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Comment

The final frontier in connectomics: Forward engineering brain networks
Comment on "What would a synthetic connectome look like?" by Ithai Rabinowitch

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It reads like science fiction. A world in which we can design arbitrary wiring patterns between the neurons in our brains, and realise them in living systems. In this review, Rabinowitch posits that this world may be closer than we think [1]. What are the possibilities synthetic connectomes will enable? How might we go about engineering them? And what are the societal implications and technological applications?

Connectomics has entered an era of explosive progression, driven by the advent of many novel neurotechnologies and large-scale coordinated efforts across institutions and countries. Synthetic neurobiology is rapidly progressing and providing important contributions to connectome mapping [2], for example through genetic sequencing [3], viral tracing [4], and fluorescence imaging techniques [5]. Theoreticians and data analysts are racing to keep up with the volume and novelty of multimodal data of unprecedented detail [6]. Network neuroscience has made strides, identifying common features in connectomes across species such as rich clubs [7–9], laying the groundwork for connecting scales and data types [10,11], and shedding light on the relationships between the wiring diagram, dynamics, and behaviours [12,13].

Yet, some of these most important and stubborn questions, including how levels – from the molecular, to the neuronal, to the regional – relate to and interact with each other, and an understanding the ways in which organism behaviour emerges from neuronal activity, remain only partially answered. The promise of a synthetic connectome is the promise of the ultimate experimental playground for neuroscientists. An opportunity to *forward* engineer model systems. State of the art simulations such as those from OpenWorm [14] and the virtual brain [15] already offer an impressive computational environment in which to investigate dynamics for some neural systems, but the synthetic connectome takes this so much further. Increasingly we are acknowledging that the brain cannot be understood in isolation. That is to say, it exists as a component of a larger system – the body – which interacts with an environment. We know that organisms behave differently according to their bodily state, for instance *C. elegans* navigates chemosensory gradients in a way that varies with satiety [16]. A synthetic connectome neatly bypasses modelling

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challenges such as this, by directly interacting with the body in ways we can observe and measure, from neuronal activity to muscle contraction and relaxation, to the interaction of the whole organism with its surroundings. It affords the ability to arbitrarily and precisely alter neuronal-level connectivity, and then observe the effect at the level of the whole organism. This will allow us to identify causal paths between the wiring diagram and behaviour, and connect mechanistic descriptions of brain structure and function at different levels [17].

Beyond the excitement about scientific possibilities for advancing fundamental neuroscience, this review also considers the applications and technologies that may emerge from synthetic connectomes. Once we understand more of the principles behind the design of connectomes, we can start to design them ourselves with specific purposes in mind. This is the most impactful part of the discussion, but also the one with the most potential cause for alarm. The ethical considerations of synthetic connectomes are extremely serious, from the misuse of powerful technologies including malevolent use such as biowarfare, unintended ramifications for the ecosystem, questions of the limits on our "playing God", and the welfare of the organisms developed with synthetic connectomes themselves [18,19]. A dramatic example of unintended consequences on the wider ecosystem lies in the infamous Africanized honey bee [20]. This bee, deliberately cross-bred for increased honey production, escaped from a controlled environment into Brazil. Its aggressive nature made it highly invasive and problematic, and it swiftly spread across South America, and eventually North America. How do we avoid these potential pitfalls? What should be the rules for deciding which proposed connectome blueprints may be realised? How will these rules change with species? How will designs be protected and policed? Current literature on the ethics of synthetic biology argues that the result must be predictable, including in the face of noise and evolution [21]. This is an impossibly difficult question, especially upon release into the environment. Legalese and ethics do not keep up with technological progress, more so in the face of issues that demand cooperative agreements between nations on a global scale. For instance, effective and consistent regulation of the internet continues to elude us. Ethics cannot be an afterthought, they must be at the head of the discussion, and as Rabinowitch points out, include careful coordination between scientists, governmental bodies, and the public [22].

That said, what we stand to gain from synthetic connectomes is of enormous and revolutionary consequence. Rabinowitch imagines examples such as organisms that perform medical procedures within the body, and insects that clean the environment. Indeed, work has identified enzymes that fully degrade plastic [23]. If we can harness, direct, and deliver capabilities like this via synthetic organisms, we can imagine tackling the seemingly insurmountable problems of the devastating deluge of plastics polluting our oceans and drinking water. In the human brain, therapeutic interventions that aim to modify connectivity to treat disorder and disease already exist, albeit in their infancy. Non-invasive brain stimulation technologies such as Transcranial Magnetic Stimulation (TMS) are used to treat pathologies including stroke, depression, and epilepsy [24]. The first steps towards rewiring connectivity at the neuronal level by adding electrical synapses have already been achieved in *C. elegans* [25]. So should neuroscientific modellers fear for the future of their disciplines? Absolutely not. The design process to create connectomes will require sophisticated simulations. Better simulations will also afford better predictably in the outcome, which as discussed above, is crucial for principled and controlled regulation. Knowledge from synthetic connectomes will in turn enrich dynamical models with a vast array of information. Finally, biologically unviable or unethical realisations of connectomes may still hold scientific interest.

Human innovation is often rewarded by looking to nature: evolution has already solved many of its own enduring problems [26]. Synthetic connectomes are a natural union of synthetic biology and neuroscience, and will offer another way in which we can work together with living systems to solve some of the biggest mysteries of the brain and challenges of the modern world.

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