



Neural timescales or lack thereof

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ABSTRACT

This article aims at making readers, experimentalists and theorists, more aware of the abstractions made by an observer when measuring and reporting behavioral and neural timescales. These abstractions stow away the fact that, above lower boundaries that reflect fairly well understood physical constraints, observed and reported timescales are often not intrinsic to the biological system; rather, in most cases they reflect conditions that are imposed by the observer through the measuring procedure. This is true at practically every level of organization, from behavior down to molecules. I analyze the impacts of the resulting temporal manifold in behavioral and brain sciences on experimental designs and mathematical modeling.

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*Real time knows no turning points, there are no thunderstorms or trumpet fanfares at the start of a new month or year, and even when a new century commences - only we, human beings, fire cannon and ring bells.*¹

1. Introduction

The concept of timescale is fundamental to every aspect of science. While vaguely defined, the concept has an operational flavor: the answer to the question “What is the timescale of process X?” is expected to be a number that designates the time within which process X completes a trajectory in the relevant space of a system’s configurations. Equipped with a timescale, one may decide on measurement and modeling strategies; for instance, how frequently in time the process needs to be sampled to obtain a faithful reconstruction of its trajectory, or how detailed the representation of the process must be when incorporated into a large-scale model. Indeed, the usefulness of the timescale concept in general system analysis is beyond doubt, but as shown below, its application to analyses of biological systems is not a straightforward matter.

To start with, the very question “What is the timescale of process X?” implicitly assumes existence of uniquely defined timescales that are intrinsic to the process. In other words, it is assumed that these timescales are separable from each other in the boundaries, and that they are inherent to the observed system rather than reflecting the ways the observer chooses to measure them. But are these assumptions ubiquitously justified in the context of biological systems? If not, we face serious trouble because much of the experimental work done in biological sciences in general, and neuroscience in particular, is aimed at exposing presumably intrinsic and uniquely defined timescales; they serve as guides in the search for microscopic mechanisms, and as a basis for most of the models in the field.

Another potential difficulty arises from the fact that timescales do not reveal themselves to the observer as tangible forms to be compared with some standard. In fact, the measurement of a timescale is an inferential process that involves identification of an observable that (with any luck) reflects the degrees of freedom of the system. In the biological sciences, as much as data collected so far tells us, observables are often very remote from the system’s degrees of freedom, and are mostly dictated by technological constraints. What is the meaning of the timescale concept under such conditions?

Furthermore, while the concept of timescale is interpreted as the time taken to complete a trajectory through *any* well defined sequence of observable values, the concept gains its meaning only when the observables have some functional significance. Thus, timescale is an attribute of function; it involves reliance on one’s capacity to define a functionally significant observable in a biological context, which includes both the system itself as well as the environment within which the system is embedded.

Given the above interwoven difficulties, one is forced to acknowledge the extent of abstraction exercised by the observer while setting up an experimental design, measuring and coming up with a timescale. Robert Rosen points to the entailed irony in his deep and thoughtful analysis of the Life sciences (Rosen, 1991, p. 60):

... There can be no greater act of abstraction than the collapsing of a [natural] phenomenon down to a single number, the result of a single measurement. From this standpoint, it is ironic indeed that a mere observer regards oneself as being in direct contact with reality and that it is ‘theoretical science’ alone that deals with abstractions.

¹ Thomas Mann, *The Magic Mountain: a novel*, p. 222. Translated from German by John E. Woods. Vintage Books, New York.

This article aims at making readers, experimentalists and theorists, more aware of the abstractions made by an observer when measuring neural timescales. These abstractions, which are essential when dealing with the above difficulties, stow away the fact that in behavioral and brain sciences, timescales are very often not intrinsic to the observed system; rather, in many cases they reflect boundary conditions that are imposed by the observer through the measuring procedure. This is true at practically every level of organization, from molecules to behavior. To be sure, at each of these levels, timescales are bounded from below by rather straightforward underlying biophysical constraints; the identification of these constraints is dependent upon successful applications of the timescale concept. But above these lower boundaries, more often than not brain and behavioral phenomena are, for all practical matters, temporally unbounded. I point to commonalities underlying the manifold of temporal scales in neural systems, and bring examples of experimental and theoretical approaches that are aimed at handling neural dynamics and brain function, using minimal enforcement of scales that reflect experimental constraints.

