C

Computational Modeling of Olfactory Behavior

Christiane Linster[1] and Thomas A. Cleland[2]
[1]Computational Physiology Lab, Department of Neurobiology and Behavior, Cornell University, Ithaca, NY, USA
[2]Computational Physiology Lab, Department of Psychology, Cornell University, Ithaca, NY, USA

Definition

Computational modeling is an essential tool for developing an understanding of how nervous systems compute. This is particularly so for questions that span levels of analysis, attempting to integrate cellular, neuromodulatory, and electrophysiological data with behavioral performance. In neuroscience, computational techniques are used to study the mechanisms underlying neuronal or network responses to simple and complex inputs, analyze interactions among the parameters governing the properties of a neuron or network, and determine the coordinated mechanisms that underlie experimentally observed rich phenomena such as coherent oscillations or synaptic plasticity. In particular, computational modeling has been successful in associating neural activity with behavioral function, proposing neurophysiological mechanisms for observed behavioral capabilities, and generating novel, testable hypotheses. In our lab, computational models of behavioral phenomena have enabled us to elucidate relationships among odorant physical properties, top-down neuromodulatory signals, olfactory neural network operations, and odor perception. We here briefly review this approach and highlight some examples from the last ten years.

Detailed Description

Our standard approach to modeling olfactory behavior is as follows: (1) determine via behavioral pharmacology or similar experiments which olfactory brain areas are likely to underlie a certain aspect of olfactory perception; (2) create a computational simulation of those brain areas, incorporating as much constraining experimental detail as possible given the level of modeling chosen; (3) use the model to simulate specific relationships between neural activity patterns and perception, generating testable hypotheses; and (4) based on these hypotheses, perturb both experimental and computational variables via lesions, training parameters, pharmacology, and other experimental tools. The outcome of these studies then serves to inform the computational models and help determine the direction of future study.

One critical aspect of this process is the selection of the level of detail at which to build the model. Our modeling is nearly all based on

D. Jaeger, R. Jung (eds.), *Encyclopedia of Computational Neuroscience*,
https://doi.org/10.1007/978-1-4614-7320-6_607-2

specific neural systems – as opposed to generic neural networks – but the level of detail implemented must be appropriate given the available experimental data in order for the model to contribute meaningfully to this research approach. More abstract models of particular networks, made with relatively reduced, single-compartment neurons, are appropriate when the data include general information about neurons being excitatory or inhibitory, reasonable estimates of synaptic connectivity patterns, and neuromodulator effects that are thought to excite, inhibit, and/or affect the excitability of particular cell types. Building simpler models with fewer free parameters enables a relatively efficient exploration of what such a network can do, and how the different effects of neuromodulators, for example, could combine to produce a functional outcome that corresponds to behavioral data. Following up on hypotheses generated by such models can increase the efficiency of experimental design, ultimately producing data sufficient to build the richer and more complex biophysical models.

Biophysical models require considerably more experimental data in order to be useful. They define physical membrane properties such as surface area, capacitance, and cell morphology, model many individual mechanisms such as sodium channels, calcium diffusion, and NMDA receptors, deploy these mechanisms into or with respect to the cell membrane, and often are morphologically multicompartmental. Oligocompartmental model neurons, in particular, are built using perhaps 2–20 compartments that may serve to accurately model spike propagation times, segregate electrotonically distant parts of the neuron, construct cells with heterogeneous channel distributions, and/or implement other phenomena in which spatial heterogeneity matters. (Neuron models with hundreds of compartments, in contrast, usually are constructed to replicate the arbor of a specific neuron measured from imaging data.) If there are constraining data for enough of these parameters, then such models are singularly powerful, as they are able to implement underappreciated computational elements like shunt inhibition, intrinsic resonance properties, and the partial isolation of spines, and at their best they can predict the network-level consequences of, for example, localized effects on ion channel properties. In the absence of sufficient data, however, such models lose most of their predictive value, as they simply contain too many free parameters which, if unconstrained, can enable meaningless fits to many datasets; simpler models should be used in such situations. Irrespective of the level of complexity, however, useful models usually do not simply replicate established data but employ their capacity to quantify and juxtapose diverse datasets in order to explain what is known and explore what that might imply. Models can range from being quite tightly based on cellular data (e.g., Li and Cleland 2013, 2017) to being more speculative (e.g., Linster and Cleland 2010), but in either case the task is to understand how best to ask the next question. While models that stand the test of time are laudable, models that are subsequently superseded by new data have served their scientific purpose well.

