Neural morphological development for brain modeling and neuromorphic learning

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Neural morphological development is a daunting problem in biology and interests physicians and computer scientists for its intriguing physics mechanisms and potential applications in neuromorphic architecture designs. Here we present an semi-analytical framework to formalize key biophysical processes underlying single neuron and neural cluster morphological development, such as the coupled reaction-diffusion of tubulin, calcium, and MAP-2 and the synaptic guidance by netrin-1. An efficient computational implementation of this framework, *Asuka*, is proposed to reproduce critical development steps, such as synapse growing, competing, branching, path finding, and connecting. The high-resolution, large-scale, and long-term neural morphological dynamics computed by this system is consistent with in-vivo and in-vitro experimental observations. Then, we have applied *Asuka* on the largest brain connectome of the fruit fly ($\sim 2.5 \times 10^4$ neurons) to model whole brain development in weeks. Furthermore, we have designed a technique to make *Asuka* couple with the training framework (e.g., PyTorch) of artificial neural networks (ANNs), regulating neural morphological development by learning tasks and training ANNs according to biophysical mechanisms. These works demonstrate our theory and *Asuka* as promising foundations towards the unified understanding of neural morphological development mechanisms and their applications in neuromorphic computation and learning.

Morphological development, a kind of biological development happening on organism morphology (e.g., size, geometry, and topology) during the life cycle, remains as one of the most daunting problems in biology [1]. Meanwhile, the development process, essentially a dynamic system, also interests physicians for the intriguing underlying mechanisms [2–8]. Among various types of morphological development, the one underlying neural cluster formation may be the most elusive one. It remains largely unknown how single neuron morphological development proceeds, interacts between neurons, and eventually accumulates to the changes of neural cluster morphology [9–11]. Studying this cross-scale morphological dynamics not only helps address the biological questions concerning neural cluster development but also benefits statistical physics and active matter physics in understanding the formation of ultra-complex systems [12–15]. Moreover, it may lay the foundation of reproducing advantageous neural morphological characteristics in neuromorphic architecture designs, promoting the progress of this emerging non-Von Neumann computation direction [16–21].

Over decades, the difficulties of studying neural morphological development have been met by researchers in different aspects [9–11]. The development involves a compound system of numerous coupled reaction-diffusion processes of ions and biomacromolecules, regulated by complex macroscopic phylogenesis mechanisms (e.g., DNA) but showing microscopic randomness [12]. The intricate transformation from biochemical reactions to physical deformation is costly to be recorded and technically infeasible to be manipulated in experiments. As another choice, physics and mathematics play pivotal roles in studying neural morphological development [12–15], just like in other developmental biology topics [2–8]. They not only offer concise explanations of experimental observations but also force hypotheses to be formulated precisely and verified rigorously [12, 15]. From neurulation [22, 23], cortical folding [24, 25], neurogenesis [26, 27], neural migration [28–32] and polarization [33, 34] to synapse growing (birth [14, 35, 36], differentiation [33, 37, 38], elongation [39–42], branching [42–44], and guidance [45–48]) and neural cluster formation [49–65], substantial progress has been accomplished in embedding neural morphological development in physics foundations. Of course, potential limitations coexist with achievements in previous studies. Perhaps the most threatening limitation is the dependence of abstract parameters in these phenomenological theories. Some abstract parameters may not be verifiable by experimental data, leading to contingent risks that theories are not physically valid [12, 15]. Moreover, the reductionism tendency, a tradition of classical mathematical biology, may be misleading in specific situations. Although over-claiming the effects of emergence phenomena is not safe, it is less rational to pre-assume mechanical rules for every biological element, which imposes too much complexity on neurons and contradicts the microscopic randomness [12, 15]. Furthermore, the role of neural activities in neural morphological development is analyzed in a black-or-white form, which deviates from reality [12, 15]. Two families of theories remain to compromise, where neural activities either surpass molecular processes to dominate the development of neural clusters (e.g., see models [49–51, 57–60]) or are neglected completely when molecular effects take charge of neural cluster formation (e.g., see models [55, 56, 61–65] and hypotheses [66]).

