Stable continual learning through structured multiscale plasticity manifolds
Poonam Mishra and Rishikesh Narayanan

Abstract
Biological plasticity is ubiquitous. How does the brain navigate this complex plasticity space, where any component can seemingly change, in adapting to an ever-changing environment? We build a systematic case that stable continuous learning is achieved by structured rules that enforce multiple, but not all, components to change together in specific directions. This rule-based low-dimensional plasticity manifold of permitted plasticity combinations emerges from cell type–specific molecular signaling and triggers cascading impacts that span multiple scales. These multiscale plasticity manifolds form the basis for behavioral learning and are dynamic entities that are altered by neuromodulation, metaplasticity, and pathology. We explore the strong links between heterogeneities, degeneracy, and plasticity manifolds and emphasize the need to incorporate plasticity manifolds into learning-theoretical frameworks and experimental designs.

Addresses
Cellular Neurophysiology Laboratory, Molecular Biophysics Unit, Indian Institute of Science, Bangalore 560012, India

Corresponding author: Narayanan, Rishikesh (rishi@iisc.ac.in)

Current Opinion in Neurobiology 2021, 70:51–63
This review comes from a themed issue on Computational Neuroscience
Edited by Julijana Gjorgjieva and Ila Fiete
For a complete overview see the Issue and the Editorial
Available online 17 August 2021
https://doi.org/10.1016/j.conb.2021.07.009
0959-4388© 2021 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Introduction
Plasticity is ubiquitous in the brain, with lines of evidence suggesting that changes can occur in any component that governs brain physiology [1]. However, akin to Rubik’s cube puzzle (Figure 1a), the ability of each component to change does not translate to independent random changes in individual components. Instead, there are strong structured rules that permit only certain components to change together. We consider stable adaptation to continually changing environmental stimuli as the ultimate goal of learning-driven plasticity, where learning and homeostasis are achieved without cross-interferences from each other (stable learning) and without catastrophic forgetting of prior learning (continual learning) [2,3]. In this review, we build a systematic case that this ultimate goal of brain plasticity is achieved through structured rules that govern the ability of multiple, but not all, components to change concomitantly. These rules are enforced by the current state of the components and the nature of stimuli and permit only certain combinations of these components to undergo plasticity. We refer to the low-dimensional manifold of permitted plasticity combinations, within the high-dimensional space involving all possible changes spanning all components, as a plasticity manifold. The framework of plasticity manifolds is inspired by the well-established neural manifold framework, which is restricted to represent the rules that govern the population dynamics of correlated firing in interconnected neurons [4–7]. Plasticity manifolds, on the other hand, represent the strong rules that govern conjunctive long-term plasticity in multiscale components and measurements, geared toward adaptation to an altered environment (Figure 1b).

Emergence of multiscale plasticity manifolds
Theoretical and computational frameworks that consider neurons as simplified computational units with synaptic plasticity as the substrate for learning (Figure 2a) have a long and cherished history [8,9]. However, most of these theories predate the discovery of active dendrites (Figure 2b), which transform single neurons into powerful computational machines [10,11], and active glial signaling [12–14]. Furthermore, as learning-induced biological plasticity is ubiquitous [1,15–18] (Figure 2c-f), the strong constraints imposed by plasticity manifolds are essential in avoiding disruptive changes (Figure 1).
Rubik’s cube puzzle as an analogy for illustrating the structured configuration-dependent conjunctive changes in multiple components that constitute plasticity manifolds. (a) There is a single valid solution to Rubik’s cube puzzle, where each face displays a unique color. When the cube’s pieces are analyzed individually, it appears that changes are ubiquitous. However, when movements of multiple pieces are tracked simultaneously, it becomes evident that multiple, but not all, components change together in each step. Importantly, there are strong structured rules, enforced by the current configuration (X vs. Y) of the cube, that permit only certain combinations of pieces to change together. There are several sequences of changes that could yield the final solution, all of which should respect the specific variant of the cube puzzle (e.g., differences in number of sides) and not get entangled in scenarios where solving one side would disrupt the other(s). (b) Schematic representation of multiscale plasticity manifolds. Analogous to Rubik’s cube puzzle, independently viewed, plasticity might look ubiquitous, but there are structured rules governing plasticity.
induce localized increases in synaptic strength, back-
propagating action potentials and dendritic spikes, 
accompanied by a global reduction in sub- and supra-
threshold excitability [19–25], together yielding a 
cellular-scale plasticity manifold (Figure 2g). In the hip-
pocampus, multiscale plasticity manifolds are involved in 
the emergence of a subpopulation of engram cells, through specific combinations of synaptic and intrinsic plasticity 
[18,26,27], driving context-dependent behavioral changes 
(Figure 3c). Here, baseline neural excitability plays a 
critical role in permitting specific subsets of cells to 
become engram cells and be part of the network-scale 
plasticity manifold [18,26,28–33]. In the suprachias-
matic nucleus, a network of specific genes mediates the 
day–night rhythms in excitability properties of neurons. 
These rhythms recruit plasticity manifolds involving a 
specific subset of ion channels [34,35] that dramatically 
alter cellular, network, and behavioral physiology [34–36]. 
Importantly, the cellular-scale plasticity manifolds in 
circadian rhythm generation and memory formation also 
involve glia [12,14,18,26,27,36,37]. Similar examples of 
multiscale plasticity manifolds are found across different brain regions [1,16,38–41].

As biological plasticity invariably recruits the activation of 
biochemical signaling cascades, the molecular scale 
forms the lynchpin in the emergence of plasticity 
manifolds. The strength and dynamics of signaling 
species, including cytosolic calcium, activate a specific 
subset of downstream signaling cascades [42–44]. Once 
activated, dynamical interactions between these 
signaling cascades, along with their specific target mol-
ecules, regulate the molecular-scale plasticity manifold 
[42,43,45–48]. The impact of these signaling cascades 
on each molecular substrate results in gain or loss of 
function of that substrate, together yielding specific 
changes in cellular, network, and behavioral-scale func-
tion (Figure 3). The continual dependence of the 
strength and direction of different forms of plasticity on 
cytosolic calcium and on the graded activation of different signaling molecules constitutes the prime motivation for the framework of a manifold considered here [19,21,49–53].