Over the past quarter century, we have developed computational models of many behavior-related processes within olfaction, including the cholinergic, noradrenergic, and dopaminergic modulation of bulbar circuitry (Linster and Gervais 1996; Hasselmo et al. 1997; Linster and Hasselmo 1997; Linster and Cleland 2002; Linster et al. 2003; Mandairon et al. 2006a; Escanilla et al. 2009; Linster et al. 2011; Devore and Linster 2012; Devore et al. 2012; de Almeida et al. 2013; Li and Cleland 2013; Devore et al. 2014; de Almeida et al. 2015; Li et al. 2015; de Almeida et al. 2016), perceptual learning (Mandairon et al. 2006b), mixture processing in the olfactory bulb (Linster and Cleland 2004), the bulbar mechanisms regulating differentiation among similar odors (Cleland and Sethupathy 2006; Cleland et al. 2007; Cleland et al. 2012), the role of spike synchronization in antennal lobe odor processing (Linster et al. 1994; Linster and Cleland 2001) and synaptic plasticity in olfactory bulb and cortex (Linster et al. 2007; Linster et al. 2009; Linster and Cleland 2010; Mandairon et al. 2014), the dynamical mechanisms underlying

lateral communication and synchronization across the bulbar circuit (David et al. 2008, McIntyre and Cleland 2016; Li and Cleland 2017), and the multiple concerted processes required to enable concentration invariance in odor perception (Cleland and Linster 1999; Cleland et al. 2007; Cleland et al. 2012). In each case, a critical factor affecting model validity has been the comparison between model output and behavioral results. How does one determine whether and how the values of model output variables correspond to measured indices of behavior? While this is always ultimately an experimental question, we have determined several behavioral indices that can be reliably predicted by specific output metrics from our computational models, including perceptual similarity, discrimination performance, learning rate, memory capacity, and memory persistence. For example, we first demonstrated that the pairwise overlap in neuronal activation patterns across the olfactory bulb input layer could predict pairwise perceptual similarity (Linster et al. 2001; Cleland et al. 2002). To the extent that this result is generalizable as a basic principle of olfactory coding, one then can, in subsequent studies, compare changes in pairwise overlap within the computational model to behavioral changes in perceptual discrimination. This in turn enables, for example, the effects of neuromodulators on olfactory discrimination to be modeled and tested against behavioral data (e.g., Mandairon et al. 2006a). Importantly, while this principle of pattern overlap among glomeruli has been largely supported experimentally, its basis is inductive and it cannot be reliably extrapolated; e.g., it may not extend reliably to spatial patterns among mitral cells, or within piriform cortex. Like theoretical models in general, these models serve to organize our understanding of complex data sets until a superior theory can be constructed.

We here describe three specific examples of the modeling of olfactory behavior that provided useful insights into the underlying neural mechanisms. First, an abstract model of spike timing and oscillations in the honeybee antennal lobe explained how neuronal synchronization patterns could underlie seemingly paradoxical behavioral generalization effects observed across different odor concentrations (Linster and Cleland 2001; Cleland and Linster 2002; Linster and Cleland 2010). Second, a large-scale, reduced model of olfactory bulb outlined a feedback normalization network enabling concentration invariance in bulbar output, consistent with behavioral performance (Cleland et al. 2007). Third, a moderately detailed computational model of cholinergic modulation in the olfactory bulb glomerular layer predicted coordinated network-level and behavioral outcomes from the properties and localization of nicotinic cholinergic receptors in the olfactory bulb (Mandairon et al. 2006a; de Almeida et al. 2013; Devore et al. 2014; de Almeida et al. 2016.

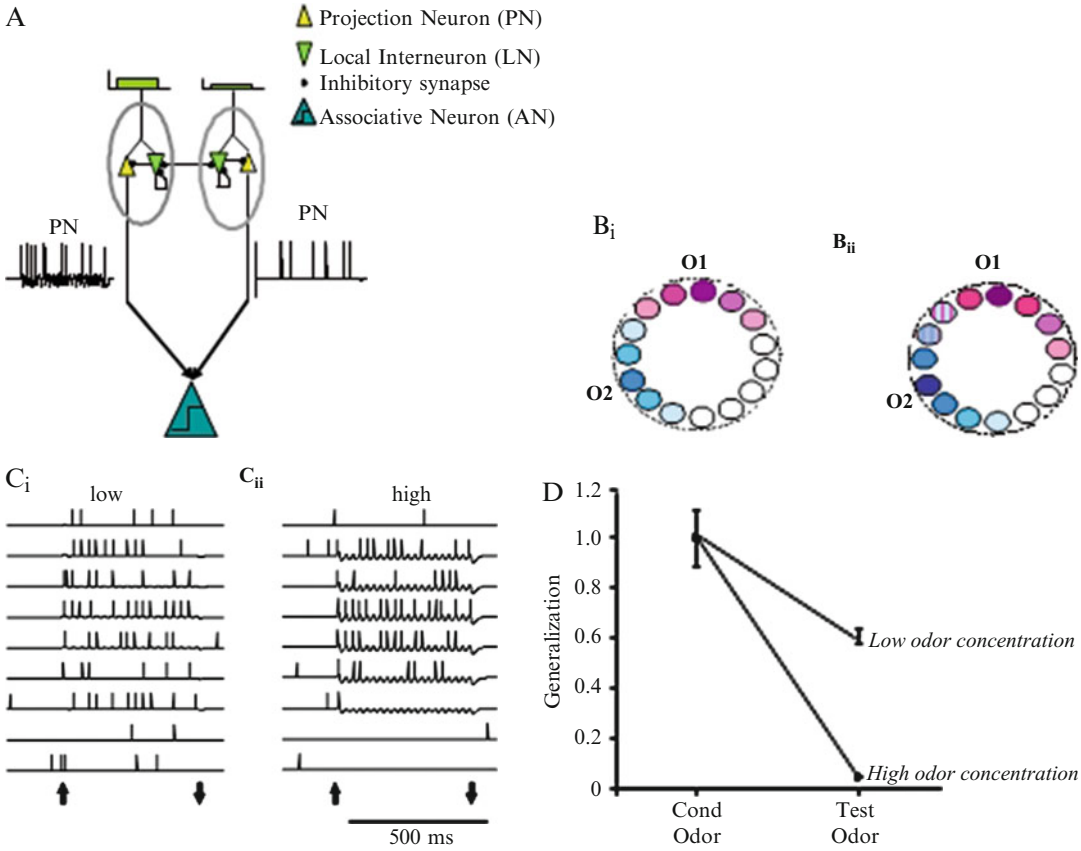
Example 1: Odor Concentration and Spike Timing in the Insect Antennal Lobe