Motivated by the scientific value in biology and physics and the potential to inspire cutting-edge neuromorphic architecture designs, the present research concentrates on single neuron and neural cluster morphological development, an elusive compound and cross-scale process. We attempt to formalize neural morphological dynamics in a semi-analytical framework of real physical mechanisms, avoiding unverifiable parameters and phenomenological models, limiting pre-assumptions of mechanical rules, and balanc-

ing the effects of neural activities and molecular processes in different development stages. We release an open-source and multi-platform computational system, *Asuka*, for efficient reproduction of the neural morphological development process. Quantitative validation of *Asuka* is implemented based on different in-vivo and in-vitro experimental data, demonstrating *Asuka* as a reliable foundation for future explorations. These works enable us to compute the multi-week whole brain development in the largest yet brain connectome of the fruit fly [67], benefiting biology in understanding brain development. Furthermore, we directly apply *Asuka* on neuromorphic computation and learning, realizing the learning-task-regulated neural morphological development and the biophysics-based artificial neural network training.

Results

Neural morphological development of single neuron

Imagine that neurons have migrated to their destinations and become polarized after the early development of the brain. According to previous studies, neural morphological deformation will dominate the next development stages of these neurons. Synapses start to grow on somas and compete over chemical substance supplies. Such competition eventually leads to differentiation among synapses [68], where stronger synapses (referred to as axons) travel long distance to find their targets [69, 70] while weaker synapses (referred to as dendrites) branch into highly elaborate tree structures [71]. Although this process seems to be easy in description, its underlying mechanisms are rather complex [12, 15]. To characterize it, we need to formulate synapse birth, differentiation, elongation, branching, and guidance mathematically.

Let us begin with synapse birth, the starting point of synapse growth. The soma membranes of neurons are born to be asymmetrical rather than spherically symmetrical [34]. These asymmetrical geometries frequently imply non-uniform sub-membrane concentrations of diffusive morphogen (e.g., calcium) and, therefore, create wavelike membrane protrusions after non-homogeneous development processes [34]. Even for ideal soma membranes that are perfectly symmetrical, the growth controlled by diffusive morphogen is shown analytically to be unstable after specific transitions, generating membrane protrusions instead of enlarging circular border smoothly [35]. These wavelike membrane protrusions, called lamellipodia, condense into nascent synapses on soma membranes [34]. We build on previous works [36] to describe this birth mechanism applying a calcium-stimulated stochastic process, in accordance with the bell-shaped modulation of synapse birth by calcium [72]. We also distinguish between active and passive membranes based on [34–36] to define calcium diffusivity under different conditions. Please see the **Methods**.

Once nascent synapses occur on soma membranes, they compete over chemical substance supplies to grow. Rather than use the stochastic process governing synapse birth to simplify the subsequent synapse growth following previous works [36], we pursue an analytical and experimentally validated formulation of synapse growth. In real neurons, tubulin is produced in somas and diffuses or actively transported to growth cones, where it assembles into microtubules to elongate them [73]. Tubulin assembly at growth cones is modulated by micro-tubule associated protein-2 (MAP-2) [73, 74], whose modulation rate is determined by the phosphorylation state of MAP-2 [75–77]. Meanwhile, MAP-2 phosphorylation and de-phosphorylation are involved in synapse destabilization, switching synapse state between elongation and branching [76, 77]. Calcium plays a role in these processes by regulating the phosphorylation of MAP-2 through multiple biochemical pathways [74, 78–80]. These experimental findings inspire us to study synapse elongation and branching based on the coupled reaction-diffusion system of tubulin, calcium, and MAP-2. In the system, molecular dynamics (e.g., diffusion, membrane transport, and sub-membrane active transport) on the hour-scale is characterized by solving Laplace equations with the relaxation method. Chemical reactions are formalized according to the approaches in [40, 42]. Taking the positive feedback of synapse elongation on protein trafficking into considerations [81, 82], this system can also be used to characterize synapse differentiation. Similar to [37], we modulate the active transport of tubulin from somas to growth cones with synapse elongation rate. Taken together, synapse differentiation, elongation, and branching can be characterized uniformly by a group of biophysical mechanisms rather than separately, as assumed in previous studies (e.g., see [83]). Please see the **Methods** for details.

As synapses grow, chemotaxis plays a pivotal role in their guidance. Chemotaxis happens when growth cones detect and follow the specific gradients, guiding synapses to extracellular matrix or other neurons. In general, these gradients can be generated by of diffusive biomacromolecules (e.g., see the guidance of commissural axons to the spinal cord floor plate [84]) or by graded expression of guidance molecules in substrates (e.g., see retinal projection [85, 86]). The gradient of diffusive factors fluctuates according to diffusion, while the gradient of non-diffusive factors can be translated into local concentrations of ligand molecules in substrates. In both cases, growth cones evaluate gradients and travel in the increasing or decreasing direction of attractant or repellent factors [87].

