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The case for emulating insect brains using anatomical "wiring diagrams" equipped with biophysical models of neuronal activity

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ABSTRACT: Developing whole-brain emulation (WBE) technology would provide immense benefits across neuroscience, biomedicine, artificial intelligence, and robotics. At this time, constructing a simulated human brain lacks feasibility due to limited experimental data and limited computational resources. However, I suggest that progress towards this goal might be accelerated by working towards an intermediate objective, namely insect brain emulation (IBE). More specifically, this would entail creating biologically realistic simulations of entire insect nervous systems along with more approximate simulations of non-neuronal insect physiology to make "virtual insects." I argue that this is realistically achievable within the next 25 years.

In silico brain emulation represents a much sought-after dream within the field of computational neuroscience (Jordan et al., 2018; Koene, 2013; Markram, 2006; Markram et al., 2015). I propose that developing emulations of insect brains will galvanize the global community of scientists, businesspeople, and policymakers towards pursuing the loftier goal of emulating the human brain. By demonstrating that WBE is possible via IBE, simulating the human brain will no longer be viewed as too radically ambitious to deserve substantial funding and resources. This shift may facilitate a large-scale organized push towards human WBE, making the goal potentially reachable during the 21st century. Because of the strong possibility that in silico organisms will possess consciousness, a publicly transparent ethical framework will need to be developed in parallel with technical efforts. By implementing IBE, large-scale scientific infrastructure may shift towards developing more WBEs and move in the direction of comprehensively understanding neural computation.

Applications of Insect Brain Emulation

Despite its status as an intermediary step, IBE has immense promise for elucidating a more generalized understanding of cognitive processes and disorders because insects exhibit remarkably complex behaviors for their apparent simplicity. Even with its fairly small brain of 135,000 neurons (Alivisatos et al., 2012), *Drosophila melanogaster* integrates multiple streams of sensory information and exhibits decision making which goes beyond instinctually programmed responses (Gorostiza, 2018). In addition, *Drosophila* has demonstrated success as an animal model for intellectual disability and Alzheimer's disease, highlighting the utility of insects in biomedicine (Chakraborty et al., 2011; van der Voet, Nijhof, Oortveld, & Schenck, 2014). Honeybees demonstrate even more advanced cognitive abilities (Menzel, 2012). They show numerical cognition or "counting" (Pahl, Si, & Zhang, 2013), long-term memory on the scale of months (Menzel, 1999), and social communication regarding the spatial location of food through the "bee dance" (Menzel et al., 2011). As such, gaining a thorough understanding of insect cognitive machinery through IBE would represent an enormously valuable advance towards understanding neurological function and dysfunction.

IBE also has numerous applications in artificial intelligence and robotics since many insects exhibit high-level decision making and social communication. By contrast, current artificial intelligence systems are "savants" that learn to perform certain tasks efficaciously but lack the agility of biological intelligence when dealing with the myriad challenges found in navigating a complicated world. Artificial intelligence can play games like chess and Go (Silver et al., 2017), accurately diagnose diseases based on symptomatic criteria (Yu, Beam, & Kohane, 2018), recognize and classify images containing particular objects (Akata, Perronnin, Harchaoui, & Schmid, 2014), and find elusive patterns within scientific data (Jimenez & Landgrebe, 1998). However, more humanlike artificial intelligence which can perform a myriad of distinct tasks as necessitated by the environment has proven challenging (Petrović, 2018).

IBE may greatly accelerate the development of stronger artificial intelligence by enabling rapid and detailed studies of the neural computations related to versatile and complex insect behaviors. Furthermore, the immense diversity of macroscopically visible adaptations found among insects likely coincides with a similarly vast array of untapped cognitive

mechanisms that may serve as the basis for biomimetic artificial intelligence and robotics. Understanding such mechanisms and their systems-level interactions could facilitate design of substantially more adaptable artificially intelligent agents. Even without complete mechanistic understanding, the circuits of insect intelligence could be borrowed and incorporated into synthetic cognitive agents. It should be noted that this possibility may partly depend on the modularity of insect brain structures. There is some evidence for modularity within insect brains, though the data still indicate that modules exhibit substantial crosstalk (Menzel & Giurfa, 2001). Nonetheless, IBE would still open the door for borrowing cognitive subsystems from insects to use in artificial intelligence since IBE would allow for extremely rapid and precise "virtual lesion studies" in which the functional interdependence of anatomically distinct regions could be tested. Studying IBEs would make available an enormous wealth of evolutionarily validated cognitive tools for the field of artificial intelligence.