Honeybee olfaction is an important model system for olfactory learning due to its well-developed and efficient behavioral conditioning paradigms and the relatively well-understood neural circuits involved in odor learning. The behavioral relevance of spike timing regulation in olfaction was first demonstrated in the honeybee antennal lobe, in which it was demonstrated that stimulus-evoked synchronous spiking was necessary for fine odor discrimination. Specifically, in combined electrophysiological and behavioral experiments, when fine-scale spike synchrony was disrupted, bees' odor discrimination performance was impaired, even though the overall profile of evoked activity in antennal lobe neurons remained intact (Stopfer et al. 1997; Stopfer et al. 2003). Using the same behavioral paradigm, it subsequently was demonstrated that honeybees discriminate odorants better when they are presented at high concentrations than when they are presented at lower concentrations (Bhagavan and Smith 1997). Neurophysiologically, this result was counterintuitive because calcium imaging studies have shown that higher concentration odor stimuli activate correspondingly larger and more overlapping areas of the antennal lobe (Strauch et al. 2012), which, given that overlap predicts perceptual similarity, should result in

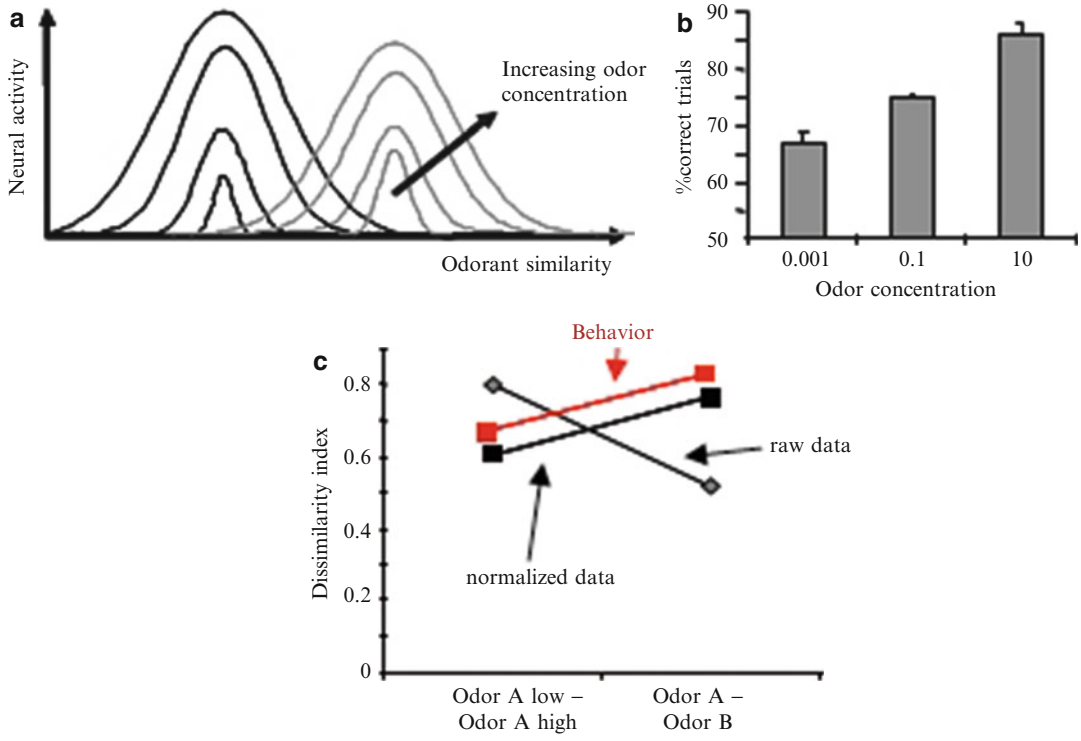
poorer discrimination. Computational modeling resolved this behavioral conundrum by combining the findings of these two lines of research (Linster and Cleland 2001; Cleland and Linster 2002). The model exhibited oscillations and spike synchronization patterns similar to those recorded in the antennal lobe and demonstrated that while higher-intensity odor inputs would evoke broader neural activity overall, an increasingly narrow subpopulation of neurons within this broad ensemble would be increasingly strongly synchronized. Synchrony-sensitive follower neurons and plasticity processes responding selectively to these highly synchronous inputs would therefore interpret higher-concentration inputs as more discriminable from one another, matching behavioral observations, while blocking these synchronization processes would impair fine odor discrimination. In contrast, lower-concentration inputs would evoke weaker synchrony among antennal lobe projection neurons and generate less activity or plasticity in follower cells (Fig. 1). This work illustrated how computational modeling can fuse separate datasets derived from a common system to explain seemingly unrelated results, constructing a common theoretical basis upon which subsequent experiments can be based. Since this time, the study of spike synchronization processes within olfactory coding research has grown substantially, particularly with the elaboration of timing-dependent synaptic plasticity algorithms in the brain (Song et al. 2000; Gao and Strowbridge 2009; Linster and Cleland 2010).