References

[1] S. N. Salthe, Development and evolution: complexity and change in biology, Mit Press, 1993.

[2] A. C. Oates, N. Gorfinkiel, M. Gonzalez-Gaitan, C.-P. Heisenberg, Quantitative approaches in developmental biology, Nature Reviews Genetics 10 (8) (2009) 517–530.

[3] N. Bellomo, B. Carbonaro, Toward a mathematical theory of living systems focusing on developmental biology and evolution: A review and perspectives, Physics of Life Reviews 8 (1) (2011) 1–18.

[4] A. Kicheva, M. Cohen, J. Briscoe, Developmental pattern formation: insights from physics and biology, Science 338 (6104) (2012) 210–212.

[5] G. Forgacs, S. A. Newman, Biological physics of the developing embryo, Cambridge University Press, 2005.

[6] D. St Johnston, The renaissance of developmental biology, PLoS biology 13 (5) (2015) e1002149.

[7] J. Prost, F. Jülicher, J.-F. Joanny, Active gel physics, Nature physics 11 (2) (2015) 111–117.

[8] J. Lewis, From signals to patterns: space, time, and mathematics in developmental biology, Science 322 (5900) (2008) 399–403.

[9] H. J. Karten, Evolutionary developmental biology meets the brain: the origins of mammalian cortex, Proceedings of the National Academy of Sciences 94 (7) (1997) 2800–2804.

[10] F. H. Gage, Neurogenesis in the adult brain, Journal of neuroscience 22 (3) (2002) 612–613.

[11] P. Rakic, Evolution of the neocortex: a perspective from developmental biology, Nature Reviews Neuroscience 10 (10) (2009) 724–735.

[12] A. Van Ooyen, Using theoretical models to analyse neural development, Nature Reviews Neuroscience 12 (6) (2011) 311–326.

[13] H. D. Simpson, D. Mortimer, G. J. Goodhill, Theoretical models of neural circuit development, Current topics in developmental biology 87 (2009) 1–51.

[14] A. Van Ooyen, Modeling neural development, MIT Press, 2003.

[15] G. J. Goodhill, Theoretical models of neural development, Iscience 8 (2018) 183–199.

[16] C. Mead, Neuromorphic electronic systems, Proceedings of the IEEE 78 (10) (1990) 1629–1636.

[17] S. Furber, Large-scale neuromorphic computing systems, Journal of neural engineering 13 (5) (2016) 051001.

[18] D. Marković, A. Mizrahi, D. Querlioz, J. Grollier, Physics for neuromorphic computing, Nature Reviews Physics 2 (9) (2020) 499–510.

[19] J. Zhu, T. Zhang, Y. Yang, R. Huang, A comprehensive review on emerging artificial neuromorphic devices, Applied Physics Reviews 7 (1) (2020) 011312.

[20] M. Davies, Benchmarks for progress in neuromorphic computing, Nature Machine Intelligence 1 (9) (2019) 386–388.

[21] C. Mead, How we created neuromorphic engineering, Nature Electronics 3 (7) (2020) 434–435.

[22] J.-F. Colas, G. C. Schoenwolf, Towards a cellular and molecular understanding of neurulation, Developmental dynamics: an official publication of the American Association of Anatomists 221 (2) (2001) 117–145.

[23] X. Chen, G. W. Brodland, Multi-scale finite element modeling allows the mechanics of amphibian neurulation to be elucidated, Physical biology 5 (1) (2008) 015003.

[24] T. Tallinen, J. Y. Chung, F. Rousseau, N. Girard, J. Lefèvre, L. Mahadevan, On the growth and form of cortical convolutions, Nature Physics 12 (6) (2016) 588–593.

[25] P. Bayly, L. Taber, C. Kroenke, Mechanical forces in cerebral cortical folding: a review of measurements and models, Journal of the mechanical behavior of biomedical materials 29 (2014) 568–581.

[26] J. M. Gohlke, W. C. Griffith, E. M. Faustman, Computational models of neocortical neuronogenesis and programmed cell death in the developing mouse, monkey, and human, Cerebral Cortex 17 (10) (2007) 2433–2442.

[27] D. J. Cahalane, C. J. Charvet, B. L. Finlay, Modeling local and cross-species neuron number variations in the cerebral cortex as arising from a common mechanism, Proceedings of the National Academy of Sciences 111 (49) (2014) 17642–17647.