2. Behavioral timescales

2.1. Lower boundaries of behavioral timescales

There are two kinds of lower boundaries to human performance timescales, both are relatively easy to observe and well-documented within the framework of psychological reaction time paradigms. The first lower boundary to human performance is the minimal time it takes for a perceptual object to penetrate the sensory sheath and be reflected in action. Experiments involving one stimulus and one response, show that in humans this simple reaction time cannot go much below 150 ms. Reaction time dependence upon the kind of sensory modality involved (vision, sound or touch) amounts to ca. 40 ms, largely reflecting differences in the very early stages of the sensory path. The second lower boundary to human performance timescales has to do with the temporal gap required, between two different stimuli that appear one after the other, such that they are perceived as separate objects.² The minimal discrimination time for the simplest sensory objects is in the range of 10–30 ms. Syntheses of the above lower temporal boundaries (simple reaction time and discrimination time gap) with well-defined underlying biophysical constraints are neurobiological *tours de force* that are critically dependent upon successful applications of the timescale concept. On the whole, the physiological and biophysical origins of these lower temporal boundaries are well-understood; this will be shown in later sections of the present article. But what if we depart from the lower boundaries and observe the dynamics of behavior over longer timescales? Here, things become murky.

2.2. Slower temporal scales of behavior

Probably the earliest and most extensive application of the timescale concept above the lower boundaries, concerns the relationship between learning, memory and time. There are many aspects to this issue, but for the purpose of clarity let us focus on one, which seems amenable to quantitative characterization: the timescale of forgetting. In 1885 Hermann Ebbinghaus published his classical book “Memory: A Contribution to Experimental Psychology” (Ebbinghaus, 1913). Chapter VII of that book

² In auditory system research, this temporal discrimination task is often named “between channel”, to be differentiated from the “within channel” task in which the subject is required to identify a discontinuity between two spectrally identical stimuli; in the latter case, the discrimination gap is in the order of 1 ms.

introduces a method for quantifying a forgetting process using the concept of *saving*: First, the time (T_0) taken for a subject to memorize a set of syllables is recorded. Then, the time ($T_{\Delta t}$) taken to re-learn that same list after a definite interval (Δt) is measured. The quantity $T_0 - T_{\Delta t}$ is taken as a measure for the retained memory. The latter is not a benign assumption; for, if the relations between the measure $T_0 - T_{\Delta t}$ and the retained memory are non-linear (indeed, why should they be linear?), the apparent time course of forgetting becomes a non-trivial transform of the actual one. Justification for a linear relation between the saving measure and retained memory is operational: what matters when one is interested in retained memory, is the accessibility (in terms of “time saved”) of the memory trace. Be that as it may, Ebbinghaus used the saving measure to show data with Δt ranging from minutes to 1 month. He reported that the extent of retained memory decreases at a rate that is proportional to $1/\Delta t$. The longer the time that elapses from the original learning session, the slower the rate of memory loss; thus the rate of loss is said to be “retarded” as time goes by.

Many facets of Ebbinghaus’ study touch upon the subject matter of the present article, but let us consider two. The *first* is methodological and concerns the wide range of timescales (here the range of Δt) used to record the retention of memory: It is not at all obvious that when measuring across a month timescale, one finds it necessary to observe intervals at the scale of minutes; Ebbinghaus did. We will have more to say about this issue of range of temporal sampling later on. The *second* point relates to the nature of the fitted function. Specifically, the rate of forgetting, being $1/\Delta t$, is (by definition) not constant; it continuously and monotonically retards with time. Timescale and rate are two aspects of the same entity - hence, according to Ebbinghaus, the decay of memory has no uniquely defined scale. Rather, the amount of retained memory, $R(\Delta t)$, is proportional to $\log \Delta t$ (the integral of $1/\Delta t$), a very strong finding that nicely coincides with the old notion of memory consolidation, introduced over 100 years ago (McGaugh, 2000; Müller and Pilzecker, 1900), i.e.—the stabilization of memory traces the longer they survive.

