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Tools, flies and what to do next

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Abstract. In these brief notes addressed to students and researchers, recent advances of modern neurobiology are discussed in the light of some of its challenges. I use fly larval chemotaxis as a platform to debate about how much we are able to do with the available tools as opposed to how little we actually understand what it means to decide.

Keywords: behavioral neuroscience; decision making; noise; drosophila; science and society.
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Chemotaxis is a paradigm to study decision making. Orienting in a chemical environment requires a repertoire of computational abilities to transform sensory information into motor action. In the fruit fly larva, odor-search behavior represents an active sampling process more elaborated than the biased random walks of bacteria and worms, and analogous to sniffing in rats and humans [1, 2, 3, 4, 5]. The *Drosophila* larva is capable of purposeful rich behaviors under the control of a nervous system whose general anatomical layout is similar to, but yet far simpler than, that of vertebrates. The larval brain consists of two hemispheres, each composed of approximately 1000 neurons, compared to millions in mice and billions in humans. Its olfactory system is composed of two bilaterally symmetrical nostrils, called dorsal organs, each hosting 21 olfactory sensory neurons [6]. Olfaction in the fruit fly larva represents a trade-off between numerical simplicity and behavioral complexity. Bilateral sensory input is not a necessary condition for chemotaxis behavior [7], suggesting that temporal computations in such a miniature brain can direct robust, efficient and adaptive orientation behaviors. Computer-vision tracking systems allow to measure animal posture and movement in an automated fashion and at high resolution [8]. By mapping the stimulus landscape to the position of the olfactory organs, the sensory dynamics while crawling towards an attractive odor source can then be inferred. Such accurate sensory-motor data provides a quantitative basis to examine the algorithms that determine whether a maggot will decide to turn left or right.

The study of the mechanisms underlying active sensing during orientation maneuvers represents an experimentally tractable entry point into the general problem of sensory perception and motor control [9]. Together with chemotaxis, it has been applied in other modalities such as phototaxis and thermotaxis [1, 10, 11]. Making use of the detailed knowledge about larval anatomical and physiological properties, there is great promise that testing extraordinary large collections of transgenic lines in behavioral screens will identify sparse neural substrates or critical neurons mediating the observed behaviors. Furthermore, electrophysiological recordings [12] and functional imaging via genetically encoded calcium indicators [13] represent invaluable measurements of the neural activity responsible for such computations and behavioral decisions. Incidentally, functional imaging in behaving animals is just starting to be realized [14, 15]. Transgenic

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and transparent, the larva is an optimal system in which the recent advent of optogenetic tools can be applied, allowing causal links to be established. By ectopically expressing light-activated ion channels in specific neurons, neural activity can be manipulated at single spike level without use of invasive methods [16]. Maximizing control and maintaining realism, engineers have built virtual reality arenas where real-time tracking and closed-loop stimulation gives us the opportunity to scrutinize, at an unprecedented level, animal behavior and decision making [17]. These exquisite cutting-edge tools have triggered a renaissance in genetic model organisms such as worms, flies, fish and mice.

But, what does it mean, to decide? This simple question seems to be either trivial or extremely difficult to answer. Thoughts, actions, feelings, and nearly everything we believe we are have a neural basis. As the tools to study the nervous system become more and more sophisticated, we in fact approach more elusive, slippery, and controversial topics. Concepts that in the past were circumscribed to pure speculative reasoning and excluded from serious empirical research, now for the first time, may be amenable to incisive scientific inquiry. What is consciousness? What are its neural correlates [18]? If some animals are conscious, why are others not? How could unconscious matter give rise to a conscious mind? Is it a difference of kind or degree? Is freewill an illusion [19]? An oxymoron from the start? Perhaps reformulated as a biological trait, can it be empirically revisited by modern neuroscience [20, 21]? Regardless whether I am free or not, who am I? What are the neurobiological basis of agency, volition, and the self [22, 23]? Can objective experiments be attributed to subjective experiences [24, 25]?

The answers to many of these questions require an evolutionary and developmental perspective [26]. Why did animals evolve brains? The brain is one of the most complex and remarkable information processing systems in nature. Still, it may have evolved, not only to sense or process information, but primarily to generate actions and control movement [27]. What is behavior, then? In the same way that action potentials define the principal language for neural activity [28], is there an analogous universal descriptor for behavior? Is behavior fundamentally continuous or discrete? For instance, what is the degree of arbitrariness when classifying a larval trajectory segment as a turn or a run? Are responses and actions qualitatively different? Brought to the extreme, is creativity in essence a complex reflex? Animals exhibit a set of responses that are definitely hard-wired, still behavior is variable between and within individuals. Same same but different, should we not be looking beyond the mean for discovering the origins of phenotypic variability? How is spontaneity generated [29]? Can stereotypical behavior emerge from the dynamics of behavior itself [30]? Is the input-output view able to explain how animals act, rather than react to the world [31]? Living organisms are obviously capable of generating novel actions, never performed before. Is that choice or noise?

