Chapter 1

Introduction

Rod C. Scott and J. Matthew Mahoney

This book takes a view of the brain as a *complex adaptive system* and seeks to identify mechanisms underlying the clinical outcomes as well as the therapeutic opportunities for epilepsy using this framework.

Complex systems theory is a nebulous field whose overarching goal is to understand the dynamical behavior of systems consisting of many interconnected component parts. It has attracted widespread interest from many domains that study examples of such systems, including ecologists, sociologists, engineers, artificial intelligence researchers, condensed matter physicists, neuroscientists, and many others. The results of these collected, multi-disciplinary efforts have not been so much a comprehensive theory of Complex Systems (capital-C, capital-S), but rather a set of techniques, analogies, and attitudes toward problem solving that emphasize interactions and dynamics over individual components and their functions. The chapters are written in a complex adaptive systems frame and therefore it is useful to provide a provisional theoretical description of such systems. Following Holland [1], a generalizable description of complex adaptive systems is that they are collections of relatively simple *agents* that have the property that they can *aggregate*, so that collections of agents can form meta-agents (and meta-meta-agents etc.) with higher-order structure. These aggregates interact *nonlinearly*, so that the aggregate behavior of a collection of agents is qualitatively different from the behavior of the individual agents. The interactions among agents mediate *flows* of materials or information. Finally, the agents are typically *diverse* with distinct specialties that are optimized through adaptation to selective pressures in their environments.

To manifest these properties, complex adaptive systems have mechanisms that underpin the formation and function of the whole system. In full generality, these mechanisms may seem unnecessarily abstract or obscure for application to a specific system, like the neural circuits of the brain. Nevertheless, the abstraction is precisely what accounts for the cross-disciplinarity of complex systems theory, and the applicability of its approaches across biological length scales from subcellular structures to whole brains. The first mechanism is *tagging*, which allows diverse agents in the system to signal their identities to other agents thus enabling complex self-organization into aggregates. The second mechanism is the ability to generate *internal models* that approximate and anticipate the world external to the system, which enables adaptive behavior by the aggregate system.

From the above description, brains are clearly complex adaptive systems par excellence. There are several hierarchical layers of agents. A diversity of genes aggregates into gene networks that form a diversity of proteins that aggregate from a diversity of cells (e.g., neurons and glia) that aggregate and form a diversity of brain regions that aggregate and form the brain with a diversity of emergent phenomena. Indeed, individual cells themselves are complex adaptive systems, where biomolecules as agents interact through electrostatic fields generated by patterns of charges (tags) that facilitate aggregation into complexes and structures. These structures implicitly compute models of the world outside the cell and generate an appropriate transcriptional response. For example, the presence of a phosphorylated signaling molecule inside a cell carries information about the concentration of particular ligands outside the cell. This organization is approximately repeated at the level of neural networks. Neurons as agents use a variety of biochemical and electrical cues (tags) to form into circuits that mediate the flow of sensory information into motor output, memory etc., through massively parallel nonlinear dynamics. These dynamics implicitly compute internal models of the external world to generate adaptive behavioral responses.

https://doi.org/10.1017/9781108582285.001 Published online by Cambridge University Press

The brain is one of the guiding metaphors of complex systems science, so that other examples – economies, ecological systems, social networks, transportation networks – are often conceptualized as "brain-like" in one way or another within complex systems theory. However, these other systems repay the favor and invite tantalizing metaphors of their own. For example, the synchronous blinking of fireflies has long fascinated mathematical biologists [2]. In this system, nonlinear interactions among blinking fireflies causes a spontaneous synchronized blinking that spans a whole swarm. Intriguingly, a lone firefly does not even display periodic blinking, so the drive to synchronous blinking is fully mediated by the network of interactions. In the 1990s, as mathematical tools and computer simulations began to clarify these dynamics, the potential connection to synchronous brain activity, and specifically epilepsy, began to be seriously considered [3]. One of the major discoveries in complex systems theory over the last few decades was the "small-world" phenomenon in many real-world networks [4]. Small-world networks have the property that most nodes are not directly connected to each other, but nevertheless most pairs of nodes can be connected by short paths. In their seminal paper on small-world networks, Watts and Strogatz showed that the synchronizability of a network is highly sensitive to the structure of connections – the *topology* – of the network, where small-world networks synchronize more readily than other patterns of connections, and they speculated that this may underlie the synchronizability of physically distant pairs of neurons in the visual cortex. There has since been a wealth of research on small-world and other topological properties of many kinds of brain networks in health and disease (see, for example, Chapters 9 and 10). It is interesting from the "complex systems perspective" that the early luminaries in the mathematics of synchronization were inspired as much by brains as by firefly swarms.

The example of synchronizing fireflies highlights a dictum in complex systems coined by the physicist Philip Anderson in the title of a classic essay "More is Different" [5]. The essential point of that essay, beyond the particular physical examples given, is that aggregates of many things can have qualitatively distinct collective behavior from any of the parts (whole brains do not behave like big neurons). For the fireflies, a network of interacting, asynchronous fireflies becomes a wave of synchronous blinking over length scales many orders of magnitude larger than an individual firefly blinking. This *emergence* of new phenomena has achieved highly refined mathematical description in condensed matter physics, but has echoes across many disciplines, and forms an organizing metaphor in complex systems thinking [6–8].