A series of well established experimental studies corroborate Ebbinghaus’ conclusion on forgetting rate retardation. Results published 12 years following Ebbinghaus’, are most notable (Jost, 1987)³: Adolf Jost showed that memory age (that is Δt) may affect the forgetting rate so dramatically, that under some circumstances newly learnt tasks may vanish before older learnt tasks are forgotten (a.k.a. Jost’s law of forgetting). Over the years, forms of forgetting other than $R(\Delta t) \propto \log \Delta t$ were considered, and a strong case was made by Wickelgren (1973) and Wixted and Ebbesen (1991, 1997) and others for a power law function of the form $R(\Delta t) \propto \Delta t^{-D}$, or versions of it. In all these cases, the rate of forgetting is retarded as time goes by; hence, no uniquely defined timescale(s) of forgetting.

The above picture of scale-free time-course of forgetting was extended and generalized to many other aspects of human behavior. Timescale-free functions, and power law functions in particular, are now accepted as appropriate mathematical forms to describe the time course of human performance. A partial list of behaviors that show timescale-free courses include as diverse processes as skill acquisition (Anderson, 1982; Logan, 1988; Newell et al., 2001), somatosensory stimulus detection (Monto et al., 2008), sensorimotor coordination and time estimation (Chen et al., 1997; Gilden, 2001), adaptation to sensory percepts (Rose and Lowe, 1982; Magnussen and Greenlee, 1985; Greenlee and Magnussen, 1987) and recall of autobiographical items (Rubin, 2002).

Thus, there seems to be a consensus amongst researchers that human performance obeys a timescale-free (mostly power) law.

How do psychologists interpret this mathematical form? To some, the exact mathematical form does not mean much since they are merely interested in a mathematical “... shorthand statement of the results...”⁴ to be incorporated into higher level models. To others, who favor reduction, the mathematical form is a valuable clue to the nature of the underlying biological/psychological processes (Simon, 1966; Wickelgren, 1974; Rubin et al., 1999; Sikstrom, 1999; Newell et al., 2001; Wixted, 2004). Views diverge amongst members of the latter group over the impacts of behavioral time courses on our picture of underlying processes. Let us expound on the roots of the debate; it will prove useful because, as later sections of this article show, the essence of the debate crosses behavioral modalities and levels of organization. It reappears each time an underlying microscopic machinery is sought for, as a possible explanation to a macroscopic time course. Such is the case when a reduction is attempted of a given behavioral time course to a neural assembly level; and when a neural assembly time course is interpreted in terms of processes at the level of individual neurons; and when the activity of individual neurons is mapped to their underlying protein population machinery; and even when the dynamics of protein population is interpreted in terms of individual proteins and their substructures. There might be a lesson to be learnt here; let us enquire into it.

Attempts to interpret the phenomenon of scale-free time course of behavior may grossly be classified as belonging to those that assume *scale-free* components, or those that assume underlying processes that are characterized by *uniquely defined timescales*. At first sight, the scale-free component interpretation is a straightforward, admittedly naive, yet (in principle) testable postulate. It roughly says that if a macroscopic measure (e.g. an aggregate score of memory retention) shows a timescale-free decline, it is logical to start approaching its microscopic machinery by searching for scale-free underlying processes. In contrast, proponents of the second class of interpretations argue that the assumption of components with well-defined timescales is “more natural”. They point to the fact that there is an infinite number of ways to superpose microscopic processes to a macroscopic scale-free time course, even though each of the underlying microscopic processes may be characterized by a uniquely defined timescale. While a unified formal mathematical proof for the emergence of a timescale-free function from superposition of independent relaxation processes is not presently available,⁵ there exists a range of physical mechanisms that give rise to such microscopic to macroscopic relations, mostly within the context of $1/f^\alpha$ “noise”. The intuition, strongly supported by numerical analyses (Montroll and Shlesinger, 1982; Anderson, 2001), is that macroscopic scale-free function may emerge when the variance of independent microscopic relaxation processes is sufficiently large. While the exact form of the microscopic relaxation process is probably not critical for the emergence of macroscopic scale-free time course (Anderson, 2001; Kahana and Adler, 2002), superposition of elementary relaxations with uniquely defined timescales is a common assumption in behavioral models in general, and memory models in particular.