The rules associated with plasticity manifolds should 
not be generalized across different cell types or different 
contexts. For instance, activation of group 1 metabo-
tropic glutamate receptors results in depression of syn-
aptic strength combined with an enhancement of 
intrinsic excitability [21] in CA1 pyramidal neurons, but 
induces concomitant enhancement of synaptic strength and 
intrinsic excitability in amygdalar neurons [54]. 
Theta-burst firing reduces sub- and supra-threshold 
excitability through changes in HCN channels in CA1 
pyramidal neurons [19,22], but enhances supra-
threshold excitability and reduces sub-threshold excit-
ability through conjunctive changes in HCN, inward-
rectifier potassium, and persistent sodium channels in 
dentate gyrus granule cells [40]. Phosphorylation of 
AMPARs increases AMPAR-mediated current in hippo-
campal pyramidal neurons, but reduces the current in cerebellar Purkinje cells [55] as a consequence of the 
differential expression of AMPAR subunits. Thus, it is 
important that cell type specificity of molecular and 
cellular plasticity manifolds is explicitly accounted for 
[19,22,34–36,38,40,54–58].

Degeneracy, heterogeneities, and plasticity 
manifolds

Degeneracy is the ability of disparate combinations of structural components to perform the same function 
[59] and provides multiple degrees of freedom to bio-
 logical systems in achieving functional robustness (Figure 4a). However, the consequent complexity re-
 sults in parametric variability across animals (or cells or networks), thereby precluding one-to-one relationships between individual components and functional outcomes. The existence of plasticity manifolds represents 
constraints that restrict unruly changes and therefore 
provides a valuable handle to probe for order in complex systems manifesting degeneracy.

How do systems (e.g. neurons, networks) expressing 
degeneracy switch from one valid solution to another 
toward maintaining functional homeostasis in the face of 
perturbations? We argue that plasticity manifolds provide 
a structured substrate for multiple components to change 
together, thereby seamlessly traversing the valid 
solution landscape (Figure 4a). Degeneracy implies that 
for a system in a given state, several plasticity combina-
tions could yield the same function, thereby maintaining 
functional homeostasis (Figure 4a). Given this, what 
 factors contribute to the system’s ‘decision’ on choosing a 
specific position on the plasticity manifold versus another 
(Figure 4a and b)? A critical requirement in systems 
expressing degeneracy is an error-correcting feedback 
mechanism that regulates constituent components in 
achieving a specific function [44,60]. In rhythmogenic 
circuits where the goal is to maintain specific activity 
patterns, this feedback signal could be defined as sta-
bility of molecular- (e.g. calcium levels), cellular-
(e.g. firing rate), or network-scale (e.g. excitation—inhi-
bition balance) physiology. For plasticity manifolds 
involved in stable learning, however, there is a need to 
alter the current state of the system toward adapting 
responses to a novel stimulus (Figure 3b) while still 
maintaining homeostasis [44]. The feedback signal 
therefore should convey errors in both stability and 
learning goals, with learning-related error signals 
recruiting circuit components implicated in task-
dependent sensory or motor feedback [61–63]. These 
junctive feedback signals would then drive the 
system toward a subset of signaling cascades 
[27,57,60,64–66], resulting in the choice of a specific 
plasticity combination (as part of the plasticity manifold)
(A–F) Neurons endowed with active dendrites are powerful computational devices, and plasticity is ubiquitous. (a) Several learning-theoretical frameworks use distributed processing by well-connected integrate-and-fire ‘neurons’, which learn through modifications in their ‘synapses’. (b) The integrate-and-fire approximation of neurons is contingent on the assumption that neuronal dendrites are passive and house only synaptic receptors. Active dendrites extend single-neuron function beyond passive integration, allowing dendritic spike initiation, bidirectional flow of intraneuronal information, location-specific filtering, and coincidence detection. (c–f) Learning-induced plasticity is not confined to synaptic weights, but is ubiquitous with different loci of plasticity. c: changes in numbers of receptors and vesicles; d: changes in size of the spine and the terminal; e–f: changes in intrinsic components (e.g. ion channels) confined to a single dendritic branch (e) or manifesting globally (f). Note that there are global forms of synaptic (e.g. synaptic scaling) and structural plasticity as well. (g) The TBP protocol as an example for the emergence of molecular- and cellular-scale plasticity manifolds. The TBP protocol was initially developed to induce robust synaptic plasticity in hippocampal synapses. TBP elicits cytosolic calcium influx, which differentially activates CaMKII, PKA, and MAPK (structured signaling manifold, a specific subset of the several signaling cascades) depending on the strength of the TBP protocol [19–25, 49]. These enzymes, in turn, induce changes in AMPARs, HCN, SK, and KA channels (structured molecular-scale plasticity manifold). The consequent cellular-scale plasticity manifold involves concomitant localized increases in synaptic strength, back-propagating action potentials, and dendritic spikes, accompanied by global reduction in sub- and supra-threshold excitability, elicited in response to the same protocol. Note that the same signaling molecule (e.g. PKA) conjunctively induces plasticity in multiple molecular-scale components (AMPARs, KA, and SK channels), which in turn change multiple cellular-scale measurements (synaptic strength and local excitability). These observations show that only a very specific subset of components is permitted to change together in specific directions, and such changes are restricted to specific locations.
required to achieve stable learning. In addition, degeneracy explains why different systems (performing the same function) react differently to the same perturbation (Figure 4c) and require disparate combinations of plasticity toward achieving stable function (Figure 4a and b) [27,44,57,66–68].

Degeneracy also expresses in the emergence of plasticity manifolds, manifesting as the ability of distinct structural components to yield the same plasticity profile [69], defined as the plasticity rules spanning different values of specific parameters (e.g. calcium-dependent or spike-timing–dependent plasticity profiles). Plasticity degeneracy spans multiple scales, with several possible changes to lower-scale components capable of inducing functional plasticity at a given scale of analysis. For instance, changes in several ion channels could yield similar changes in neuronal firing rate [44]. It is also
Illustration of the relationship between degeneracy and plasticity manifolds and the dynamical nature of plasticity manifolds. (a–b) The expression of degeneracy implies that several parametric combinations (green, black, and purple spheres in the parametric space spanning $P_x$, $P_y$, and $P_z$) yield the same function (red sphere in the functional space spanning $F_x$, $F_y$, and $F_z$), thereby forming a many-to-one mapping between the parametric and functional spaces. (c) Identical perturbation in different systems that yielded the same function through different parametric combinations. (d) Dynamical nature of plasticity manifolds showing the changes in $P_x$, $P_y$, and $P_z$ before and after plasticity.
possible that distinct forms of plasticity, involving different structural components in disparate brain regions, could come together to yield the same learning outcome [27,38,70]. These observations translate to considerable variability in parameters yielding similar plasticity manifolds, implying a lack of one-to-one relationships between individual forms of plasticity and behavioral outcomes. Together, the expression of degeneracy emphasizes the need to account for plasticity manifolds at every scale of analysis, as the rules for emergence of function are distinct across scales [44,71].