[28] J. R. Caffrey, B. D. Hughes, J. M. Britto, K. A. Landman, An in silico agent-based model demonstrates reelin function in directing lamination of neurons during cortical development, PloS one 9 (10) (2014) e110415.

[29] Y. Setty, C.-C. Chen, M. Secrier, N. Skoblov, D. Kalamatianos, S. Emmott, How neurons migrate: a dynamic in-silico model of neuronal migration in the developing cortex, BMC systems biology 5 (1) (2011) 1–13.

[30] D. F. Newgreen, S. Dufour, M. J. Howard, K. A. Landman, Simple rules for a "simple" nervous system? molecular and biomathematical approaches to enteric nervous system formation and malformation, Developmental biology 382 (1) (2013) 305–319.

[31] W. R. Holmes, L. Edelstein-Keshet, A comparison of computational models for eukaryotic cell shape and motility, PLoS computational biology 8 (12) (2012) e1002793.

[32] M. Nickaeen, I. L. Novak, S. Pulford, A. Rumack, J. Brandon, B. M. Slepchenko, A. Mogilner, A free-boundary model of a motile cell explains turning behavior, PLoS computational biology 13 (11) (2017) e1005862.

[33] M. Toriyama, Y. Sakumura, T. Shimada, S. Ishii, N. Inagaki, A diffusion-based neurite length-sensing mechanism involved in neuronal symmetry breaking, Molecular systems biology 6 (1) (2010) 394.

[34] H. Naoki, S. Ishii, Mathematical modeling of neuronal polarization during development, Progress in molecular biology and translational science 123 (2014) 127–141.

[35] H. Hentschel, A. Fine, Instabilities in cellular dendritic morphogenesis, Physical Review Letters 73 (26) (1994) 3592.

[36] H. Hentschel, A. Fine, Diffusion-regulated control of cellular dendritic morphogenesis, Proceedings of the Royal Society of London. Series B: Biological Sciences 263 (1366) (1996) 1–8.

[37] D. C. Samuels, H. Hentschel, A. Fine, The origin of neuronal polarization: a model of axon formation, Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences 351 (1344) (1996) 1147–1156.

[38] A. P. Barnes, F. Polleux, Establishment of axon-dendrite polarity in developing neurons, Annual review of neuroscience 32 (2009) 347–381.

[39] K. Franze, J. Guck, The biophysics of neuronal growth, Reports on Progress in Physics 73 (9) (2010) 094601.

[40] G. Kiddie, D. McLean, A. Van Ooyen, B. Graham, Biologically plausible models of neurite outgrowth, Progress in brain research 147 (2005) 67–80.

[41] B. P. Graham, K. Lauchlan, D. R. Mclean, Dynamics of outgrowth in a continuum model of neurite elongation, Journal of computational neuroscience 20 (1) (2006) 43–60.

[42] T. A. Hely, B. Graham, A. Van Ooyen, A computational model of dendrite elongation and branching based on map2 phosphorylation, Journal of theoretical biology 210 (3) (2001) 375–384.

[43] H. Cuntz, F. Forstner, A. Borst, M. Häusser, One rule to grow them all: a general theory of neuronal branching and its practical application, PLoS computational biology 6 (8) (2010) e1000877.

[44] J. J. Hjorth, J. van Pelt, H. D. Mansvelder, A. van Ooyen, Competitive dynamics during resource-driven neurite outgrowth, PLoS One 9 (2) (2014) e86741.

[45] E. M. Forbes, A. W. Thompson, J. Yuan, G. J. Goodhill, Calcium and camp levels interact to determine attraction versus repulsion in axon guidance, Neuron 74 (3) (2012) 490–503.

[46] D. Mortimer, J. Feldner, T. Vaughan, I. Vetter, Z. Pujic, W. J. Rosoff, K. Burrage, P. Dayan, L. J. Richards, G. J. Goodhill, A bayesian model predicts the response of axons to molecular gradients, Proceedings of the National Academy of Sciences 106 (25) (2009) 10296–10301.

[47] D. Mortimer, Z. Pujic, T. Vaughan, A. W. Thompson, J. Feldner, I. Vetter, G. J. Goodhill, Axon guidance by growth-rate modulation, Proceedings of the National Academy of Sciences 107 (11) (2010) 5202–5207.