Why do we tend to explain macroscopic scale-free processes by superposing elements with uniquely defined timescales? Why does it “feel” more convenient compared to explanations that delegate timescale freeness to elements all the way down the ladder of reduction? The answer might be related to what Bridgman (1927) phrased as “... an apparent demand of our thinking apparatus to be furnished with discrete and identifiable

⁴ A phrase used by Ebbinghaus (1913) in his discussion of the forgetting data. Chapter VII, Section 29, p. 79.

⁵ But see Kahana and Adler (2002).

³ As cited in (Wixted, 2004).

things to think about. The mind seems essentially incapable of dealing with continuity as a property of physical things” (Bridgman, 1927, p. 93).⁶ As argued below, the incapability that Bridgman talks about is not inconsequential. But to fully apprehend the nature of the problem at hand, we must further dwell on the archetypal function that has a uniquely defined timescale—the exponential relaxation term, a spook that haunts every life-scientist (psychologists included) who tries to uncover the time-dependency of a relaxation process,⁷ regardless of the level of organization involved.

3. The exponent spook

As pointed out by Wixted (2004) and others, in the case of what experimental psychologists call “curvilinear” function, there is a natural tendency to assume an exponential relaxation process. There are seemingly good reasons to do so. Exponential relaxation is probably the simplest way to describe a function that has a well defined timescale. Moreover, exponential relaxation has the aura of being in direct contact with biological processes; it goes all the way back to the kinetics of elementary chemical reactions. If we are to explain a behavioral phenomenon in scientific terms, surely we wish to obtain a timescale and relate it to an underlying, yet-to-be-identified process. Indeed, at least in life sciences, the seamless conflation of the three concepts: *timescale*, *exponential relaxation* and *mechanism*, is ubiquitous. Of course, it is acknowledged that most relaxation processes, from the behavioral level to the molecular level, are not well-fitted by a single exponential function; a sum of exponential terms is required (e.g. $f(\Delta t) = a_1 e^{-k_1 \Delta t} + a_2 e^{-k_2 \Delta t} + \dots + a_n e^{-k_n \Delta t}$). But this fact is usually interpreted as reflecting the minimal number of independent processes that is required to explain the observed relaxation; each such process is said to proceed with a uniquely defined timescale, $\tau_n = 1/k_n$, and often serves as a trigger to search a microscopic physical entity that is characterized by that timescale.

A lucid example to such an application of the timescale concept, conflated with exponential relaxation and underlying mechanism in the study of forgetting, is found in the extensive analyses of Rubin et al. (1999). They fit retention data, obtained in five different experimental settings, at high resolution over one or (almost) two orders of magnitude of both dependent and independent variables (time and retained memory, respectively). They report a retention function that may be fitted to all their experimental conditions: $f(\Delta t) = a_1 e^{-\Delta t/\tau_1} + a_2 e^{-\Delta t/\tau_2} + a_3 e^{-\Delta t/\tau_3}$, with τ_1 being in the order of 1 s, τ_2 in the order of 10 s, and $\tau_3 \gg \tau_2$. The authors further propose that τ_1 is a signature of the working memory, and the remaining two terms describe long-term memory, and even suggest possible links to underlying biological processes. In other words, the researchers find a mathematical description that fits well to a wide range of retention data, and go on to make theoretical claims, supported by plausible underlying biological mechanisms that explain the function.

While a perfectly valid approach to quantification of relaxation data, two caveats need be kept in mind while taking the path of adding exponential terms to fit biological (psychology included) relaxation data and trying to phrase a theoretical claim based on the resulting function. The *first* caveat concerns methodology: Care must be taken in constructing the experiment to “open” the