Dynamical nature of plasticity manifolds

Plasticity manifolds are dynamic entities, whereby the rules binding the specific components that undergo conjunctive plasticity could themselves change. A prominent behaviorally relevant route to alter plasticity rules is neuromodulation, a well-established substrate for altering brain states, functional connectivity, and behavior [57,72–74]. Mechanistically, neuromodulation operates by recruiting diverse receptors that activate disparate signaling pathways, with each pathway acting on specific molecular substrates and cellular measurements. Although the impact of neuromodulation in altering synaptic plasticity is well studied [73,74], neuromodulatory regulation of intrinsic plasticity and plasticity manifolds is not fully explored.

The molecular substrates modified by the implementation of the changes that are imposed by a plasticity manifold could alter the plasticity profiles of synapses and neurons. The consequent changes to the rules governing conjunctive changes in several components, including the directions and strengths of such changes, constitute metaplasticity of plasticity manifolds. The mechanistic basis for such metaplasticity could be through changes in synaptic or neuronal properties or through alteration to specific signaling molecules [44,69,75,76]. In the context of stable learning, certain forms of metaplasticity could play a stabilizing role by avoiding run-away excitation. For instance, plasticity in HCN channels [21,22,50,76] and relocation of inhibitory receptors onto synaptic locations [77], both accompanying excitatory synaptic plasticity, have been attributed to stabilizing metaplastic roles.

From the continual learning perspective, one of the several routes to avoid catastrophic forgetting of prior learning [278–80] is to ensure that distinct resources (e.g., neurons, ion channel subtypes, or synapses) are allotted for encoding distinct behavioral contexts [18,26,28–31]. Such differential allocation could be achieved if mnemonic plasticity in a subset of resources also introduces concurrent metaplasticity that negatively regulates future recruitment of this subset for other contexts. For instance, TBP recruits a plasticity manifold, inducing suppression of global excitability and concomitant enhancement of local synaptic excitability (Figure 2). Although the localized plasticity specifically enhances the response efficacy of potentiated synapses, the global suppression of excitability ensures that responses to other synaptic inputs are lowered [22] along with a global metaplastic suppression of synaptic potentiation [21,22,50,76]. At the network scale, there is evidence for dynamic resource allocation, established through changes in the subset of cells that are permitted to undergo plasticity toward forming engram cells, based on prior learning tasks and other molecular factors [18,26–28,33].

Plasticity manifolds are recruited and altered by pathological conditions [75,81–94]. An example for the recruitment of plasticity manifolds is repeated stress, where behavioral deficits have been associated with diverse combinations of synaptic, intrinsic, and structural changes in different neurons spanning several brain regions [93–95]. Neurons in animal models of autism spectrum disorders [81–87] and visual cortical neurons undergoing activity-driven changes induced by visual deprivation [88–91,96] offer examples for altered plasticity manifolds (Figure 4d) involving synaptic (excitatory and inhibitory) and intrinsic plasticity. These structured pathology-driven changes involving plasticity and functional spaces (red arrows across the two spaces). Consider the purple sphere to constitute the present parametric state of the system. In the face of perturbations, functional homeostasis could be achieved in this system through transitions to the black or the green spheres. Such transitions require structured changes in multiple parameters, thus recruiting specific plasticity combinations on the plasticity manifold (either the green or the black arrows in panel a; also represented as green and black circles in panel b). Furthermore, although all three parametric combinations yield the same function, the specific plasticity combinations required to achieve functional homeostasis are dependent on the present state of the system (say, green vs. purple spheres in panel a). (c) The expression of degeneracy implies that different systems facing the same perturbation would react differently. Consider three distinct systems (transparent spheres in green, purple, and black in the parametric space) yielding the same function (red sphere in the functional space). Now consider an identical artificial perturbation (downward cyan arrow along the z axis of the parametric space) to affect all these three systems (respective solid spheres). These off-manifold perturbations yield distinct functional outcomes because they are in different locations in the parametric space. (d) Plasticity manifolds are dynamic entities and can change in response to neuromodulation, metaplasticity, or pathological conditions. Left, the plasticity manifolds before (black) and after (red) such changes are shown. Right, concomitant plasticity along the P1 and P2 axes of the parametric space was permitted before changes to the plasticity manifold, whereas permitted changes were confined to the P1 axis after the plasticity manifold changed. The black arrowhead (in both left and right panels) points to a specific location on the manifold. As an example of alteration in cellular-scale plasticity manifolds, in wild-type mice, TBP results in changes to synaptic strength and to neural excitability through changes in HCN channels (Figure 2g). However, in fmr1−/− mice, TBP results in enhanced synaptic strength, but not in changes to neural excitability [84]. Thus, in wild-type mice, the manifold involved changes in both synaptic and intrinsic properties, but in the mutant mice, there is change in the plasticity manifold. With reference to network-scale plasticity manifolds, considering the example of engram cell formation (Figure 3), there are lines of evidence for the dynamic nature of the specific subset of cells that are permitted to change, based on timing of prior learning tasks and manipulations of neural excitability [27,28]. Similar changes to the plasticity manifold could result through neuromodulation (reflecting behavioral state of fear, satiety, etc.), metaplasticity, or other pathological conditions.
manifolds underscore the need for a holistic approach that measures and incorporates all changes across different brain regions.

Implications for the existence of plasticity manifolds to computational frameworks and experimental design

The primary implication for the existence of multiscale plasticity manifolds is their ability to sustain stable continual learning in the face of widespread biological heterogeneities, by recruiting disparate components toward efficiently adapting to an ever-changing environment. Learning-theoretical frameworks should incorporate plasticity manifolds, including the synergistic interactions between distinct forms of multiscale plasticity, as a substrate toward stable continual learning (Box 1). Such frameworks for plasticity manifolds could seek inspiration from the well-established neural manifold framework, where the emphasis on conjunctive dynamics provides critical insights on neural encoding [4–7]. Although the neural manifold literature serves as an inspiration, the canvas for plasticity manifolds is much larger (Figures 3 and 4) involving all scales of analyses (from genes to behavior) and all cell types (including all types of neurons and glia).