Roboticists often attempt to design robots that mimic the motor abilities of biological organisms, so investigations on how virtual insect nervous systems control motor actions could benefit the design of autonomous mechanical agents. Many robots already use insect locomotion as an inspiration, including ground-based robots (Lambrecht, Horchler, & Quinn, 2005; Lim, McCarthy, Shaw, Cole, & Barnes, 2006; Nguyen et al., 2018) and aerial robots (Y. Chen et al., 2017; Zou, Zhang, & Zhang, 2016). In some cases, biomimetic robots have borrowed tools from insect cognition. Bagheri et al. investigated a neural circuit from dragonflies which facilitates tracking of visual targets and used this neural circuit to guide the design of a robot that follows moving objects (Wiederman, 2017). The successes of these efforts indicate that insect-inspired robotics could greatly benefit from the detailed computational understanding of insect sensorimotor circuits which may come from IBE.

High-throughput structural mapping of insect connectomes

IBE will necessitate powerful experimental tools for mapping insect brains at a level which resolves dendritic morphologies and synaptic contacts. Serial block-face electron microscopy (SBEM), expansion microscopy (ExM), and X-ray microtomography (XRM) possess promise for attacking this challenge. Serial electron microscopy provides extremely high resolution but is a very time-intensive technique even for small tissue volumes (Denk, Briggman, & Helmstaedter, 2012; Helmstaedter et al., 2013; Marx, 2013). Despite this, Zheng et al. acquired SBEM data for the entirety of the *Drosophila* brain using a customized high-throughput SBEM platform (Zheng et al., 2018). The resulting three-dimensional image will still require extensive computational efforts to trace the neuronal processes and obtain a complete reconstruction of the fly brain. Nonetheless, this achievement represents the first major success in whole-brain imaging at synaptic resolution.

Despite the customized SBEM platform, this method remains time-consuming. The authors reported that each 40 nm slice of *Drosophila* tissue took about seven minutes to image and that they successfully imaged 7,050 slices. Ignoring any possible interruptions, this means that the process took more than a month to complete. While this timescale is still impressive compared with other SBEM efforts, it might be challenging to scale the technique for the substantially larger brains of honeybees and other more complex insect species. SBEM is also unlikely to be the most efficient method for comparative connectomic studies between insect specimens in which many insect brains would undergo imaging. Even so, the dataset from this study represents an important step towards the construction of a virtual *Drosophila* and may pave the way for further connectomics efforts to facilitate the development of IBEs.

Expansion microscopy involves infusing neural tissue with a swellable polymer matrix that is equipped with fluorescent labels for desired biomolecules (F. Chen, Tillberg, & Boyden, 2015). This allows linear tissue expansion, enlarging the sample without introducing excessive distortions and facilitating higher "effective resolution" when imaging. The ExM process also makes treated samples partially translucent, which enables nondestructive optical imaging of deep tissue structures. New three-dimensional fluorescence microscopy techniques such as light-sheet microscopy show promise for working in concert with ExM (Liu et al., 2018). Although ExM has been applied more frequently to mammalian model organisms than to insects, its efficacy for imaging large regions of neural tissue with high resolution (Murakami et al., 2018) indicates that it may provide valuable contributions towards mapping insect connectomes.

X-ray microtomography represents a powerful and largely unexploited tool for structural connectomics. XRM involves staining tissue samples with high-z contrast agents, rotating the samples while scanning with X-rays, and then computationally reconstructing