[48] D. Mortimer, T. Fothergill, Z. Pujic, L. J. Richards, G. J. Goodhill, Growth cone chemotaxis, Trends in neurosciences 31 (2) (2008) 90–98.

[49] A. Van Ooyen, J. van Pelt, Activity-dependent outgrowth of neurons and overshoot phenomena in developing neural networks, Journal of Theoretical Biology 167 (1) (1994) 27–43.

[50] A. Van Ooyen, J. Van Pelt, M. Corner, Implications of activity dependent neurite outgrowth for neuronal morphology and network development, Journal of theoretical biology 172 (1) (1995) 63–82.

[51] C. Van Oss, A. Van Ooyen, Effects of inhibition on neural network development through activity-dependent neurite outgrowth, Journal of theoretical biology 185 (2) (1997) 263–280.

[52] M. Butz, A. Van Ooyen, F. Wörgötter, A model for cortical rewiring following deafferentation and focal stroke, Frontiers in computational neuroscience 3 (2009) 10.

[53] M. Helias, S. Rotter, M.-O. Gewaltig, M. Diesmann, Structural plasticity controlled by calcium based correlation detection, Frontiers in Computational Neuroscience 2 (2008) 7.

[54] H. F. Kwok, P. Jurica, A. Raffone, C. van Leeuwen, Robust emergence of small-world structure in networks of spiking neurons, Cognitive neurodynamics 1 (1) (2007) 39.

[55] F. Zubler, R. Douglas, A framework for modeling the growth and development of neurons and networks, Frontiers in computational neuroscience 3 (2009) 25.

[56] R. A. Koene, B. Tijms, P. Van Hees, F. Postma, A. De Ridder, G. J. Ramakers, J. Van Pelt, A. Van Ooyen, Netmorph: a framework for the stochastic generation of large scale neuronal networks with realistic neuron morphologies, Neuroinformatics 7 (3) (2009) 195–210.

[57] D. J. Willshaw, C. Von Der Malsburg, How patterned neural connections can be set up by self-organization, Proceedings of the Royal Society of London. Series B. Biological Sciences 194 (1117) (1976) 431–445.

[58] S. Song, L. F. Abbott, Cortical development and remapping through spike timing-dependent plasticity, Neuron 32 (2) (2001) 339–350.

[59] J. M. Young, W. J. Waleszczyk, C. Wang, M. B. Calford, B. Dreher, K. Obermayer, Cortical reorganization consistent with spike timing–but not correlation-dependent plasticity, Nature neuroscience 10 (7) (2007) 887–895.

[60] K. B. Godfrey, S. J. Eglen, N. V. Swindale, A multicomponent model of the developing retinocollicular pathway incorporating axonal and synaptic growth, PLoS computational biology 5 (12) (2009) e1000600.

[61] H. Honda, Topographic mapping in the retinotectal projection by means of complementary ligand and receptor gradients: a computer simulation study, Journal of theoretical biology 192 (2) (1998) 235–246.

[62] H. Honda, Competition between retinal ganglion axons for targets under the servomechanism model explains abnormal retinocollicular projection of eph receptor-overexpressing or ephrin-lacking mice, Journal of Neuroscience 23 (32) (2003) 10368–10377.

[63] M. Prestige, D. Willshaw, On a role for competition in the formation of patterned neural connexions, Proceedings of the Royal Society of London. Series B. Biological Sciences 190 (1098) (1975) 77–98.

[64] C. von der Malsburg, D. J. Willshaw, How to label nerve cells so that they can interconnect in an ordered fashion, Proceedings of the National Academy of Sciences 74 (11) (1977) 5176–5178.

[65] D. Willshaw, Analysis of mouse epha knockins and knockouts suggests that retinal axons programme target cells to form ordered retinotopic maps, Development 133 (14) (2006) 2705–2717.

[66] R. W. Sperry, Chemoaffinity in the orderly growth of nerve fiber patterns and connections, Proceedings of the National Academy of Sciences of the United States of America 50 (4) (1963) 703.

[67] C. S. Xu, M. Januszewski, Z. Lu, S.-y. Takemura, K. J. Hayworth, G. Huang, K. Shinomiya, J. Maitin-Shepard, D. Ackerman, S. Berg, et al., A connectome of the adult drosophila central brain, BioRxiv (2020).

[68] A. M. Craig, G. Banker, Neuronal polarity, Annual review of neuroscience 17 (1) (1994) 267–310.

[69] B. J. Dickson, Molecular mechanisms of axon guidance, Science 298 (5600) (2002) 1959–1964.