Experimental designs and technical advances should strongly focus on simultaneously measuring plasticity across cell types in multiple brain regions [70], rather than restricting measurements to changes in a single component (say synaptic strength or neural excitability) in a given brain region. Experimental measurements of multiscale plasticity manifolds are essential because a restricted measurement palette would invariably bias the interpretation on the mechanistic basis of learning-induced adaptation. These measurements of multiscale plasticity and theoretical frameworks on plasticity manifolds could together delineate the functional roles of different components in stable continual learning. Specifically, the changes in components predominantly associated with encoding of the novel environmental context would be attributed a mnemonic role [1]. There would be other components with a homeostatic role toward maintaining stability of multiscale physiology [1]. Furthermore, to sustain the continual nature of the learning process, additional mechanisms could focus on eliminating catastrophic forgetting (e.g. sparse allocation of disparate sets of components to distinct contexts). It is also possible that individual components have different functions under distinct behavioral contexts, whereby plasticity in a specific component might have a homeostatic or a mnemonic or a continual-learning role in distinct contexts.

How do learning-theoretical frameworks and experimental designs account for plasticity manifolds? As the cell type–dependent signaling pathways form the substrate for plasticity manifolds, addressing this requires the entire set of regulatory components in a cell, involving genes, mRNAs, proteins, and metabolites, which has been called the regulome [97]. It is important that techniques are developed to assess the regulome of

---

**Box 1. How to account for plasticity manifolds in theoretical and experimental studies?**

**Molecular scale**

- Identify the mechanistic basis for the structure in plasticity manifolds by experimental characterization of cell type–dependent regulome
- Experimentally determine the subcellular loci and temporal evolution of plasticity in molecular components
- Experimentally characterize cell-to-cell variability in signaling molecules and their targets to evaluate heterogeneity in signaling networks and plasticity manifolds through theoretical frameworks
- Decipher rules for molecular-scale plasticity manifolds, accounting for degeneracy and neuromodulation

**Cellular scale**

- Identify the functional implications for molecular-scale plasticity manifolds, and define mnemonic, homeostatic, and continual-learning roles for sub-manifolds
- Incorporate active dendritic structures and localized dendritic plasticity into stable continual learning models
- Recognize roles of ion-channel plasticity beyond their roles in regulation of intrinsic excitability (e.g. frequency-dependent filtering, coincidence detection)
- Recognize that plasticity in different components could play distinct roles depending on neuronal subtype, behavioral context, afferent activity, and neuromodulatory tone
- Systematically study metaplasticity of intrinsic plasticity and plasticity manifolds

**Network scale**

- Assess molecular- and cellular-scale plasticity manifolds from all neuronal subtypes and glia, accounting for neuromodulation and degeneracy
- Assess stability in network function and probe the implications and mechanisms underlying network stability using conductance-based models
- Implement phenomenological equivalents of plasticity manifolds in neuromorphic hardware that allows for massively parallel computations to assess network-scale plasticity manifolds

**Systems scale**

- Characterize and account for feedback loops across different subnetworks, specifically focusing on their roles in driving the system toward achieving stability and learning goals
- Build multiscale models of several interconnected brain regions, each endowed with distinct network architectures. Evaluate the impact of connectivity on activity patterns and plasticity manifolds, while systematically accounting for degeneracy and neuromodulation
Stable learning through plasticity manifolds Mishra and Narayanan 59

activity-dependent plasticity in a cell type—dependent manner, evaluating the roles of location and dynamics of different molecular species in the recruitment of specific signaling cascades in yielding plasticity spanning multiple timescales [45,66,98–101]. Theoretical frameworks should then derive rules for plasticity, not just involving synaptic or intrinsic or glial plasticity, but for conjunctive changes in all components of the multiscale manifold involving multiple brain regions to accomplish stable and continual learning.

Conclusions
Together, learning-theoretical frameworks should build and assess experimentally constrained multiscale models of plasticity manifolds, which are driven by cell type—specific regulomes. Toward achieving stable continual learning, these frameworks should strive to harness (i) the tremendous multiscale computational power of molecular signaling networks, active dendritic structures, and neuron-glia networks spanning different brain regions and (ii) the flexibility and the robustness offered by degeneracy, parametric variability, and neuromodulation (Box 1). The phenomenological and mechanistic insights on the origins of and implications for multiscale plasticity manifolds in biological learning systems could then provide a substrate for incorporating stable continual learning into artificial systems.

CRediT author statement
Poonam Mishra: Conceptualization; Visualization; Writing – original draft; Writing – review & editing; Rishikesh Narayanan: Conceptualization; Visualization; Writing – original draft; Writing – review & editing.

Conflict of interest statement
Nothing declared.

Acknowledgements
The authors thank Dr. Neeja Soni, Dr. Sufyan Ashhad, Ms. Harsha Gurnani, Dr. Sunandha Srikanth, and members of the cellular neurophysiology laboratory for helpful discussions and comments on a previous version of the manuscript. The authors acknowledge funding support from the Wellcome Trust-DBT India Alliance (Senior fellowship to R.N.; I/S/16/2/502727), the Human Frontier Science Program (HFSP) Organization (R.N.), the Department of Biotechnology through the DBT-IISc partnership program (R.N.), the Revati & Satya Nadham Atluri Chair at IISc (R.N.), and the Ministry of Human Resource Development (R.N. and P.M.).

References
Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Kim SJ, Linden DJ: Ubiquitous plasticity and memory storage. Neuron 2007, 56:582–592.
2. Patisi GI, Kemker R, Part JL, Kanan C, Wemter S: Continual lifelong learning with neural networks: a review. Neural Network 2019, 113:54–71.
3. Turrigiano GG, Nelson SB: Hebb and homeostasis in neuronal plasticity. Curr Opin Neurobiol 2000, 10:358–364.
4. Jazayeri M, Araz A: Navigating the neural space in search of the neural code. Neuron 2017, 93:1003–1014.
5. Vyas S, Golub MD, Sussillo D, Shanoy KV: Computation through neural population dynamics. Annu Rev Neurosci 2020, 43:249–275.

An integrative synthesis on neural manifolds, which elucidates the principles and theories of dynamical system employed to understand the population activity of neurons in motor control. Neural manifolds constitute a well-established framework, inspirations from where could be employed to expand the theoretical framework of plasticity manifolds.