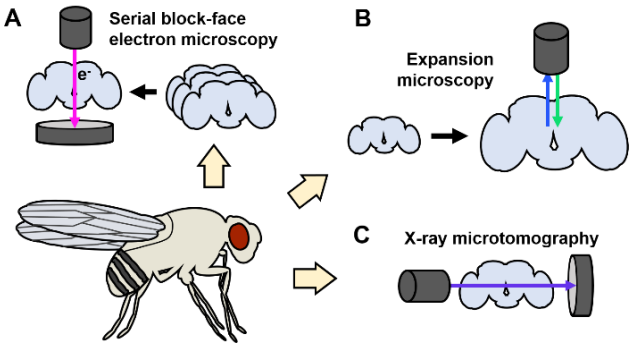

Figure 1 | techniques for structural mapping of insect brain tissue. **(A)** Serial block-face electron microscopy (SBEM) requires preparation of ultrathin tissue slices. An electron beam is then passed through each slice and the resulting images are computationally stacked to obtain a 3D reconstruction with nanometer-scale resolution. Even with high-throughput automation, this technique is highly time-intensive. Nonetheless, SBEM was recently used to acquire data on the entire *Drosophila* brain (Zheng et al., 2018). Novel computational techniques may facilitate neuronal tracing of this volume and complete a *Drosophila* structural connectome. **(B)** Expansion microscopy (ExM) physically enlarges tissue via an infused polymer matrix (F. Chen et al., 2015). This facilitates "effective super-resolution imaging" using fluorescence microscopy. Emerging technologies like light-sheet microscopy may enable rapid 3D imaging of tissue volumes using ExM (Liu et al., 2018). **(C)** X-ray microtomography (XRM) passes X-rays through a sample positioned on a rotating stage and allows 3D reconstruction. For imaging soft tissue, XRM requires a high-Z contrast agent. Although XRM has lower resolution than SBEM, it can be performed much more efficiently for larger tissue volumes while still retaining a resolution sufficient to observe dendritic and axonal processes (Mizutani et al., 2011). In addition, XRM is a nondestructive method.

three-dimensional images. Although it has a lower resolution than SBEM, axonal and dendritic processes are still visible in XRM images (Mizutani et al., 2011). XRM is nondestructive, works on timescales of hours rather than months, and needs less computational resources than SBEM for three-dimensional reconstruction (Mizutani et al., 2016). It has been applied in human tissue samples to help understand neural circuits (Mizutani et al., 2010). Furthermore, XRM has successfully reconstructed a skeletonized version of a *Drosophila* brain hemisphere with a resolution of around 600-800 nm, highlighting its potential for imaging insect brains (Mizutani, Saiga, Takeuchi, Uesugi, & Suzuki, 2013). Much like SBEM, the technique is still limited in terms of the person hours required for tracing neuronal processes, though improved neural tracing software which operates in a fully automated fashion may ameliorate this problem (Acciai, Soda, & Iannello, 2016; Donohue & Ascoli, 2011). If this computational problem is overcome, XRM could provide a platform for rapid imaging and reconstruction of insect connectomes.

While purely structural data allows for detailed biophysical modeling of isolated neurons, the type of synaptic coupling will be essential for describing the insect brain at the network level. Fortunately, the outlined tools can be adapted for the purpose of synapse classification. In some cases, SBEM possesses sufficient resolution to allow identification of excitatory and inhibitory synapses by observing their morphological characteristics (Kleinfeld et al., 2011). Expansion microscopy is compatible with immunohistochemistry and genetically encoded fluorescent markers (F. Chen et al., 2015). XRM may allow absorption-based tagging of synaptic features using contrast agents that have distinct electron densities. Downstream, these methods may facilitate the construction of better models for IBE.

Translating structural data to biophysical models

I propose that to construct an effective IBE, detailed neuroanatomical data from the desired insect will need to be combined with conductance-based biophysical models of neurons. The Human Brain Project (HBP) has made strides towards a similar goal, but this effort has not emphasized biologically accurate neural connectivity (Markram, 2006; Markram et al., 2015; Reimann et al., 2017). The Human Brain Project has instead created virtual cortical columns using known densities of distinct morphological cell types within cortical layers and modeling synaptic coupling by implementing "typical" connectivity patterns for the layer under consideration. This technique develops rough approximations of biological neuroanatomy and is unlikely to be suitable for making IBEs that accurately reproduce behavior in silico. Nonetheless, the Human Brain Project does use multicompartmental electrophysiological models at the network scale and so may provide valuable lessons on the practice of modeling detailed neurophysiology within large neuronal ensembles.