temporal observation window (independent variable) and thus to free the data as much as possible from experimental constraints. This is critical because compound power, log or exponential decay functions may easily be fitted to *any* relaxation data in narrow time windows; indeed even a linear function may be fitted to data if the observation time window is narrow enough. Ebbinghouse understood this; he reports his saving data over a wide range of times, with intervals ranging from minutes to weeks. Similarly, the measured performance (the dependent variable) should ideally be spread over several orders of magnitude. One cannot over-estimate the importance of opening the scales of both the dependent and independent variables (e.g. Δt and $T_0 - T_{\Delta t}$, respectively, in the case of saving time course) for rigorous analysis. Failing to do so may result in an interpretation that reflects experimental constraints rather than the object of interest. Curiously, Rubin and his colleagues show that the generic exponential function that fits nicely the retention data that was collected in experiments of relatively narrow observation windows (barely one order of dependent variable magnitude and two orders of independent variable magnitude), does not fit their data on retention of autobiographic memories. The latter spans four to five orders of magnitude in both dimensions (time and number of retained items, respectively); a power-law is required there.

The *second* caveat cuts deeper into the nature of things and has to do with the interpretation of fitted (single or compound) exponential functions. Fitting an exponent and attributing it to an underlying memory mechanism involves assumptions that are extremely oversimplified. The picture in mind, as far as exponential relaxation is concerned, is of a very large reservoir of N elements that are *independent* of each other, and are not affected by their density; each element has a *fixed* probability (k) per unit time to “escape” the reservoir.⁸ Under these conditions, we expect a population escape rate that is kN , which translates to $N(t) = N(0)e^{-kt}$. Elementary physics suggests that this simple picture is true in the case of radioactive discharge, or similarly reduced and restrictive contexts. Is this the picture we have in mind for human performance? Is memory a reservoir of independent elements that do not interact with each other and with probability per unit time to “vanish”, which is independent of the milieu? Wouldn’t that be too facile? Even in the case of a bipartite chemical reaction, quite strong assumptions are needed in order to justify a constant rate (and hence a timescale). Not too many people in the fields outside chemistry and physics are aware of the fact that the law of mass action, the entry level to kinetic analysis, *assumes* constant rates; this assumption holds under quite restrictive conditions at the microscopic level, very far from the complexity encountered in behavioral and brain sciences. Yet, an exponential relaxation rate is “naturally assumed” by psychologists for complex processes such as forgetting an item in a list. Given the above, the inescapable conclusion is that if one observes what seems to be an exponential relaxation in a complex biological or psychological setting (aren’t they all?), one better check and recheck the result; probably something is wrong here and the apparent timescale is a manifestation of experimental constraints. If the result persists and the process is indeed characterized by uniquely defined timescale(s), a good measure of biophysical skill need be implemented to explain it. Of course, one may always claim that the use of an exponential relaxation function in complex designs is only a “first” approximation. But when such a “first” approximation gives rise to theories about unique mechanisms, it may lead us to a dangerous scientific path.

Going back to the form of forgetting; needless to say, exponential relaxation is incompatible with data that is collected

⁶ Physics, of course, has gone a long way in developing methods to deal with continuity since Bridgman’s critical analysis on “The Logic of Modern Physics” was published. But the “... apparent demand of our thinking apparatus...” remains.

⁷ While in memory studies people tend to use the term *decay*, there is no *a priori* reason to exclude the possibility of memory trace strengthening. Therefore, I prefer using the physical notion of *relaxation*, thus avoiding the attribution of direction to a time-dependent process. This will serve us well in later sections of this article, where biological processes are analyzed.

⁸ Similarly simple assumptions are made when theorizing about population growth.

with broad enough dependent and independent scales. It is also incompatible with Jost's law of forgetting, one of the most established results in memory research. It took no less than 70 years, in a note by Herbert Simon, to point at that trivial mathematical fact (Simon, 1966).

The following sections on neural timescales show that the behavioral level picture repeats itself: scale invariance⁹ dominates from neuronal assemblies through individual neurons to their underlying molecular machines, modulo identifiable lower physical boundaries that we will carefully analyze at each of these levels.