6. Gallego JA, Perich MG, Miller LE, Solla SA: Neural manifolds for the control of movement. Neuron 2017, 94:978–984.
7. Chaudhuri R, Gerek B, Pandey B, Peyrache A, Fiete I: The intrinsic attractor manifold and population dynamics of a canonical cognitive circuit across waking and sleep. Nat Neurosci 2019, 22:1512–1520.
8. Magee JC, Grienberger C: Synaptic plasticity forms and functions. Annu Rev Neurosci 2020, 43:95–117.
9. Lillcrag TP, Santoro A, Marris L, Akerman CJ, Hinton G: Backpropagation and the brain. Nat Rev Neurosci 2020, 21:335–346.
10. Johnston D, Narayanan R: Active dendrites: colorful wings of the mysterious butterflies. Trends Neurosci 2008, 31:309–316.
11. Stuart GJ, Spruston N: Dendritic integration: 60 years of progress. Nat Neurosci 2015, 18:1713–1721.
12. Kol A, Goshen I: The memory orchestra: the role of astrocytes and oligodendrocytes in parallel to neurons. Curr Opin Neurobiol 2020, 67:131–137.
13. Ashhad S, Narayanan R, Stores: Channels, glue, and trees: active glial and active dendritic physiology. Mol Neurobiol 2019, 56:2278–2299.
14. Santello M, Toni N, Volterra A: Astrocyte function from information processing to cognition and cognitive impairment. Nat Neurosci 2019, 22:154–166.
15. Mozzachiodi R, Byrne JH: More than synaptic plasticity: role of nonsynaptic plasticity in learning and memory. Trends Neurosci 2010, 33:17–26.
16. Titley HK, Brunel N, Hansel C: Toward a neurocentric view of computation. Neuron 2017, 95:19–32.
17. Nelson SB, Turrigiano GG: Strength through diversity. Neuron 2008, 60:477–482.
18. Josselyn SA, Tonegawa S: Memory engrams: recalling the past and imagining the future. Science 2020, 367:aew4325.

This review presents an integrative synthesis on the current status of the engram literature, pointing to the presence of plasticity manifolds.
involving conjunctive synaptic and intrinsic plasticity and the mechanisms underlying their expression. The authors also point to disparate roles for these plasticity manifolds and underlying components in memory allocation, retrieval and consolidation. Engram-cell formation recruits changes to synaptic receptors and ion channels at the molecular scale to enhance synaptic strength and intrinsic excitability in the cellular scale. These changes are restricted to a specific subset of cells in the network scale, constrained predominantly by the baseline excitability of the cells involved. Thus engram cell formation provides an example of multi-scale plasticity manifolds, involving specific subset of molecules, cellular properties and neurons that are recruited toward executing a learning task.

19. Fan Y, Fricker D, Brager DH, Chen X, Lu HC, Chitwood RA, Johnston D: Activity-dependent decrease of excitability in rat hippocampal neurons through increases in Ih. Nat Neurosci 2005, 8(15):1542–1551.

20. Lin MT, Lujan R, Watanabe M, Adelman JP, Maylie J: SK2 channel plasticity contributes to LTP at Schaffer collateral-CA1 synapses. Nat Neurosci 2008, 11:170–177.

This electrophysiological study, along with (Fan et al., 2005, Frick et al., 2004), provide a well-structured plasticity manifold involving synaptic receptors, HCN channels, A-type K+ channels and SK channels. This study provides lines of evidence for localized plasticity in SK channels along with synaptic changes, and demonstrates the dependence of synaptic and channel plasticity on the activation of SKA. These changes are in response to the same induction protocol, and provide empirical evidence that different cellular components undergo concomitant changes. These studies provide clear directions for identifying and characterizing molecular, cellular-scale and multi-scale plasticity manifolds through rigorous electrophysiological techniques. The emphasis here is on simultaneously measuring multiple physiological characteristics, rather than focusing on changes pertaining to a single component.

21. Brager DH, Johnston D: Plasticity of intrinsic excitability during long-term depression is mediated through mGluR-dependent changes in Ih (m s) in hippocampal CA1 pyramidal neurons. J Neurosci 2007, 27:13926–13937.

22. Narayanan R, Johnston D: Long-term potentiation in rat hippocampal neurons is accompanied by spatially widespread changes in intrinsic oscillatory dynamics and excitability. Neuron 2007, 56:1061–1075.

23. Frick A, Magee J, Johnston D: LTP is accompanied by an enhanced local excitability of pyramidal neuron dendrites. Nat Neurosci 2004, 7:13–15.

24. Lozaczyz A, Makara JK, Magee JC: Compartmentalized dendritic plasticity and input feature storage in neurons. Nature 2008, 452:436–441.

25. Magee JC, Johnston D: A synthetically controlled, associative signal for Hebbian plasticity in hippocampal neurons. Science 1997, 275:209–213.

26. Josselyn SA, Frankland PW: Memory allocation: mechanisms and function. Annu Rev Neurosci 2018, 41:389–413.

27. Swies BM, Mau W, Rabinowitz S, Cai DJ: Dynamic and heterogeneous neuron ensembles contribute to a memory engram. Curr Opin Neurobiol 2021, 67:199–206.

28. Lau JMH, Rashid AJ, Jacob AD, Frankland PW, Schacter DL, Josselyn SA: The role of neuronal excitability, allocation to an engram and memory linking in the behavioral generation of a false memory in mice. Neurobiol Learn Mem 2020, 174:107284.

29. Zhou Y, Won J, Karlsson MG, Zhou M, Rogerson T, Balaji J, Neve R, Poirazi P, Silva AJ: CREB regulates excitability and the allocation of memory to subsets of neurons in the amygdala. Nat Neurosci 2009, 12:1438–1443.

30. Lisman J, Cooper K, Sehgal M, Silva AJ: Memory formation depends on both synapse-specific modifications of synaptic strength and cell-specific increases in excitability. Nat Neurosci 2018, 21:309–314.

31. Park A, Jacob AD, Walters BJ, Park S, Rashid AJ, Jung JH, Lau J, Woolley GA, Frankland PW, Josselyn SA: A time-dependent role for the transcription factor CREB in neuronal allocation to an engram underlying a fear memory revealed using a novel in vivo optogenetic tool to modulate CREB function. Neuropsychopharmacology 2020, 45:916–924.