Are we machines or like machines [32]? The difference being subtle, the consequences of confusing an analogy with its literal meaning can be bewildering, if not dangerous. If worms and flies are complex and intricate organic hardware, what about mice and men? Why would a machine then be unable to feel love, pain or guilt [33, 34]? May your next generation iPhone need a lawyer to defend its rights? Indeed, some working hypotheses are nowadays operating as scientific dogmas [35]. Regarding model organisms, to what extent is that which we learn from a fly in the lab is informative about humans? Is animal behavior in laboratories representative of that in the wild? And is it wise to concentrate 99% of the research on 1% of the species? Coming back to biological complexity, what is life [36]? A necessary process out of pure chance [37]? Is life's most inner secret really a curly thread of DNA [38]? Are the enduring mysteries of the mind hiding within a complex circuit? According to the circuit doctrine, my connectome should be who I am. But, what is a 1 to 1 scale map useful for? The whole may be understandable, not despite the fact that we do not have all the details of every single part, but precisely because of that [39]. In order to make sense of so much data, powerful frameworks such as information theory or the theory of critical phenomena are good candidates to comprise the essential and direct further experiments [40, 41, 42]. That depends on whether we are looking for exceptions or searching for principles [43].

In these times of crisis, we should ask ourselves who decides where funding goes and under what criteria [44]. What is our return to taxpayers and is economic growth the only acceptable metric to evaluate scientific impact in terms of benefits for society [45]? Since lobbying has become a common and desperate practice, we could simultaneously explore other avenues like open science. How do we reconcile competitiveness with cooperativity [46]? In a world where resources are finite, is the emphasis on certain established lines of research leaving small and creative projects under starvation? Budgets reflect choices. Have we been asking certain questions simply because we are technically capable and to appease others? Many tools that until very recently were a luxury, have become a necessity *per se*. Is the *Homo sapiens* involving into *Homo habilis*? Concerning interdisciplinary science, are we literate, or at least interested, in the problems of other research areas? What are the implications of decision making experiments on medicine or law [47]? True multidisciplinary approaches have been reasonably successful. However, integration of philosophical, sociological, ethical and historical considerations is still lacking and seems daunting or of little value to many scientists. Possibilities for progress are far from being exhausted. How many interfaces are we ready to accept [48]? Are we willing to apply the scientific method to science itself?

What to do next? The above questions are not meant to be rhetorical or pop-philosophy entertainments. They try to reflect the imbalance between how successful we are in terms of what we can do versus how little we actually know. In my opinion, many of these questions are not asked because they end up being consequential. The reality that neuroscience paints appears to be in serious conflict with the actual beliefs of the very same neuroscientists who spearhead it. And that incoherency is extensive to other areas of science and society. I believe we should be educated to be critical, rather than trained to be complacent. I also believe we can become creative individuals, beyond mere productive human resources [49]. In the face of the present situation, young researchers need the courage to freely and fearlessly explore the very many exciting paths neuroscience has to offer. As we step into the unknown [50], let us not accept what is unproven, nor deny what is yet to be disproven.