Although IBE will require fairly detailed whole-brain data from insects, some simplifications might be possible while still maintaining strong biological

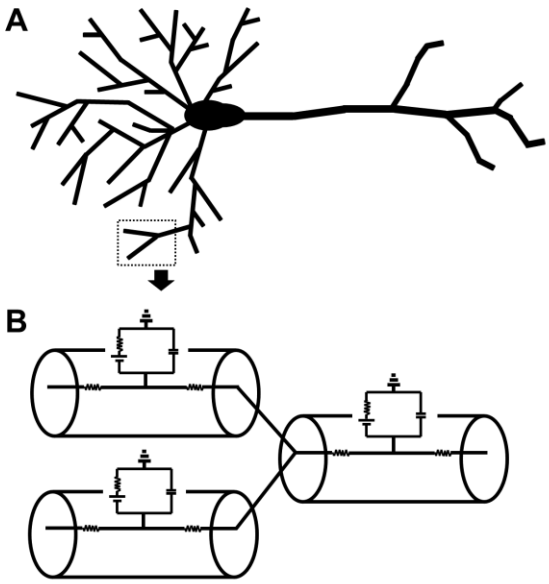

Figure 2 | Multicompartmental Hodgkin-Huxley-type models. **(A)** Most biological neurons possess complex dendritic trees. These morphologies combine numerous excitatory and inhibitory postsynaptic potentials via a nonlinear process. As a result, a neuron's geometric constraints exert spatiotemporal control over membrane voltage propagation and dendritic computation. **(B)** Biologically realistic neurons can be modeled in silico using multicompartmental models that decompose the dendritic arbor into a set of interlinked segments and describing membrane voltage dynamics using a partial differential equation known as the cable equation. The neuronal cable equation is derived from a Hodgkin-Huxley-type model of an electrical circuit and equipping the equation with appropriate parameters including the length constant and the membrane time constant (Gerstner, Kistler, Naud, & Paninski, 2014).

realism. Despite neglecting molecular details, multicompartmental conductance-based models are highly predictive of biological neural activity (Herz, Gollisch, Machens, & Jaeger, 2006). I contend that multicompartmental models equipped with modifications which emulate synaptic potentiation, non-canonical electrophysiological influences (i.e. dendritic calcium spikes), chemical signaling, and glial modulation may produce sufficient biological accuracy.

These simulations will not need to follow the dynamics of individual biomolecules. For synaptic potentiation, models may take the form of spike-timing dependent plasticity functions equipped with terms that account for cooperativity among spike inputs (Rabinovich, Varona, Selverston, & Abarbanel, 2006; Sjöström, Rancz, Roth, & Häusser, 2008). Non-canonical electrophysiology might be incorporated into existing multicompartmental models (Destexhe, Contreras, Steriade, Sejnowski, & Huguenard, 1996; Holcman & Yuste, 2015). Glial modulation and other chemical signaling processes could be simulated using reaction-diffusion models that describe spatiotemporally dependent concentrations of various signaling molecules (McDougal, Hines, & Lytton, 2013). Neuronal connectivity can be computationally described using directed adjacency matrices, a graph theoretic technique (Bullmore & Sporns, 2009). Iterative comparison of IBEs to biological insects and refinement of models will be essential for achieving biological accuracy. Using these kinds of methods, virtual insect behavior may demonstrate close resemblance to the behavior of biological insects.

Emulating non-neuronal physiology

To create IBEs that provide meaningful insights regarding the connection between brain function and behavior, models of non-neuronal insect physiology will also require implementation. Fortunately, these processes may necessitate less detailed modeling to achieve biological realism. The simulated *C. elegans* created by Palyanov et al. provides evidence that such a simplification could be reasonable (Palyanov, Khayrulin, Larson, & Dibert, 2012). Their emulation of the worm included a neuromuscular system in which the musculature was approximated using spring constructs linked to appropriate points on a wireframe body. Even with this very rough model, wormlike movements were observed in the virtual *C. elegans*. As such, modeling non-neuronal physiology like that of the musculature might be feasible without the single-cell resolution mapping which is more important for emulating nervous systems.

The insect endocrine system may represent one of the more challenging and important non-neuronal systems to describe for IBE. Insect endocrine systems, including those of the *Drosophila* and the honeybee, are fairly well-characterized (Bloch, Hazan, & Rafaeli, 2013; Even, Devaud, & Barron, 2012; Farooqui, 2012; Hauser, Cazzamali, Williamson, Blenau, & Grimmelikhuijzen, 2006; Orchard & Lange, 2012). However, endocrine physiology exhibits multiscale dynamics which range from molecular to whole-organism levels. Because of this, it will be essential to develop models that incorporate necessary mechanistic features of insect endocrine physiology via approximations which