32. Yu AP, Mercaldo V, Yan C, Richards B, Rashid AJ, Hsiang HL, Pressey J, Mahadevan V, Tran MM, Kushner SA, et al.: Neurons are recruited to a memory trace based on relative neuronal excitability immediately before training. Neuron 2014, 83:722–735.

33. Park S, Kramer EE, Mercaldo V, Rashid AJ, Insel N, Frankland PW, Josselyn SA: Neuronal allocation to a hippocampal engram. Neuropsychopharmacology 2016, 41:2987–2993.

34. Harvey JRM, Plante AE, Meredith AL: Ion channels controlling circadian rhythms in suprachiasmatic nucleus excitability. Physiol Rev 2020, 100:1415–1454.

This review provides instances of existence of plasticity manifolds involved in circadian rhythm generation. The findings described here show changes in multiple ion channels, but not all of them, in mediating circadian changes in neural intrinsic properties. This review also emphasizes the critical role of neuromodulation in facilitating synchronization and plasticity of neurons involved in circadian rhythm generation.

35. Patke A, Young MW, Axelrod S: Molecular mechanisms and physiological importance of circadian rhythms. Nat Rev Mol Cell Biol 2020, 21:67–84.

An integrative multi-scale synthesis of the several plasticity manifolds that are involved in circadian rhythm generation, tracking the mechanistic origins of the conjunctive changes and the behavioral outcomes of such plasticity involving multiple components. This review covers lines of evidence for conjunctive plasticity in multiple components across different scales of analysis, spanning a slew of techniques — including electrophysiology, imaging molecular biology, behavior, genetics, pharmacology — that are essential in identifying and characterizing multi-scale plasticity manifolds. A critical requirement in identifying plasticity manifolds is the need to simultaneously measure changes in multiple components at each scale of analysis, rather than focusing on any single component.

36. Brancaccio M, Edwards MD, Patton AP, Smlylie NJ, Chesham JE, Maywoord ES, Hastings MH: Cell-autonomous clock of astrocytes drives circadian behavior in mammals. Science 2019, 363:187–192.

37. Steadman PE, Xia F, Ahmed M, Mocie AJ, Penning ARA, Geraghty AC, Steenland HW, Monje M, Josselyn SA, Frankland PW: Disruption of oligodendrocyte generation impairs memory consolidation in adult mice. Neuron 2020, 105:150–164.e156.

This study demonstrates a critical role for experience-dependent changes in the generation of myelin-forming oligodendrocytes in memory consolidation, thereby adding an additional component to the plasticity manifold involved in memory consolidation. This study also emphasizes the need to measure and account for plasticity in different cell types while assessing molecular and cellular mechanisms underlying behavioral outcomes. This study constitutes an ideal example of how different cell types could be targeted in identifying and characterizing plasticity manifolds involving multiple cell types.

38. Ohtsuki G, Shishikura M, Ozaki A: Synergistic excitability and plasticity in cerebellar functioning. FEBS J 2020, 287:4557–4593.

This review provides several lines of evidence for the existence of multi-scale plasticity manifolds, with a focus on cerebellar physiology. The review elegantly summarizes multiple forms of plasticity (spanning different induction protocols) expressed in different neuronal subtypes within the cerebellum. The authors present a comparative analysis of the functional relevance of intrinsic plasticity across different brain regions and provides relevance of different forms of plasticity to specific behavioral contexts. These analyses systematically emphasize the need to simultaneously measure multiple components at each scale of analysis in identifying and characterizing multi-scale plasticity manifolds, employing an array of techniques spanning all scales of analysis.

39. Ohtsuki G, Piochon C, Adelman JP, Hansel C: SK2 channel modulation contributes to compartment-specific dendritic plasticity in cerebellar Purkinje cells. Neuron 2012, 75:108–120.

This electrophysiological study demonstrates that both synaptic and non-synaptic induction protocols result in the expression of intrinsic plasticity in cerebellar Purkinje cell dendrites. The authors show that dendritic plasticity is dependent on the downregulation of SK channels and is selective to the specific dendritic location receiving strong activation. The study demonstrates consequent changes in specific synaptic amplitudes, thereby providing a scenario where multiple cellular...
measurements, but not all, change in response to the induction protocol.

40. Mishra P, Narayanan R: Plasticity manifolds: conjunctive
     • changes in multiple ion channels mediate activity-dependent
       plasticity in hippocampal granule cells. bioRxiv 2020, https://
       doi.org/10.1101/747550.

This electrophysiological study in the dentate gyrus and (Fan et al.,
2009; Narayanan and Johnston, 2007) in the CA1 together emphasize
the cell-type-dependence of plasticity manifolds. This study shows that
results theta-burst firing results in enhanced supra-threshold excit-
ability and reduced sub-threshold excitability through changes in HCN,
inward rectification, and persistent sodium channels in dentate
 gyrus granule cells. On the other hand, theta-burst firing reduces sub-
and supra-threshold excitability through changes in HCN channels in
CA1 pyramidal neurons. Thus the molecular-scale manifold involves
changes in different sets of ion channels and the cellular-scale mani-
fold manifests opposing changes in supra-threshold excitability among
the two cell types. These studies provide ideal examples of the
methodology that could be employed to characterize cellular-scale
plasticity manifolds, and emphasize the utility of the
physiology-pharmacology approach in identifying the ion chan-
nel mechanisms governing these plasticity manifolds.

41. Lee JS, Briguglio JJ, Cohen JD, Romani S, Lee AK: The statisti-
cal structure of the hippocampal code for space as a function of time, context, and value. Cell 2020, 183.
620–635.e622.

This study links intrinsic neuronal excitability to the propensity of a
place-cell to have place fields, also showing preservation of propriety
across environments. Given the role of intrinsic excitability in
allocation (Josselyn and Frankland, 2018), these observations have
strong implications for continual spatial learning in the hippocampus
and for the mapping of individual place cells to specific behavioral
contexts.

42. Kotaleski JH, Blackwell KT: Modelling the molecular mecha-

nisms of synaptic plasticity using systems biology ap-
proaches. Nat Rev Neurosci 2010, 11:239–251.

43. Manninen T, Hituri K, Kotaleski JH, Blackwell KT, Linne ML:
Postsynaptic signal transduction models for long-term
potentiation and depression. Front Comput Neurosci 2010, 4:
152.