4. Neuronal correlates of behavioral timescales

Basic physiological and anatomical considerations indicate that behavior, from simple to most complex, must involve orchestrated activation of neural cell assemblies. Accordingly, the search for neural correlates of behavioral timescales is, by-and-large, focused on the level of neuronal assemblies. Functionally defined by Hebb, neuronal assembly is a group of cells that share similar static and dynamic response properties when activated through a specific subset of receptors, constituting the simplest instance of a representative process (image or idea) (Hebb, 1949, p. 60). In a series of classical electrophysiological studies (Mountcastle, 1998, and references therein), as well as in later experiments where large-scale imaging technologies were applied (Slovin et al., 2002; Ohki et al., 2005), the abstract notion of cell assembly was mapped to actual neural entities. These studies show that, depending on the nature and complexity of the stimulus, the numbers of neurons constituting an assembly range from hundreds to many hundreds of thousands (Gerstein et al., 1989; Singer et al., 1997; Roland, 2002; Derdikman et al., 2003).

Neurons constituting an assembly synchronize upon presentation of a matching stimulus, as well as during ongoing activity in the absence of sensory stimulation (Kenet et al., 2003). These synchronizations are reflected in large-scale measures such as electroencephalogram (EEG), magnetoencephalogram (MEG) and functional magnetic resonance imaging (fMRI). At the more fine spatial scales, stimuli presented to the sensory sheath may affect the nature of electrical activities emitted by single neurons that are members of the matching assembly. These changes at the single neural level are detectable using micro-electrodes, or arrays of such (Nicoletis and Lebedev, 2009). And finally, there exist well-established techniques to stimulate and measure the activity of neural assemblies in a reduced set-up, *in vitro*: the natural tendency of neural populations to assemble functional groups that respond to various input patterns in a selective manner, even outside the body, enables in-depth biophysical analyses of assembly development and functionality at high spatiotemporal resolution and under well controlled condition (Marom and Shahaf, 2002; Eytan and Marom, 2006; Shahaf et al., 2008, and references therein).

In what follows I show that experiments using the above battery of technologies uncover strong correlations between the lower temporal boundaries of human performance and the lower boundaries of timescales at the assembly level. But, similarly to behavioral timescales, above these lower boundaries, assembly dynamics are dominated by scale invariance.

4.1. Origins of the lower boundaries of behavioral timescales

The rapidity of simple behavioral reaction times is probably the result of a feed-forward sweep of activity (VanRullen and Koch,

2003; VanRullen, 2007), rushing through a chain of neural stations: from the receptive sensory sheath, through the thalamus, cortex, down the motor tract and to the muscles involved. Altogether there are about ten different neural stations involved in that feed-forward chain. As expected from a feed forward process, behavioral responses to a sensory object presented at time t are not affected by sensory objects presented at a later time $t + \Delta t$, with Δt values as short as ~ 20 ms (Nowak and Bullier, 1997; VanRullen and Koch, 2003; VanRullen, 2007). This short temporal gap, the minimal discrimination time, provides a meaningful indication for underlying constraints; its analysis over the past decade is an example for elegant implementation of the timescale concept in neuroscience.

Rapid visual categorization is probably the most intensively studied phenomenon in this context, thoroughly analyzed and integrated by many investigators.¹⁰ The resulting story may be told as follows: The minimal discrimination time implies that each of the neural stations along the sensory-motor feedforward chain must transfer stimulus selective activity to its downstream station within less than ~ 20 ms. A beautiful measurement, showing exactly this, was performed by Slovin et al. (2002) using voltage sensitive dye imaging of V1 and V2 neural activity in a monkey. They applied a small retinotopic visual stimulus, and recorded a 10–20 ms time delay between the initiation of detected population activity in V1 and V2 (ca. 45 compared to ca. 60 ms following the retinal stimulation). Concordant with this, neurons in the inferior temporal cortex, six or seven neural stations downstream the retina, and two-three stations downstream of V2, selectively respond to a visual stimulus after about 100 ms following stimulus onset (Oram and Perrett, 1992; Thorpe et al., 2001), and are capable of doing so in response to a rapid series of visual presentations with a minimal discrimination time of ~ 15 ms (Keyers et al., 2001). These and similar observations in visual and other sensory modalities, taken together with anatomical constraints on the number of neural stations leading from the sensory sheath to the acting muscles, clearly show that the lower boundary on simple behavioral reaction time (~ 150 ms¹¹) is the sum of time delays within the chain of neural stations.