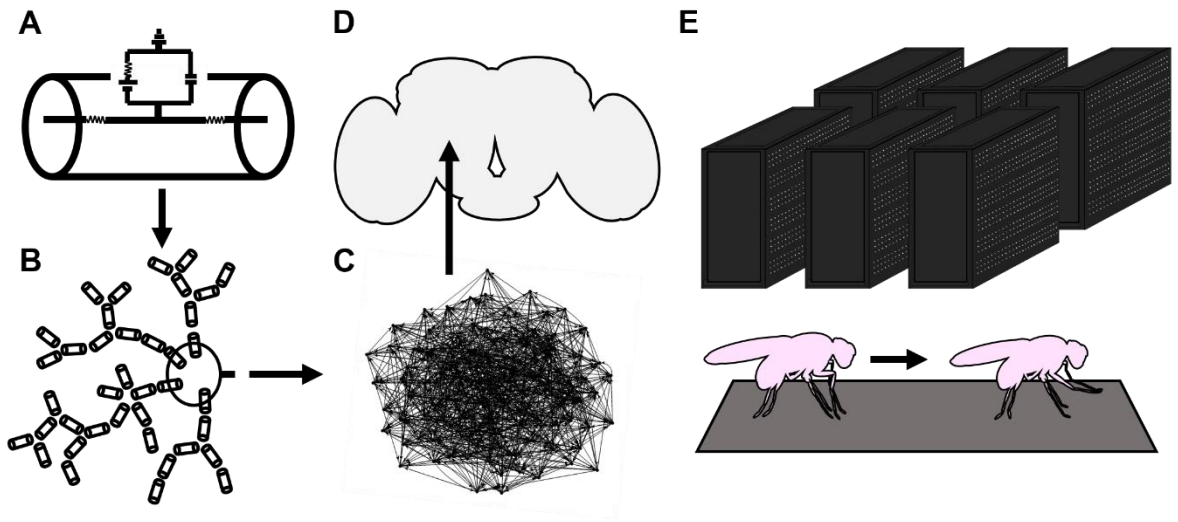

Figure 3 | IBE will require integrated multiscale modeling to create biologically realistic simulations of insects. **(A)** Single compartment Hodgkin-Huxley-type model. **(B)** Multicompartmental model for accurate simulation of a dendritic arbor. **(C)** Graph-theoretic techniques (Bullmore & Sporns, 2009) will be used to construct networks of emulated multicompartmental neurons with connectivity mirroring the anatomy of biological insects. **(D)** Entire insect brains along with models of non-neuronal physiology (not shown) will be simulated in order to create virtual insects. **(E)** Even currently existing supercomputers might be capable of handling IBE and reproducing the behavior of insects in silico.

circumvent excess computational demands while still mediating reasonably accurate behavioral outcomes in silico.

As hemolymph undergoes continuous flow throughout the insect haemocoel, the well-mixed system assumption is likely applicable to insect hormone transport. More difficulties may arise in modeling the complex modulatory effects of hormones on insect physiology, particularly when considering that the interplay of hormonal influences exhibits highly context-dependent properties (McKenna & O'Malley, 2002). High-throughput assays in which the context-dependent effects of many insect hormones are tested in a combinatorial fashion may aid in the development of entomological endocrine models. Endocrine systems present a challenge to IBE but are not an insurmountable obstacle.

Computational resources

Though IBE models may allow simplifications relative to the biological systems they mimic, even a single IBE would demand a large amount of computational resources. While precisely estimating these requirements would be challenging without more detailed specifications on model construction, I will speculate on some possibilities using floating-point operations per second (FLOPs) to describe the necessary levels of computational demands. Though FLOPs represent a fairly rough metric, they still provide a reasonable "first guess." One method for generating such estimates involves multiplying the neuronal population size times the average input synapses per neuron times the mean spike frequency (Furber, Temple, & Brown, 2006). Assuming 1,000 input synapses per neuron on average with a mean spike frequency of 10 Hz, emulating the *Drosophila* brain would require 10^9 FLOPs and emulating the honeybee brain would require 10^{10} FLOPs.