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REFERENCES

1. A. Gomez-Marin, G. J. Stephens, and M. Louis, *Nature Comm.* **2**,441 (2011).
2. H. C. Berg, and D. A. Brown, *Nature* **239**, 500–504 (1972).
3. J. T. Pierce-Shimomura, T. M. Morse, and S. R. Lockery, *J. Neurosci.* **19**, 9557–9569 (1999).
4. A. G. Khan, M. Sarangi, and U. S. Bhalla, *Nature Comm.* **3**,703 (2012)
5. J. Porter, *et al.*, *Nature Neurosci.* **10**, 27–29 (2007).
6. A. Gomez-Marin, B. J. Duistermars, M. A. Frye, and M. Louis, *Front. Cell. Neurosci.* **4**,6 (2010).
7. M. Louis, *et al.*, *Nature Neurosci.* **11**, 187–199 (2008).
8. A. Gomez-Marin, and M. Louis, *PLoS One* **7**(8), e41642 (2012).
9. A. Gomez-Marin, and M. Louis, *Curr. Opin. Neurobiol.* **22**(2), 208–15 (2012).
10. M. Busto, B. Iyengar, and A. R. Campos, *J. Neurosci.* **19**, 3337–3344 (1999).
11. L. Luo, *et al.*, *J. Neurosci.* **30**, 4261–4272 (2010).
12. D. J. Hoare, C. R. McCrohan, and M. Cobb, *J. Neurosci.* **28**, 9710–9722 (2008).
13. L. Tian, *et al.*, *Nature Methods* **6**, 875–881 (2009).
14. J. D. Seelig, *et al.*, *Nature Methods* **7**, 535–540 (2010).
15. M. B. Ahrens, *et al.*, *Nature* **485**, 471–477 (2012).
16. J. Y. Lin, M. Z. Lin, P. Steinbach, and R. Y. Tsien, *Biophys. J.* **96**, 1803–1814 (2009).
17. A. M. Leifer, *et al.*, *Nature Methods* **8**, 147–152 (2011).
18. K. Koch, *The quest for consciousness: a neurobiological approach*, Roberts & Co, Denver, 2004.
19. S. Harris, *Free Will*, Random House, 2012.
20. B. Brembs, *Proc. Royal Soc. B: Biol. Sci.*, **278**(1707), 930–939 (2010).
21. B. Gerber, *EMBO Rep.* **13**, 17–19 (2012).
22. A. Damasio, *Self Comes to Mind*, Ediciones Destino, 2010.
23. R. D. V. Glasgow, *Split Down the Sides: on the subject of laugher*, University Press of America, 1997.
24. M. Heidelberger, *Nature from within*, University of Pittsburgh Press, 2004.
25. A. J. Duggins, *Biosystems* **102**, 124–33 (2010).
26. G. L. G. Miklos, *J. Neurobiol.* **24**(6), 842–890 (1993).
27. D. W. Franklin, and D. M. Wolpert, *Neuron* **72**, 425 (2011)
28. F. Rieke, *et al.*, *Spikes: exploring the neural code*, MIT Press, Cambridge, Mass, 1999.
29. A. Maye, C. Hsieh, G. Sugihara, and B. Brembs, *PLoS One* **5**, e443 (2007).
30. G. J. Stephens, M. B. de Mesquita, W. S. Ryu, and W. Bialek, *PNAS* **108**(18), 7286–7289 (2011).
31. R. M. Costa, *Curr. Opin. Neurobiol.* **21**(4), 579–86 (2011).
32. R. Descartes, *Discours de la méthode*, Tecnos, 2008.
33. V. Braitenberg, *Vehicles: Experiments in Synthetic Psychology*, Cambridge, MA, MIT Press, 1984.
34. R. Penrose, *The Emperor's New Mind*, Oxford University Press, 1999.
35. R. Sheldrake, *The Science Delusion: Freeing the Spirit of Enquiry*, Hodder and Stoughton, 2012.
36. E. Schrodinger, *What is life?*, Tusquets, 2001.
37. J. Monod, *Chance and Necessity*, Tusquets, 2000.
38. J. D. Watson, *DNA: The secret of life*, Alfred A. Knopf, Random House, 2004.
39. Y. Lazebnik, *Biochemistry (Moscow)* **69**(12), 1403–1406 (2004).
40. A. Borst, and F. E. Theunissen, *Nat. Neurosci.* **2**, 947–957 (1999).
41. D. C. Knill, and A. Pouget, *Trends in Neurosci.* **27**, 12 (2004).
42. D. R. Chialvo, *Nature Phys.* **6**, 744–750 (2010).
43. W. Bialek, *Biophysics: Searching for Principles*, Princeton University Press, 2012.
44. P. A. Lawrence, *PLoS Biol.* **7**(9), e1000197 (2009).
45. G. Hardin, *Growth: Real and Spurious. Living Within Limits*, Oxford University Press, 1995.
46. G. Hardin, *Science, New Series* **162**(3859), 1243–1248 (1968).
47. D. M. Eagleman, *Houston Lawyer* **16**(6), 36–40 (2008).
48. E. A. Abbott, *Flatland: A Romance of Many Dimensions*, Dover Publications, 1992.
49. D. H. Pink, *Drive: The Surprising Truth About What Motivates Us*, Canongate Books, 2011.
50. J. Campbell, *The Hero with a Thousand Faces*, New World Library, California, 2008.