Example 2: The Problem of Concentration Invariance in the Olfactory Bulb

Odorants elicit widely distributed patterns of activity across the olfactory bulb input layer, as evidenced by 2-deoxyglucose activity mapping (Johnson and Leon 2000), intrinsic imaging (Meister and Bonhoeffer 2001), and other imaging techniques. These activation patterns are substantially altered when odor concentration is changed (Johnson et al. 1999; Johnson and Leon 2000; Meister and Bonhoeffer 2001), to the extent that the pattern evoked by a given odor may more closely resemble that of a different odor than that of itself when presented at a different concentration (Cleland et al. 2007). Despite this fact, animals can identify a given odor over a reasonable concentration range, and – critically – neural response patterns at the output of the olfactory bulb are less affected by odor concentration than are those measured at the input. Interestingly, simple normalization (z-scoring) of these odor-evoked patterns rendered them reasonably consistent across concentrations (Johnson et al. 1999; Johnson and Leon 2000), and behavioral tests measuring the pairwise perceptual similarities of odorants showed that perception was better predicted by normalized activity patterns than by nonnormalized activity (Cleland et al. 2007) (Fig. 2). These results, together with physiological demonstrations that mitral cell spike rates do not monotonically increase with odor concentration (Harrison and Scott 1986; Wellis et al. 1989; Meredith 1986), suggested that these odor-specific patterns are actively normalized within olfactory bulb circuitry. Computational modeling based on these data, and on contemporary understandings of cellular properties in the olfactory bulb, demonstrated how these neural circuits in the olfactory bulb glomerular layer could perform such a normalization function. Specifically, a laterally interconnected network of interneurons, then believed to be excitatory, synapsing onto local inhibitory interneurons and with a broad distribution of lateral projection distances estimated from anatomical data (Aungst et al. 2003), was shown capable of performing feedback normalization uniformly across the bulb (Cleland et al. 2007). These simulations showed that a partially localized network of microcircuits could underlie a nonlocalized, uniform effect, utilizing this small-world effect to normalize mitral cell odor responses in order to render them more concentration-invariant. In this example, behavioral experiments were necessary to validate the basis for the computational model by demonstrating that global normalization correctly predicted perceptual similarities. Interestingly, in subsequent experimental studies, the role of these



Computational Modeling of Olfactory Behavior, Fig. 1 Synchronization and odor perception in the honeybee antennal lobe. (**a**) Network diagram of honeybee antennal lobe model. The network was created based on known neuron types and was capable of generating odor-evoked, GABAergic neuron-dependent field potential oscillations that shaped spike timing as described experimentally. Briefly, input from olfactory sensory neurons (SNs) directly activates projection neurons (PNs) as well as inhibitory local interneurons (LNs). Local interneurons are reciprocally connected with each other in a feedback network which generates synchronous oscillations when activated. Local interneurons also inhibit projection neurons and are capable of synchronizing projection neuron spikes with respect to these network oscillations. Because local interneurons in the model have higher activation thresholds than projection neurons, highly activated glomeruli oscillate more strongly and the corresponding projection neurons are most strongly synchronized. The associative neuron (AN), corresponding to the reward-activated neuron VUMmx1 in honeybees, is sensitive to synchronized spike inputs. (**b**) In the model, increasing odor concentration at the input of the antennal lobe generates more widespread activation patterns and hence increased overlap among odor representations (Bi designates a lower concentration odorant, Bii a higher concentration odorant). Each circle represents a glomerulus receiving input from sensory neurons expressing a shared olfactory receptor; darker colors symbolize stronger activation and striped glomeruli indicate glomeruli substantially activated by both inputs. Glomeruli are mapped onto a hypothetical one-dimensional circular axis of receptive field similarity (Cleland and Linster 2002). O1 and O2 denote the centers of the glomerular patterns activated by two different odors. (**c**) Increased odor concentration also generates stronger oscillations in activated glomeruli, resulting in greater synchrony among a narrower population of the most strongly activated projection neurons. (**d**) Increased synchrony leads to reduced generalization between two odors presented at higher concentrations than when presented at lower concentrations, despite their larger overlap at the input to the antennal lobe. Odor conditioning was simulated by presenting a conditioning odor stimulus to the model at a low (25% of maximum activation) or high (100% of maximum activation) intensity and training the network on the odor. Subsequently, the network was presented with a novel odor and the degree of overlap between the representations of the conditioned and novel odors was calculated (generalization). The graph shows the degree of generalization to the novel test odor after conditioning at low and high stimulus intensities. (Figures adapted from Cleland and Linster (2002))