But how can we put these ideas to work in understanding clinical phenomena and designing new treatments for epilepsy? Said more stridently, what is the added value of taking this abstract, complicated, and potentially sterile perspective? Or more sympathetically, how does complex systems theory help us understand clinical variability and design new interventions in the brain to produce desired outcomes?

An interesting observation among genetic epilepsies is that mutations in a single gene can result in vastly different phenotypes. Specific examples include variability in outcomes in tuberous sclerosis even within single families [9], and the wide clinical variability associated with sodium channel mutations [10]. Given that patients with identical mutations can have outcomes ranging from cognitively normal and medically tractable epilepsy to developmental delay, intellectual disability, and intractable epilepsy, within a complex systems framework it is clear that the individually variable adaptation of the whole brain system to the same genetic perturbation is a critical driver of outcomes. Understanding the nature of the adapted network that predicts good vs. poor outcomes will provide extremely important pathophysiological information that cannot be inferred from the mutation per se. The same ideas can be applied to acquired epilepsies. For example, the variability of outcomes following traumatic brain injury [11] is partly a function of the injury itself but also a function of network adaptation that is likely to be influenced by the nature of the individual pre-injury networks.

In terms of treatment, a few analogies help emphasize the perils of ignoring complexity and the promise of embracing it. The networks in which humans intervene most deliberately and totally are traffic networks. The purpose of any traffic network is to facilitate the efficient transfer of people and goods in space. All else being equal, we would expect that adding more roads to a network would necessarily add efficiency – there is more room for cars to drive, more possible paths from point A to point B. Alas, this is not so, as

https://doi.org/10.1017/9781108582285.001 Published online by Cambridge University Press

described in what is now known as Braess' "paradox." This classic argument shows that adding roads (under reasonable assumptions about driver behavior) can cause the overall traffic within the network to slow down. Conversely, there have been several real-world examples in which a temporary shutdown of major roads in cities has actually improved traffic flow [12]. The key point is that the overall traffic flow is a function of the whole network's topology. Thus, local heuristics, like "adding an expressway between two popular points will improve traffic flow," can have highly counterintuitive, negative consequences. A "toy" example of this effect can be seen in the ancient Hindu game Snakes and Ladders, where the addition of some ladders can lengthen the expected game length, while the strategic addition of snakes can actually shorten the expected length [13].

Now let us operationalize this analogy for epilepsy. Instead of cars on roads, the brain transports information along connectomes. Among the major therapeutic decisions in epilepsy is the strategic resection of some brain tissue or, more recently, the implantation of a neurostimulator device. However, if we take the traffic network analogies seriously, we must accept that local heuristics can lead us badly awry. If the emergent dynamics of the brain are determined by the whole connectome, then we must treat the whole connectome. Like adding or shutting down roads in a city center, adding or removing electrical pathways in the brain can have potent positive effects on whole brain function, but only if the rest of the brain is considered. Advances in imaging, machine learning, and dynamical modeling are facilitating such a holistic view, where virtual surgeries can be used to predict outcomes based on patient-specific network data (see Chapter 4).

Considering drug interventions, we can again consult far flung metaphors. The purpose of a drug in epilepsy is to suppress seizures. Medications do not directly influence the emergent phenomenon of seizures, but rather interact with a set of target molecules within cells and tissues in the body. In response, cells change their physiology, ideally toward a non-seizure-prone state. As is well known, however, the fraction of patients who are seizure free on any medication has remained stuck at around two-thirds for decades [14], and existing medications can have debilitating side effects, particularly when multiple treatments are prescribed simultaneously. The ability to predict what kinds of novel molecules will interact in just the right ways to normalize and stabilize the ceaseless molecular activity of the brain to prevent seizures is a goal of therapy development in a complex systems framework.

This problem is at least as hard as intervening in an ecosystem to normalize and stabilize population dynamics. Analogous to molecules within cells, organisms in ecosystems have diverse interactions forming a trophic network defining energy and material flows. There is an ignoble history of abject failures and a few instructive successes of human intervention into ecological systems. Canonical among the failures is the introduction of cane toads to Australia to control cane beetles; a strategy that had broad scientific consensus at the time. Not only did the toads fail to control cane beetles, they also destabilized the native ecosystem, endangering several species that did not coevolve with them [15]. In contrast, the reintroduction of wolves to Yellowstone National Park in the United States was successful beyond expectations [16]. Unlike the cane toads, the Yellowstone ecosystem evolved with wolves as an apex predator, who were extirpated by human activities. The reintroduced wolves had a number of salutary effects. Principally, as apex predators, they induced significant changes in behavior in their main prey species, elk, who no longer ventured out into the open to graze exclusively on the most desirable plants. This change in behavior had the downstream effect of allowing multiple plant populations to recover from overgrazing, which in turn allowed their roots to stabilize the soil, which arrested the erosion that was causing rivers to change course and further disrupt other niches. Furthermore, the availability of elk carcasses helped restore other scavenger species. Overall, biodiversity and population stability are both markedly improved.