But why 10–20 ms delay between stations? Axonal delay between adjacent stations is in the order of 1 ms (Girard et al., 2001), suggesting that the lower limit on selective activity transfer from a given assembly to its downstream neighbor is constrained by the dynamics within the assembly. Let us consider the within-assembly dynamics from a population level point of view: Regardless of the sensory modality or brain area involved, assembly activation in response to a short stimulus¹² is essentially a threshold-governed all-or-none transient synchronous event (Eytan and Marom, 2006) that lasts 0.1–0.2 s, the *Network Spike*. This timescale emerges whether assembly activation is measured in the sensory (Super et al., 2001; Slovin et al., 2002), somatosensory (Derdikman et al., 2003) or motor areas (Riehle et al., 1997). The same timescale characterizes the activation of higher cortical areas during categorization tasks and during pure internal events (Riehle et al., 1997; Keyers et al., 2001). Biophysical analyses of assembly activation reveal that the process is akin to population recruitment, whereby a subset of neurons that are activated by the intruding stimulus, if sufficiently large, increases in size by recruiting more and more silent neurons through synaptic transmission, until the carrying capacity of the population is saturated. Cessation of assembly synchronization is

⁹ The term "invariance" is used here in the mathematical sense, to designate an object, law or function that do not change when rescaled. Figuratively speaking, scale invariance means that objects (e.g. relaxation curve) look the same at different scales of observation.

¹⁰ The overview of Simon Thorpe and his colleagues on this subject is most illuminating; see, for instance, Guyonnet et al. (2004), Kirchner and Thorpe (2006), Thorpe et al. (2001), VanRullen and Thorpe (2002), and VanRullen and Thorpe (2001).

¹¹ Kirchner and Thorpe (2006) have used saccadic eye movements as indicators to detection of visual objects, showing detection within 120 ms

¹² The minimal duration required to induce perception.

mainly controlled by loss of synaptic resources (i.e. synaptic depression) and, to a lesser extent, by the activation of inhibitory neurons (Eytan and Marom, 2006). Experimental and numerical analyses (Eytan and Marom, 2006; Thivierge and Cisek, 2008) of the early recruitment phase show that the rate of neural population activity growth is $\sim 0.1 \text{ ms}^{-1}$. Hence 10 ms is the time it takes for the initial stimulus-evoked nucleus of active neurons to “spread the word” throughout the network. This timescale reflects structural constraints (see below), which the network cannot violate, leading to the 10–20 ms timescale that characterizes minimal sensory discrimination and delay between neural stations in the sensory-motor chain.

From a topological point of view, considering a 2 ms minimal synaptic delay¹³ the timescale of the recruitment phase translates to about five synaptic stations to spread the activity within an assembly. Remarkably, this number is, by-and-large, independent of the assembly or network size involved (Eytan and Marom, 2006), indicating a special kind of topology that does not linearly scale with the number of elements constituting the network. It is difficult not to think in terms of the small world effect found in many natural complex networks, where most pairs of nodes seem to be connected by a short path through the network (Newman, 2003), and where the average distance between any pair of nodes scales as $\log n$ (or slower) with the number (n) of nodes. The small world effect is a hallmark of broadly distributed connectivity, with clusters that are shortcut by connections between hubs. Indeed, there are many anatomical and functional indications to that effect in brain connectivity, within local and global nets (Shefi et al., 2002; Sporns et al., 2004; Eytan and Marom, 2006; van Leeuwen, 2007; He et al., 2007; Yu et al., 2008; Chen et al., 2008; Stam et al., 2009). Intriguingly, broadly distributed connectivity may be considered as a consequence of the Hebbian principle, which is (in some sense) a biological realization of the preferential attachment algorithm for generating complex networks (Szirtes et al., 2003; Palotai et al., 2004; Antigueira et al., 2009).

Thus, the lower boundaries of behavioral timescales are fairly well understood in terms of established structural and dynamical constraints on the propagation of stimulus selective responses along chains of neural assemblies. No doubt that complete understanding of these constraints awaits further studies; yet, the general quality of what will be learnt is already (or, almost) at our grasp. What if we go above these lower temporal boundaries?