Computational Modeling of Olfactory Behavior, Fig. 2 Normalization in the olfactory bulb glomerular layer. (**a**) Schematic depiction of odor representations in the olfactory bulb glomerular layer. Odorants are ordered along a hypothetical axis of similarity onto which individual glomeruli can be mapped. Note that this is purely for representational purposes and that such orderly mapping does not exist in the system. Glomerular activation becomes stronger and spreads by activating additional glomeruli as odor intensity increases; consequently, the overlap between two odor representations increases. (**b**) Despite the increase in overlap between odorants at higher concentrations, rats and mice can differentiate odorants better as concentration increases. The graph shows the percent correct trials in a forced choice go/no-go task in rats as a function of odor concentration (Wei et al. 2006). (**c**) In certain cases, the raw and normalized activation patterns evoked by a given odorant at different concentrations are more different from one another than they are to the representation of an entirely different odorant. The graph depicts (*black lines*) indices of dissimilarity between glomerular activation patterns, calculated from raw or normalized 2-deoxyglucose uptake data, computed between a single odor (**a**) presented at two concentrations and between that odor and a different odor (**b**), both presented at the same concentration (Cleland et al. 2007). For comparison, the graph also depicts (*red line*) the corresponding behavioral results (i.e., degree of perceptual dissimilarity) in response to the same odor pairs. The normalized activation patterns predict behavioral perception, whereas the raw data do not

laterally projecting interneurons in broadly inhibiting mitral cells across the olfactory bulb was confirmed (Banerjee et al. 2015), even though the interneurons themselves since have been shown to be GABAergic and dopaminergic, rather than glutamatergic as was previously believed (Kiyokage et al. 2010). That is, the 2007 model proved correct at Marr's (1982) computational level (normalization at this level of the olfactory bulb network was required in order to explain experimental results) but not at the implementation level (the mechanism by which this normalization is achieved was incorrect in that model). This provides an excellent example for how a model can serve its purpose, being correct at a certain level and enabling the coordinated

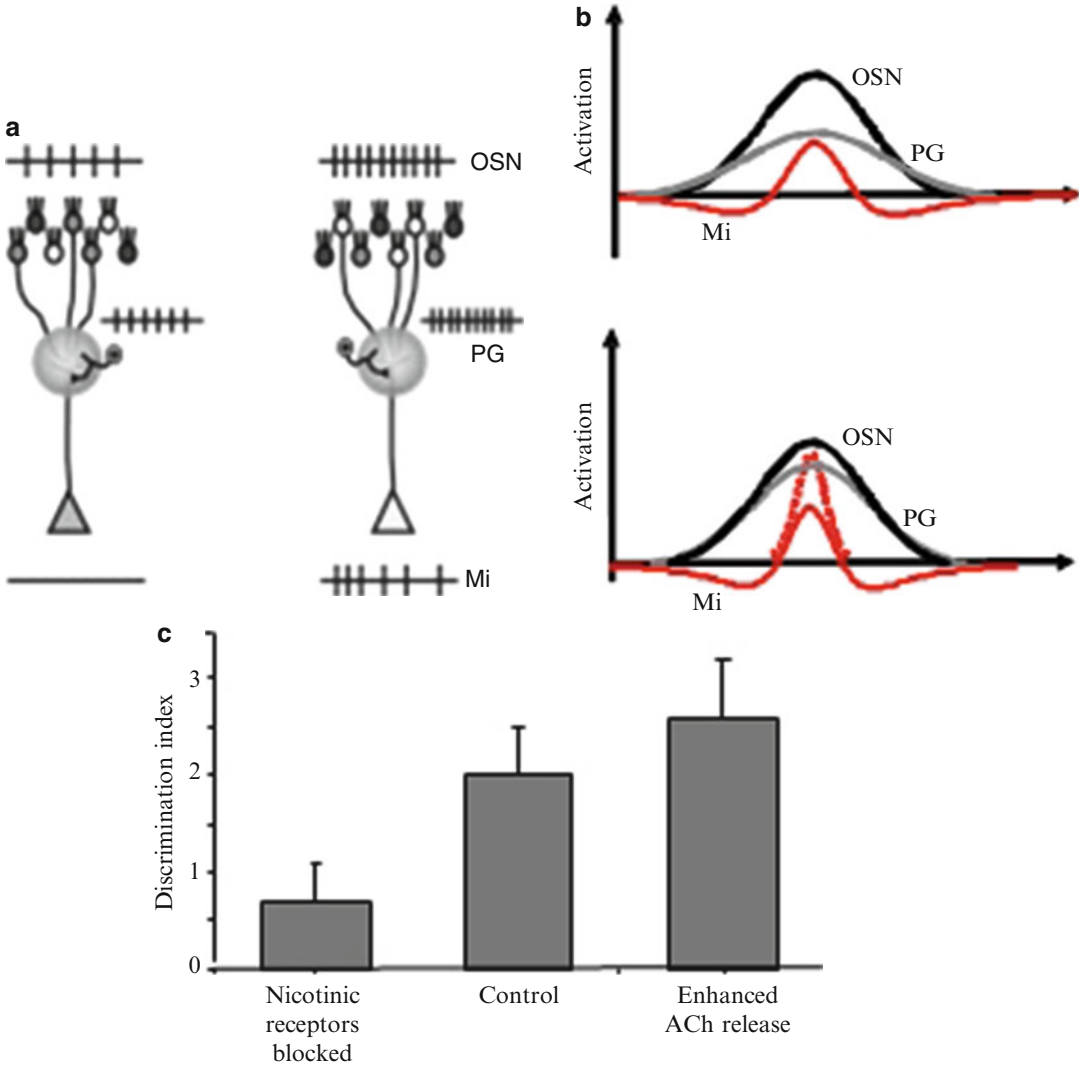
interpretation of diverse datasets, while also becoming outdated by experimental progress and requiring update or replacement. It is also important to emphasize that computational operations in neural circuits are necessarily embedded in broader networks that can enhance, impair, or prevent their function. Concentration tolerance in olfaction, for example, is not mediated solely by this single circuit; rather, its operation depends on multiple prior circuit computations that establish important prerequisites for its success (Cleland et al. 2012).