44. Rathour RK, Narayanan R: Degeneracy in hippocampal
physiology and plasticity. Hippocampus 2019, 29:980–1022.

45. Bhalla US: Molecular computation in neurons: a modeling
perspective. Curr Opin Neurobiol 2014, 25:31–37.

46. Alon U: An introduction to systems biology: design principles
of biological circuits. edn 2. Boca Raton, FL, USA: Chapman and
Hall/CRC Press; 2019.

47. Ma’ayan A, Jenkins SL, Neves S, Hasseldine A, Grace E, Dubin-
Thaler B, Ungerdragon NJ, Weng G, Ram PT, Rice JJ, et al.: Forma-
tion of regulatory patterns during signal propagation in a
Mammalian cellular network. Science 2005, 309:
1078–1083.

48. Neves SR, Iyengar R: Models of spatially restricted
biochemical reaction systems. J Biol Chem 2009, 284:
5445–5449.

49. Rosenkranz JA, Frick A, Johnston D: Kinase-dependent modi-
    fication of dendritic excitability after long-term potentiation.
    J Physiol 2009, 587:115–125.

This electrophysiological study demonstrated that a weak TBP protocol
elicits small changes in synaptic strength and in backpropagating
action potentials, whereas a strong TBP protocol results in relatively
larger changes in both these measurements. This graded dependence of
conjunctive plasticity was shown to be differentially dependent on
two different signaling molecules (MAPK and PKA). Thus, the strength
of concomitant changes in different measurements manifests a graded
dependence on the strength of the activity during the induction proto-
col. This study also provides an example of a smooth transition of
permitted combinations of changes in a manner that has a graded
dependence on the activation of the different signaling molecules
involved. Such graded changes offer the rationale for the use of the
manifold framework in this review. This study, along with (Frick et al.,
2004; Narayanan and Johnston, 2007) provides an example of how to
identify and characterize plasticity manifolds involving subcellular
components and region-specific plasticity through electrophysiological
recordings that simultaneously measurements of multiple changes.

This study also provides an example of the methodology that could be
employed to identify the signaling mechanisms that mediate cellular-
scale plasticity manifolds.

50. Honnuriah S, Narayanan R: A calcium-dependent plasticity
rule for HCN channels maintains activity homeostasis and
stable synaptic learning. PLoS One 2013, 8, e55590.

51. Shouval HZ, Bear MF, Cooper LN: A unified model of NMDA
      receptor-dependent bidirectional synaptic plasticity. Proc
Natl Acad Sci U S A 2002, 99:10831–10836.

This computational study constructed a unified synthetic model of the
dependence of synaptic plasticity on calcium level, providing a model
where the strength and direction of synaptic plasticity manifested
continual dependence on calcium influx. Extensions to this model
involving calcium-dependent plasticity rules for synergistic interactions
between synaptic and intrinsic plasticity also involved continual
dependence on calcium influx (Honnuriah and Narayanan, 2003).
These models were constructed based on several lines of experimental
evidence. Such graded changes in synaptic and intrinsic properties,
and their continual dependence on a plasticity-related parameter (calcium influx) offers the rationale for the use of the manifold framework
in this review. These models provide ideal examples of the
computational tools that could be employed to identify rules that govern
plasticity manifolds, apart from assessing the impact of synergistic inter-
actions among different forms of plasticity.

52. Ashhad S, Johnston D, Narayanan R: Activation of InsP3 re-
    ceptors is sufficient for inducing graded intrinsic plasticity in
rat hippocampal pyramidal neurons. J Neurophysiol 2015, 113:
3082–3093.

53. Markram H, Lubke J, Frotscher M, Sakmann B: Regulation of
synaptic efficacy by coincidence of postsynaptic APs and
EPSPs. Science 1997, 275:213–215.

54. Rahman MM, Kedia S, Fernandes G, Chattarji S: Activation of the
same mGluR5 receptors in the amygdala causes divergent
effects on specific versus indiscriminate fear. eLife 2017, 6.

This study in the amygdala and (Brager and Johnston, 2007) in the
hippocampus together emphasize the cell-type-dependence of plas-
ticity manifolds. This study shows that the activation of group 1
metabotropic receptors in principal neurons of the lateral amygdala
induces long-term enhancement of both synaptic strength as well as
intrinsic excitability. On the other hand, activation of group 1 metabo-
tropic receptors in CA1 pyramidal neurons results in long-term
depression of synaptic strength and enhancement of intrinsic excit-
ability. Thus, the cellular-scale plasticity manifests opposing
changes in synaptic strength in response to the activation of the same
molecule across the two cell types. These studies provide an
electrophysiology-pharmacology route to identify and characterize
plasticity manifolds through simultaneous measurements of multiple
physiological characteristics.

55. Jortell H, Hansel C: Synaptic memories upside down: bidi-
rectional plasticity at cerebellar parallel fiber-Purkinje cell
synapses. Neuron 2006, 52:227–238.

56. Gray JM, Spiegel I: Cell-type-specific programs for activity-
regulated gene expression. Curr Opin Neurobiol 2019, 56:
33–39.

57. Marder E, Goertzi ML, Otopalik AG: Robust circuit rhythms in
small circuits arise from variable circuit components and
mechanisms. Curr Opin Neurobiol 2015, 31:156–163.

58. Hamood AW, Marder E: Animal-to-Animal variability in
neuromodulation and circuit function. Cold Spring Harbor
Symp Quant Biol 2014, 79:21–26.

59. Edelman GM, Gally JA: Degeneracy and complexity in bio-
logical systems. Proc Natl Acad Sci U S A 2001, 98:
13763–13768.

60. O’Leary T, Marder E: Temperature-robust neural function from
activity-dependent ion channel regulation. Curr Biol 2016, 26:
2935–2941.
This study presents an instance of metaplasticity, demonstrating how changes in inhibitory synapses could regulate the expression of long-term potentiation in excitatory synapses, in response to same plasticity induction protocol. These observations point to the existence of a synaptic plasticity manifold involving conjunctive changes in excitatory and inhibitory synapses, where relocation of inhibitory receptors onto synaptic locations plays a regulatory role on continuous expression of excitatory synaptic plasticity. This study provides an ideal example of the use of multiple techniques — optogenetics, behavior, electrophysiology, molecular biology, imaging — spanning different scales of analysis to identify and characterize plasticity manifolds involving multiple synaptic components.

61. Ranganathan GN, Apostolides PF, Hamett MT, Xu NL, Druckmann S, Magee JC: Active dendritic integration and mixed neocortical network representations during an adaptive sensing behavior. Nat Neurosci 2018, 21:1583–1590.