However, this approach for estimating computational demands focuses on network-level processing and ignores the requirements of computation within individual neurons. Although such an approximation would be viable for an emulation that utilizes McCulloch-Pitts or integrate-and-fire neurons, these models are almost certainly too far simplified to possess sufficient biological realism. I will further multiply by a factor that describes the necessary resources to emulate each neuron using multicompartmental biophysical models. For a single neuron, such Hodgkin-Huxley-type models require around 1.2×10^6 FLOPs (Izhikevich, 2004). Taking the product of this factor with the network-based estimate, a *Drosophila* IBE would need 1.2×10^{15} FLOPs and a honeybee brain

would need 1.2×10^{16} FLOPs. As non-neuronal physiology will likely require less resources than nervous systems, a virtual *Drosophila* probably would need less than 2×10^{15} FLOPs and a virtual honeybee probably would require less than 2×10^{16} FLOPs. These demands fall within the capabilities of the fastest existing supercomputers which operate at up to 9.3×10^{16} FLOPs (Lee & Amaro, 2018; Service, 2018). As exascale supercomputers (which operate at speeds of 10^{18} FLOPs or higher) are planned for completion in the early 2020s, IBE represents a quite reasonable goal from a computational standpoint.

Application-specific hardware tools for computational neuroscience may further increase the accessibility of virtual insects. The organization of neuromorphic hardware more closely resembles neurobiology than the organization found in traditional circuitry (Indiveri et al., 2011). For this reason, neuromorphic hardware more efficiently runs emulations of neurobiological systems. SpiNNaker is a digital neuromorphic hardware architecture that facilitates large-scale simulations of neuronal networks (van Albada et al., 2018). The SpiNNaker hardware has emulated a cortical microcircuit of 80,000 leaky integrate-and-fire neurons and 300 million synapses. Field-programmable gate arrays (FPGAs) represent another type of neuromorphic architecture (Zjajo et al., 2018). FPGAs have demonstrated greater promise for emulating biologically realistic neurons via multicompartmental Hodgkin-Huxley-type models than many other types of hardware. Neuromorphic computing may enhance the efficiency of IBE and so allow for simulations to be carried out at lower cost.

Conclusions

Beyond its immediate applications, IBE raises some important philosophical considerations. If an insect's behavior is successfully reproduced in a virtual setting using a biologically accurate brain emulation, the IBE may very well exhibit consciousness. This possibility is supported by integrated information theory (IIT), an attempt to outline fundamental mathematical constraints that underlie the physical phenomena necessary for particular qualia to occur (Oizumi, Albantakis, & Tononi, 2014). IIT lends credence to substrate independence, the idea that any system with equivalent information processing will exhibit the same conscious experiences regardless of its substrate (i.e. neuromorphic silicon or biological neurons). As such, IBE provides an early opportunity to develop ethical guidelines for handling emulated minds. This will be vital if the human brain is eventually emulated in a nonbiological substrate. It would be far too easy to dismiss a human emulation as a nonhuman entity and then subject the emulation to experiments that cause terrible suffering. Although substrate independence may or may not hold true, the possibility should be thoroughly investigated since a philosophical error could result in some very disturbing consequences.

Nonetheless, I suggest that IBE and later emulations of human minds are worthwhile endeavors. If a proper ethical framework for handling WBE is developed, even human brain emulation could be carried out in a fashion that provides enormous benefit to the human species without harming the emulations themselves. Using advanced tools for mapping the brain, an emulated human may possess an identical set of memories relative to the original volunteer. In this scenario, the emulation will have provided consent for its own creation. I can envision "simulated research institutes" populated by WBEs in which time runs far more rapidly than it does outside of the simulation. Such institutes may perform decades of investigation over timescales of months or even days depending on the resources of future supercomputers. This world may seem far-fetched, but historical precedent tells us that science fictional ideas often transform into reality (Johnson, 2011).

I argue that IBE is a feasible near-term goal (within 25 years) along the path to human WBE. Furthermore, IBE possesses numerous applications in biomedicine, artificial intelligence, and robotics. Much of the structural data required to construct virtual insects may come from technologies like SBEM, ExM, and XRM. Extended versions of these tools may also facilitate the acquisition of data regarding the types of neurotransmitters secreted from synapses. Anatomical "wiring diagrams" derived from such experimental data may enable the construction of detailed multicompartmental Hodgkin-Huxley-type models that exhibit biologically realistic dynamics. Emulation of non-neuronal physiologies may necessitate less detailed experimental data to build and less computational resources to run, but it will still require substantial research to develop. Based on the outlined models and the neuronal population sizes of insect brains, I suggest that the computational demands of IBEs may fall within the capacities of existing supercomputers and well within the capacities of upcoming supercomputers currently under construction. Neuromorphic hardware architectures may further increase the computational efficiency of IBE. Building an IBE represents a difficult endeavor, but I

propose that it can be achieved given organized effort and multidisciplinary collaboration.

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