Example 3: Effects of Nicotinic Receptor Activation on Odor Discrimination – Behavioral Experiments and Biophysical Modeling

The cellular effects of nicotinic cholinergic receptor activation in the olfactory bulb are relatively well understood (Castillo et al. 1999; Pressler et al. 2007). Nicotinic cholinergic activation opens cation currents both in mitral cells, exciting them and increasing their odor-evoked activation levels, and in GABAergic periglomerular cells, increasing their inhibition of mitral cell primary dendrites. Hence, nicotinic receptor activation simultaneously excites and (indirectly) inhibits mitral cells in the bulb – two effects that initially might appear to cancel one another out. However, computational modeling of these two neuron types embedded within their glomerular microcircuit showed that, rather than canceling each other out, these two effects complement one another (Linster and Gervais 1996; Linster and Hasselmo 1997; Linster and Cleland 2002). Specifically, while the increased inhibition on mitral cell primary dendrites sharpens mitral cell responses to odorants by suppressing weak responses, the concomitant excitation near the soma maintains or enhances the strength of response within this narrower receptive field. As a consequence, receptive fields are sharper but stronger (Mandairon et al. 2006a; de Almeida et al. 2013; Devore et al. 2014; de Almeida et al. 2016; Li and Cleland 2013). When comparing ensemble responses to multiple odorants in this model, the overlap in mitral cell activation patterns is reduced when nicotinic receptors are activated, separating the representations of highly similar odors and predicting that they would become easier to discriminate. We tested this prediction behaviorally and found that, indeed, the blockade of nicotinic cholinergic receptors in the olfactory bulb reduced rats' capacity to differentiate between perceptually similar odorants, whereas it did not affect the perception of chemically and perceptually dissimilar odor pairs. Moreover, enhancing cholinergic modulation during behavior improved rats' ability to differentiate between perceptually similar odorants (Mandairon et al. 2006a; Chaudhury et al. 2009) (Fig. 3). In this study, the known cellular effects of nicotinic receptor activation were sufficient to predict perceptual effects once constructed into an appropriate network model, suggesting that the computational model captured the essence of this neuromodulatory process. Subsequent behavioral and computational studies further suggested that this reduced overlap in bulbar representations enables more rapid cortical learning and that cortical and bulbar cholinergic modulatory responses act in concert to establish efficient and stable learning processes (de Almeida et al. 2013; de Almeida et al. 2015; de Almeida et al. 2016).

Conclusion

Computational modeling of the neurons and networks of the brain provide essential tools and frameworks for understanding the neural mechanisms underlying animal behavior. By juxtaposing diverse experimental results within appropriate theoretical frameworks, constructing functional scenarios, and assessing the likelihood and consequences of each, modeling facilitates the theoretical analysis of complex datasets and the construction of testable hypotheses, providing an essential link between physiology and behavior.



Computational Modeling of Olfactory Behavior, Fig. 3 Nicotinic cholinergic neuromodulation of odor discrimination in the olfactory bulb glomerular layer. (**a**) Schematic of a simplified glomerular microcircuit annotated with relative spike rates to indicate levels of activation. Olfactory bulb output neurons (mitral cells; Mi) and GABAergic interneurons (PG) receive direct afferent input from sensory neurons (OSNs). PG cells directly inhibit mitral cells and suppress their responses to weak inputs (*left panel*), whereas strongly activated mitral cells overcome this inhibition (*right panel*). Both PG and mitral cells express nicotinic cholinergic receptors and are further activated by cholinergic neuromodulation. (**b**) Effects of nicotinic receptor activation. Graphs depict the tuning curves of neuron types to a range of similar odorants; the abscissa depicts a hypothetical axis of odor similarity. *Top panel*, Activity profiles in the unmodulated state. PG inhibition inhibits the weakly excited edges of the OSN odor representation, sharpening the resulting mitral cell representation (Cleland and Sethupathy 2006; Cleland and Linster 2012). *Bottom panel*, Effects of nicotinic cholinergic neuromodulation. Nicotinic modulation increases PG cell activity, inhibiting mitral cells more strongly and thereby sharpening their tuning curves (solid red line). Concurrently, the nicotinic activation of mitral cells amplifies their responses to odor inputs (dotted red line). (**c**) Behavioral experiments demonstrate that animals' discrimination between similar odors is reduced when nicotinic receptors are blocked and increased when cholinergic inputs are potentiated. The ordinate depicts an index of discrimination averaged among pairs of similar odorants (Chaudhury et al. 2009)