62. Brainard MS, Doupe AJ: Auditory feedback in learning and maintenance of vocal behaviour. Nat Rev Neurosci 2000, 1: 31–40.

63. Gadagkar V, Puzerey PA, Chen R, Baird-Daniel E, Farhang AR, Goldberg JH: Dopamine neurons encode performance error in singing birds. Science 2016, 354:1278–1282.

64. Srikant S, Narayanan R: Variability in state-dependent plasticity of intrinsic properties during cell-autonomous self-regulation of calcium homeostasis in hippocampal model neurons. eNeuro 2015, 2. ENEURO.0053-0015.2015.

65. O’Leary T: Homeostasis, failure of homeostasis and degenerate ion channel regulation. Curr Opin Physiol 2018, 2: 129–138.

66. Gjorgjieva J, Drion G, Marder E: Computational implications of biophysical diversity and multiple timescales in neurons and synapses for circuit performance. Curr Opin Neurobiol 2016, 37:44–52.

67. Anirudhan A, Narayanan R: Active dendritic integration and multiple timescales in neurons and synapses for circuit performance. Curr Opin Neurobiol 2016, 37:329–346.

68. Anirudhan A, Narayanan R: Analogous synaptic plasticity profiles emerge from disparate channel combinations. J Neurosci 2015, 35:4691–4705.

69. Tutsushi S, Hayashi-Takagi A: Optical interrogation of multi-scale neuronal plasticity underlying behavioral plasticity. Curr Opin Neurobiol 2020, 67:8–15.

70. Anderson PW: More is different. Science 1972, 177:393–396.

71. Brzosko Z, Mierau SB, Paulsen O: Relocation of an extrasynaptic GABA(A) receptor to inhibit synapses freezes excitatory synaptic strength and preserves memory. Neuron 2020.
89. Nataraj K, Le Roux N, Nahmani M, Lefort S, Turrigiano G: Visual deprivation suppresses L5 pyramidal neuron excitability by preventing the induction of intrinsic plasticity. Neuron 2010, 68:750–762.

90. Khibnik LA, Cho KK, Bear MF: Relative contribution of feed-forward excitatory connections to expression of ocular dominance plasticity in layer 4 of visual cortex. Neuron 2010, 68:493–500.

91. Heynen AJ, Yoon BJ, Liu CH, Chung HJ, Huganir RL, Bear MF: Molecular mechanism for loss of visual cortical responsiveness following brief monocular deprivation. Nat Neurosci 2003, 6:854–862.

92. Beck H, Yaari Y: Plasticity of intrinsic neuronal properties in CNS disorders. Nat Rev Neurosci 2008, 9:357–369.

93. Chattarji S, Tomar A, Suvarathan A, Ghosh S, Rahman MM: Neighborhood matters: divergent patterns of stress-induced plasticity across the brain. Nat Neurosci 2015, 18:1364–1375.

94. McEwen BS: Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol Rev 2007, 87:873–904.

95. Pignatelli M, Tejeda HA, Barker DJ, Bontempi L, Wu J, Lopez A, Palma Ribeiro S, Lucantonio F, Parise EM, Torres-Berto A, et al.: Cooperative synaptic and intrinsic plasticity in a disynaptic limbic circuit drive stress-induced anhedonia and passive coping in mice. Mol Psychiatry 2020.

In this study, the authors employ a mouse model for stress-induced anhedonia and passive coping states to demonstrate the simultaneous role of intrinsic and synaptic components in specific medium spiny neurons of the nucleus accumbens medial shell. This study presents a pathological role for a plasticity manifold in emotional behaviors, and constitutes an example of the methodology that can be employed to identify and characterize multi-scale plasticity manifolds. This article, along with (McEwen, 2007; Chattarji et al., 2015) constitute specific examples for the involvement of plasticity manifolds in pathological conditions in general, and repeated stress in particular. These articles show that repeated stress recruits diverse combinations of synaptic, intrinsic and structural changes in different neurons spanning several brain regions, with these concomitant changes implicated in associated behavioral deficits.

96. Brown APY, Cossell L, Margrie TW: Visual experience regulates the intrinsic excitability of visual cortical neurons to maintain sensory function. Cell Rep 2019, 27:685–689 e684.

In this in vivo study, the authors demonstrate that ongoing visual inputs alter both intrinsic and sensory-evoked synaptic properties of neurons in the mouse visual cortex. They also show that intrinsic properties of these neurons undergo plasticity following visual deprivation. In addition, with reference to visual deprivation, (Heynen et al., 2003; Maffei et al., 2006; Khibnik et al., 2010; Nataraj et al., 2010; Lambo and Turrigiano, 2013) provide examples for pathology-induced changes to plasticity profiles: activity-driven alterations to plasticity manifolds through visual deprivation involve synaptic (excitatory and inhibitory) and intrinsic plasticity profiles in visual cortical neurons. These studies provide examples of the methodology that could be employed to characterize and identify plasticity manifolds using a slew of electrophysiology, molecular biological, and behavioral techniques.

97. Townsley KG, Brennand KJ, Huckins LM: Massively parallel techniques for cataloguing the regulome of the human brain. Nat Neurosci 2020, 23:1509–1521.

This review recognizes that several genes typically manifest cell-type-dependent expression profiles, and thus regulatory influences on the transcription of these genes would recruit molecular pathways in a cell-type dependent manner. The review discusses the use of high-throughput assays in characterizing the transcriptional responses of putative regulatory elements. The characterization of these regulomes provides a potential route to identifying, characterizing and understanding cell-type-dependent plasticity manifolds spanning different brain regions.

98. Uda S, Saito TH, Kudo T, Kokaji T, Tsuchiya T, Kubota H, Komori Y, Ozaki Y, Kuroda S: Robustness and compensation of information transmission of signaling pathways. Science 2013, 341:558–561.

99. Levchenko A, Nemenman I: Cellular noise and information transmission. Curr Opin Biotechnol 2014, 28:156–164.

100. Selimkhanov J, Taylor B, Yao J, Pilko A, Albeck J, Hoffmann A, Tsimring L, Wollman R: Accurate information transmission through dynamic biochemical signaling networks. Science 2014, 346:1370–1373.

101. Punvis JE, Lahav G: Encoding and decoding cellular information through signaling dynamics. Cell 2013, 152:945–956.