The critical point to take away from the toads versus the wolves is that the wolves succeeded and the toads failed because of where they each sat within the trophic network. The wolves had an evolved function and a critical topological location within the trophic network as the apex predator. In contrast, the toads were speculatively introduced as a totally new node within a network. Importantly, both interventions had the proximal goal of controlling a target species (elk for the wolves, beetles for the toads), but it was network effects that determined success. In epilepsy terms,

https://doi.org/10.1017/9781108582285.001 Published online by Cambridge University Press

these examples ask us to think deeply about how and why we choose molecular targets for anti-seizure drugs, and our strategies for targeting them. It is interesting to speculate at this level of generality whether we think any of our modern anti-seizure medications are wolves or toads. Like the traffic and ecological examples, the effects of introducing a molecule depends in highly nontrivial ways on the dynamics of the whole network of interactions. Systems biological approaches to genetic risk prediction and drug discovery, therefore, treat molecular networks and their emergent functions as fundamental, alongside individual molecule-trait associations (see Chapters 2 and 3).

The foregoing discussion has briefly highlighted the character of complex systems theory and sought preliminary connections to the main topic of this book. We hope this inspires interested readers to seek out comprehensive treatments of complex systems theory (as can be found in [1,8,17]), and keep these analogies and principles in mind as they go through the chapters. Overall, we have chosen to organize the book by physical scale within the brain, starting with genes and ending on whole brains. It should be stressed, however, that each chapter is a self-contained treatment of a topic. Each chapter in its own way, and to the extent possible for each data domain within neuroscience, discusses the promise of networked, dynamical thinking for epilepsy research and practice.

References

1. Holland, J. H. *Hidden Order: How Adaptation Builds Complexity*. New York: Basic Books. 1996.
2. Buck, J., and Buck, E. Synchronous fireflies. *Sci Am.*, 234(5), 74–9, 82–5 (1976). doi:10.1038/scientificamerican0576-74
3. Sanger, G. F. Beyond isolation: Preferred rates of oscillation, from fireflies to epilepsy. *Med Hypotheses*, 41(3), 211–14 (1993). doi:10.1016/0306-9877(93)90232-f
4. Watts, D. J., and Strogatz, S. H. Collective dynamics of "small-world" networks. *Nature*, 393 (6684), 440–2 (1998). doi:10.1038/30918
5. Anderson, P. W. More is different: Broken symmetry and the nature of the hierarchical structure of science. *Science*, 177(4047), 393–6 (1972). www.science.org/doi/10.1126/science.177.4047.393
6. Kauffman, S. A. *The Origins of Order: Self Organization and Selection in Evolution*. New York: Oxford University Press. (1993).
7. Meadows, D. H. *Thinking in Systems: A Primer*. Vermont: Chelsea Green Publishing. (2008).
8. Bar-Tam, Y. *Dynamics of Complex Systems*. Boca Raton, FL: CRC Press. (1999). https://necsi.edu/dynamics-of-complex-systems
9. Wang, F., Xiong, S., Wu, L., et al. A novel TSC2 missense variant associated with a variable phenotype of tuberous sclerosis complex: case report of a Chinese family. *BMC Med Genet.*, 19(1), 90 (2018). Doi:10.1186/s12881-018-0611-z
10. Guerrini, R., Cellini, E., Mei, D., et al. Variable epilepsy phenotypes associated with a familial intragenic deletion of the SCN1A gene. *Epilepsia*, 51 (12), 2474–7 (2010). doi:10.1111/j.1528-1167.2010.02790.x
11. Forslund, M. V., Perrin, P. B., Røe, C., et al. Global outcome trajectories up to 10 years after moderate to severe traumatic brain injury. *Front Neurol.*, 10, 219, (2019). doi:10.3389/fneur.2019.00219
12. Easley, D., and Kleiburg, J. *Networks, Crowds, and Markets*. Cambridge: Cambridge University Press. 2021.
13. Althoen, S. C., King, L., and Schilling, K. How long is a game of snakes and ladders? *Math. Gaz.*, 77(478), 71–6, (1993). doi:10.2307/3619261
14. Brodie, M. J. Outcomes in newly diagnosed epilepsy in adolescents and adults: Insights across a generation in Scotland. *Seizure*, 44, 206–10, (2017). doi:10.1016/j.seizure.2016.08.010
15. Turvey, N. Everyone agreed: Cane toads would be a winner for Australia. The Conversation. November 7, 2013. http://theconversation.com/everyone-agreed-cane-toads-would-be-a-winner-for-australia-19881
16. Peterson, Christine. 25 years after returning to Yellowstone, wolves have helped stabilize the ecosystem. National Geographic. July 10, 2020. www.nationalgeographic.com/animals/article/yellowstone-wolves-reintroduction-helped-stabilize-ecosystem
17. Newman, M. E. J. *Networks: An Introduction*, Oxford: Oxford University Press. 2010.

https://doi.org/10.1017/9781108582285.001 Published online by Cambridge University Press