References

Banerjee A, Marbach F, Anselmi F, Koh MS, Davis MB, Garcia da Silva P, Delevich K, Oyibo HK, Gupta P, Li B, Albeanu DF (2015) An interglomerular circuit gates glomerular output and implements gain control in the mouse olfactory bulb. Neuron 87:193–207

Bhagavan S, Smith BH (1997) Olfactory conditioning in the honey bee, Apis mellifera: effects of odor intensity. Physiol Behav 61:107–117

Castillo PE, Carleton A, Vincent JD, Lledo PM (1999) Multiple and opposing roles of cholinergic transmission in the main olfactory bulb. J Neurosci 19:9180–9191

Chaudhury D, Escanilla O, Linster C (2009) Bulbar acetylcholine enhances neural and perceptual odor discrimination. J Neurosci 29:52–60

Cleland TA, Linster C (1999) Concentration tuning mediated by spare receptor capacity in olfactory sensory neurons: a theoretical study. Neural Comput 11:1673–1690

Cleland TA, Linster C (2002) How synchronization properties among second-order sensory neurons can mediate stimulus salience. Behav Neurosci 116:212–221

Cleland TA, Sethupathy P (2006) Non-topographical contrast enhancement in the olfactory bulb. BMC Neurosci 7:7

Cleland TA, Morse A, Yue EL, Linster C (2002) Behavioral models of odor similarity. Behav Neurosci 116:222–231

Cleland TA, Johnson BA, Leon M, Linster C (2007) Relational representation in the olfactory system. Proc Natl Acad Sci U S A 104:1953–1958

Cleland TA, Chen SY, Hozer KW, Ukatu HN, Wong KJ, Zheng F (2012) Sequential mechanisms underlying concentration invariance in biological olfaction. Front Neuroeng 4:21

Cleland TA, Linster C (2012) On-center/inhibitory-surround decorrelation via intraglomerular inhibition in the olfactory bulb glomerular layer. Front Integr Neurosci 6:5. https://doi.org/10.3389/fnint.2012.00005

David F, Linster C, Cleland TA (2008) Lateral dendritic shunt inhibition can regularize mitral cell spike patterning. J Comput Neurosci 25:25–38

de Almeida L, Idiart M, Linster C (2013) A model of cholinergic modulation in olfactory bulb and piriform cortex. J Neurophysiol 109:1360–1377

de Almeida L, Reiner SJ, Ennis M, Linster C (2015) Computational modeling suggests distinct, location-specific function of norepinephrine in olfactory bulb and piriform cortex. Front Comput Neurosci 9:73

de Almeida L, Idiart M, Dean O, Devore S, Smith DM, Linster C (2016) Internal cholinergic regulation of learning and recall in a model of olfactory processing. Front Cell Neurosci 10:256

Devore S, Linster C (2012) Noradrenergic and cholinergic modulation of olfactory bulb sensory processing. Front Behav Neurosci 6:52

Devore S, Manella LC, Linster C (2012) Blocking muscarinic receptors in the olfactory bulb impairs performance on an olfactory short-term memory task. Front Behav Neurosci 6:59

Devore S, de Almeida L, Linster C (2014) Distinct roles of bulbar muscarinic and nicotinic receptors in olfactory discrimination learning. J Neurosci 34:11244–11260

Escanilla O, Yuhas C, Marzan D, Linster C (2009) Dopaminergic modulation of olfactory bulb processing affects odor discrimination learning in rats. Behav Neurosci 123:828–833

Gao Y, Strowbridge BW (2009) Long-term plasticity of excitatory inputs to granule cells in the rat olfactory bulb. Nat Neurosci 12:731–733

Harrison TA, Scott JW (1986) Olfactory bulb responses to odor stimulation: analysis of response pattern and intensity relationships. J Neurophysiol 56:1571–1589

Hasselmo ME, Linster C, Patil M, Ma D, Cekic M (1997) Noradrenergic suppression of synaptic transmission may influence cortical signal-to-noise ratio. J Neurophysiol 77:3326–3339

Johnson BA, Leon M (2000) Modular representations of odorants in the glomerular layer of the rat olfactory bulb and the effects of stimulus concentration. J Comp Neurol 422:496–509

Johnson BA, Woo CC, Hingco EE, Pham KL, Leon M (1999) Multidimensional chemotopic responses to n-aliphatic acid odorants in the rat olfactory bulb. J Comp Neurol 409:529–548

Kiyokage E, Pan YZ, Shao Z, Kobayashi K, Szabo G, Yanagawa Y, Obata K, Okano H, Toida K, Puche AC, Shipley MT (2010) Molecular identity of periglomerular and short axon cells. J Neurosci 30:1185–1196