[70] A. Chédotal, L. J. Richards, Wiring the brain: the biology of neuronal guidance, Cold Spring Harbor perspectives in biology 2 (6) (2010) a001917.

[71] Y.-N. Jan, L. Y. Jan, Branching out: mechanisms of dendritic arborization, Nature Reviews Neuroscience 11 (5) (2010) 316–328.

[72] S. B. Kater, M. P. Mattson, C. Cohan, J. Connor, Calcium regulation of the neuronal growth cone, Trends in neurosciences 11 (7) (1988) 315–321.

[73] N. Kobayashi, P. Mundel, A role of microtubules during the formation of cell processes in neuronal and non-neuronal cells, Cell and tissue research 291 (2) (1998) 163–174.

[74] R. B. Maccioni, V. Cambiazo, Role of microtubule-associated proteins in the control of microtubule assembly, Physiological reviews 75 (4) (1995) 835–864.

[75] P. Friedrich, A. Aszodi, Map2: a sensitive cross-linker and adjustable spacer in dendritic architecture, FEBS letters 295 (1-3) (1991) 5–9.

[76] G. Audesirk, L. Cabell, M. Kern, Modulation of neurite branching by protein phosphorylation in cultured rat hippocampal neurons, Developmental Brain Research 102 (2) (1997) 247–260.

[77] H. Yamamoto, Y. Saitoh, K. Fukunaga, H. Nishimura, E. Miyamoto, Dephosphorylation of microtubule proteins by brain protein phosphatases 1 and 2a, and its effect on microtubule assembly, Journal of neurochemistry 50 (5) (1988) 1614–1623.

[78] K. P. Giese, N. B. Fedorov, R. K. Filipkowski, A. J. Silva, Autophosphorylation at thr286 of the α calcium-calmodulin kinase ii in ltp and learning, Science 279 (5352) (1998) 870–873.

[79] R. Vallee, Structure and phosphorylation of microtubule-associated protein 2 (map 2), Proceedings of the National Academy of Sciences 77 (6) (1980) 3206–3210.

[80] S. A. Lewis, I. E. Ivanov, G.-H. Lee, N. J. Cowan, Organization of microtubules in dendrites and axons is determined by a short hydrophobic zipper in microtubule-associated proteins map2 and tau, Nature 342 (6249) (1989) 498–505.

[81] S. S. Andersen, G.-q. Bi, Axon formation: a molecular model for the generation of neuronal polarity, Bioessays 22 (2) (2000) 172–179.

[82] N. Arimura, K. Kaibuchi, Neuronal polarity: from extracellular signals to intracellular mechanisms, Nature Reviews Neuroscience 8 (3) (2007) 194–205.

[83] J. van Pelt, H. B. Uylings, Natural variability in the geometry of dendritic branching patterns, in: Modeling in the Neurosciences, Routledge, 2019, pp. 79–108.

[84] M. Tessier-Lavigne, M. Placzek, A. G. Lumsden, J. Dodd, T. M. Jessell, Chemotropic guidance of developing axons in the mammalian central nervous system, Nature 336 (6201) (1988) 775–778.

[85] U. Drescher, C. Kremoser, C. Handwerker, J. Löschinger, M. Noda, F. Bonhoeffer, In vitro guidance of retinal ganglion cell axons by rags, a 25 kda tectal protein related to ligands for eph receptor tyrosine kinases, Cell 82 (3) (1995) 359–370.

[86] H.-J. Cheng, M. Nakamoto, A. D. Bergemann, J. G. Flanagan, Complementary gradients in expression and binding of elf-1 and mek4 in development of the topographic retinotectal projection map, Cell 82 (3) (1995) 371–381.

[87] G. J. Goodhill, Mathematical guidance for axons, Trends in neurosciences 21 (6) (1998) 226–231.

Method

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Y.T proposes the original idea, develops the formalism of neural morphological development, designs *Asuka* system in MATLAB and Python, conducts all experiments, and writes the manuscript. W.H.H collaborates with Y.T to carry out early works, create the dynamic coupling between *Asuka* and the training framework of artificial neural networks, and design learning tasks. Authors A.H.C and Y.H.X contributed equally in studying the axon guidance and neural plasticity mechanisms. H.D.H collaborates with Y.T to lay the mathematical foundation of neural morphological development. P.S and G.Q.L supervise the research project, organize the research idea, offer technical supports, and modify the manuscript.