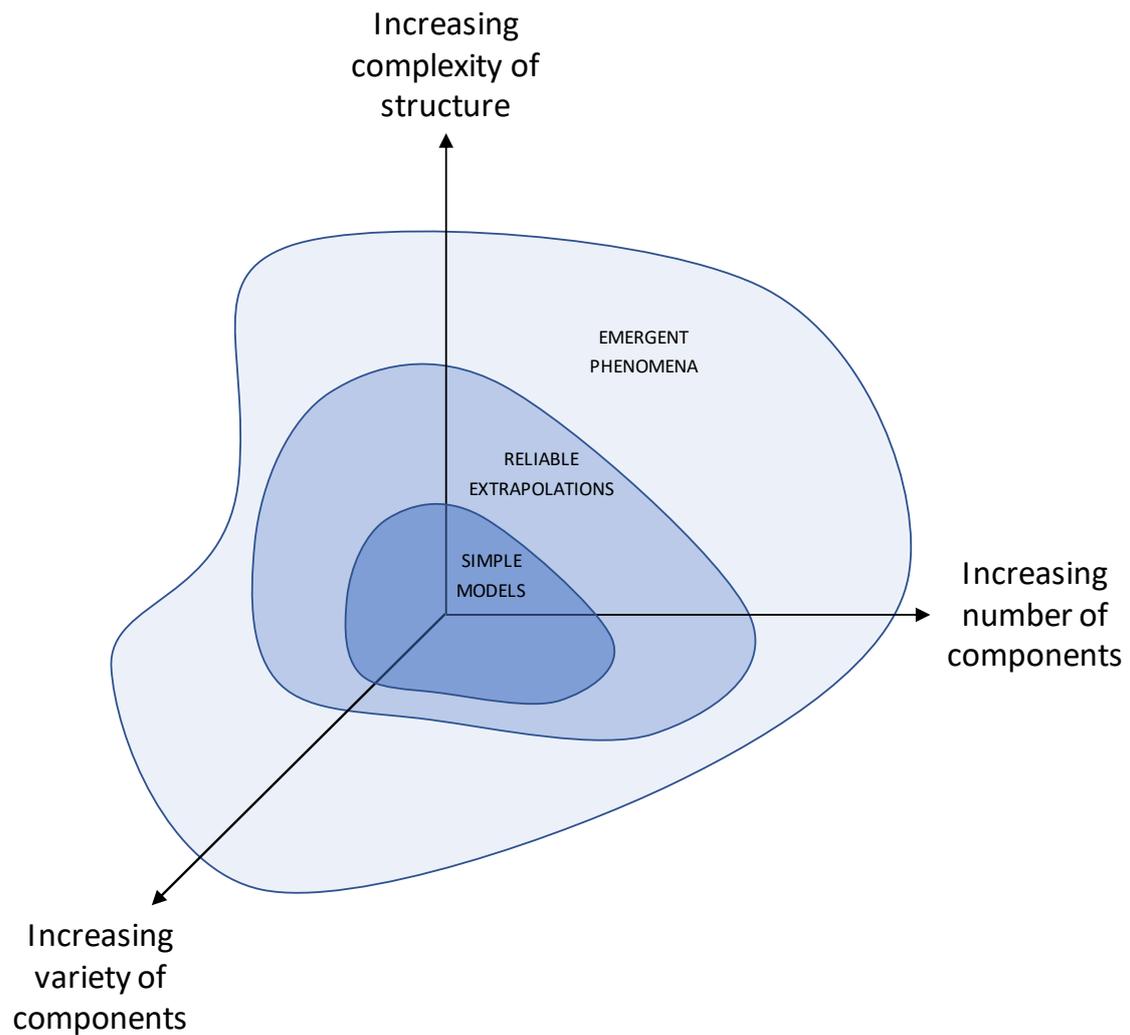


Figure 4: Representative diagram showing the relationship between emergent phenomena and simplified models across three dimensions. The shaded areas represent groups of systems with similar patterns of behaviour. For the inner areas, the behaviours are sufficiently similar to allow for reliable extrapolation. Emergent phenomena involve drastic changes in behaviour that can no longer be reliably captured by simplified models.

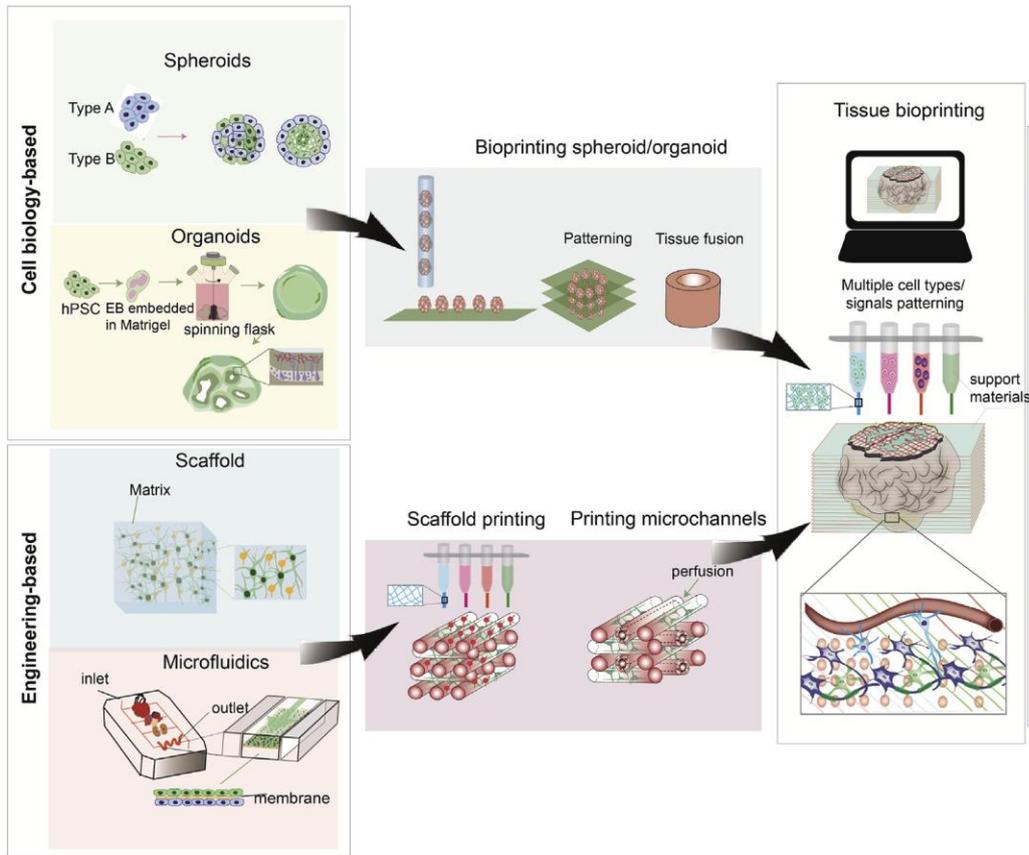


Figure 5: An overview of current in vitro neural tissue models. Cell biology-based models include spheroids and organoids, which are heavily dependent on spontaneous cell organization, resulting in a highly variable structure and composition. Engineering-based models include scaffold-based and microfluidics, which impose better control over matrix organization and tissue structure. Bioprinting combines the strengths of cell biology and engineered models by integrating cells, scaffolds and microfluidics into one neural tissue model with better quality and consistency. Adapted with permission from: (Zhuang and others 2018)