Li G, Cleland TA (2013) A two-layer biophysical model of cholinergic neuromodulation in olfactory bulb. J Neurosci 33:3037–3058

Li G, Cleland TA (2017) A coupled-oscillator model of olfactory bulb gamma oscillations. PLoS Comput Biol 13:e1005760

Li G, Linster C, Cleland TA (2015) Functional differentiation of cholinergic and noradrenergic modulation in a biophysical model of olfactory bulb granule cells. J Neurophysiol 114:3177–3200

Linster C, Kerszberg M, Masson C (1994) How neurons may compute: the case of insect sexual pheromone discrimination. J Comput Neurosci 1(3):231–238

Linster C, Cleland TA (2001) How spike synchronization among olfactory neurons can contribute to sensory discrimination. J Comput Neurosci 10:187–193

Linster C, Cleland TA (2002) Cholinergic modulation of sensory representations in the olfactory bulb. Neural Netw 15:709–717

Linster C, Cleland TA (2004) Configurational and elemental odor mixture perception can arise from local inhibition. J Comput Neurosci 16:39–47

Linster C, Cleland TA (2010) Decorrelation of odor representations via spike timing-dependent plasticity. Front Comput Neurosci 4:157

Linster C, Gervais R (1996) Investigation of the role of interneurons and their modulation by centrifugal fibers in a neural model of the olfactory bulb. J Comput Neurosci 3:225–246

Linster C, Hasselmo M (1997) Modulation of inhibition in a model of olfactory bulb reduces overlap in the neural representation of olfactory stimuli. Behav Brain Res 84:117–127

Linster C, Johnson BA, Yue E, Morse A, Xu Z, Hingco EE, Choi Y, Choi M, Messiha A, Leon M (2001) Perceptual correlates of neural representations evoked by odorant enantiomers. J Neurosci 21:9837–9843

Linster C, Maloney M, Patil M, Hasselmo ME (2003) Enhanced cholinergic suppression of previously strengthened synapses enables the formation of self-organized representations in olfactory cortex. Neurobiol Learn Mem 80:302–314

Linster C, Henry L, Kadohisa M, Wilson DA (2007) Synaptic adaptation and odor-background segmentation. Neurobiol Learn Mem 87:352–360

Linster C, Menon AV, Singh CY, Wilson DA (2009) Odor-specific habituation arises from interaction of afferent synaptic adaptation and intrinsic synaptic potentiation in olfactory cortex. Learn Mem 16:452–459

Linster C, Nai Q, Ennis M (2011) Nonlinear effects of noradrenergic modulation of olfactory bulb function in adult rodents. J Neurophysiol 105:1432–1443

Mandairon N, Ferretti CJ, Stack CM, Rubin DB, Cleland TA, Linster C (2006a) Cholinergic modulation in the olfactory bulb influences spontaneous olfactory discrimination in adult rats. Eur J Neurosci 24:3234–3244

Mandairon N, Stack C, Kiselycznyk C, Linster C (2006b) Broad activation of the olfactory bulb produces long-lasting changes in odor perception. Proc Natl Acad Sci U S A 103:13543–13548

Mandairon N, Kermen F, Charpentier C, Sacquet J, Linster C, Didier A (2014) Context-driven activation of odor representations in the absence of olfactory stimuli in the olfactory bulb and piriform cortex. Front Behav Neurosci 8:138

Marr D (1982) Vision: a computational approach. Freeman & Co, San Francisco

McIntyre ABR, Cleland TA (2016) Biophysical constraints on lateral inhibition in the olfactory bulb. J Neurophysiol 115(6):2937–2949. https://doi.org/10.1152/jn.00671.2015

Meister M, Bonhoeffer T (2001) Tuning and topography in an odor map on the rat olfactory bulb. J Neurosci 21:1351–1360

Meredith M (1986) Patterned response to odor in mammalian olfactory bulb: the influence of intensity. J Neurophysiol 56:572–597

Pressler RT, Inoue T, Strowbridge BW (2007) Muscarinic receptor activation modulates granule cell excitability and potentiates inhibition onto mitral cells in the rat olfactory bulb. J Neurosci 27:10969–10981

Song S, Miller KD, Abbott LF (2000) Competitive Hebbian learning through spike-timing-dependent synaptic plasticity. Nat Neurosci 3:919–926

Stopfer M, Bhagavan S, Smith BH, Laurent G (1997) Impaired odour discrimination on desynchronization of odour-encoding neural assemblies. Nature 390:70–74

Stopfer M, Jayaraman V, Laurent G (2003) Intensity versus identity coding in an olfactory system. Neuron 39:991–1004

Strauch M, Ditzen M, Galizia CG (2012) Keeping their distance? Odor response patterns along the concentration range. Front Syst Neurosci 6:71

Wei CJ, Linster C, Cleland TA (2006) Dopamine D(2) receptor activation modulates perceived odor intensity. Behav Neurosci 120(2):393–400

Wellis DP, Scott JW, Harrison TA (1989) Discrimination among odorants by single neurons of the rat olfactory bulb. J Neurophysiol 61:1161–1177