4.2. Neuronal correlates to behavioral scale invariance

As discussed above (Section 2.2), probably the best example for invariance of behavior over extended timescales is provided by relaxation studies of forgetting. These studies enable relatively easy access to the kinetics of behavioral entities over a wide range of timescales. It would have been natural, and very elegant indeed, if one could complement the behavioral results on the form of forgetting by directly observing the dismantlement (or relaxation) rate of the neural entities that underly memory traces. This, however, would be asking for too much; notwithstanding proliferation of abstract cellular and molecular notions regarding memory, there is not even one neural measurable that may satisfactorily be mapped to a specific memory trace. Strictly speaking, in the absence of such mapping, relaxation studies of neural memory traces are difficult to construct and impossible to interpret in a behaviorally meaningful manner. More generally, at present times, experiments that involve concurrent monitoring of behavior and neural relaxation kinetics over a wide enough temporal sampling range are, arguably, out of reach.

An alternative approach to uncover the scales involved in neural correlates of behavior over a wide temporal range, is to quantify the statistical nature of neural activity fluctuations at the presumed relevant level of organization. The connection between noise statistics and relaxation kinetics in system analysis is heavily relied upon in the physical and engineering sciences. This is the upshot of the “fluctuation-dissipation theorem”, the intuition of which being that the forces and fields that drive system fluctuations in thermal equilibrium, are those that relax a system following perturbations. The general applicability of the theorem for biological systems (that are non-linear and out of thermal equilibrium) is questionable. In spite of this limitation, many experimental studies took that path of fluctuation analysis, interpreting the results under the assumption that the fluctuation-dissipation theorem is valid in biology. Practically every piece of data available from these studies indicates that a broad distribution of timescales dominates the statistical nature of fluctuations above the lower boundaries. Scale invariant (or, at least, broadly distributed) fluctuations were described in long-term series obtained with fMRI, MEG and EEG, as well as in local field potential, neuronal assembly synchronization rate, single neuron spike counts and synaptic release *in vivo* and *in vitro* (Teich, 1989; Teich et al., 1997; Lowen et al., 1997; Linkenkaer-Hansen et al., 2001; Segev et al., 2002; Beggs and Plenz, 2003, 2004; Linkenkaer-Hansen et al., 2005; Wagenaar et al., 2006; Nir et al., 2007, 2008; Monto et al., 2008).

While psychophysical human performance does fluctuate in a scale free manner over extended scales (Gilden et al., 1995; Wagenmakers et al., 2004; Monto et al., 2008), to be satisfied with the observation that temporal fluctuations of large neural entities are also scale invariant, is to ask for too little. What one would like to see is that the scale invariant statistics of behavioral and assembly fluctuations are somehow related to each other. Indeed, in the few cases where psychophysical and electrophysiological fluctuations are concurrently monitored over extended timescales, the correlation between them is extremely tight. A most elegant demonstration of such a correlation was brought by Monto et al. (2008): they concurrently monitored slow ($< 0.1 \text{ Hz}$) fluctuations in a somatosensory detection task and EEG in humans. Monto et al. show that beyond the fact that fluctuations in both measures are distributed in a timescale free manner over this temporal range, the subjects' ability to detect the stimulus at a given point in time is tightly correlated with the instantaneous phase of the fluctuation detected using EEG.

4.3. Recapitulation

So far we have seen that at the behavioral level, there are quite sharp lower boundaries to temporal performance. These lower boundaries are the functional reflection of fairly simple and well understood neural constraints that limit the speed of feedforward neural activity propagation, from the senses to the acting muscles. Above these lower boundaries, behavior is marked by scale invariant distributions, manifested both in relaxation measures as well as in fluctuation statistics. One way to interpret this temporal invariance is to assume that the macroscopic (behavioral) dynamics reflect the sum of independent microscopic relaxation processes, each of which with a well defined timescale(s). However, analyses of underlying processes at the level of neural assemblies, does not support such an interpretation; time invariance reigns down there as well. What about single neuron and the underlying machineries of membrane excitability? Perhaps at these microscopic levels the “apparent demand of our thinking apparatus to be furnished with discrete and identifiable things to think about” (Bridgman, 1927) may be assured by uncovering uniquely defined timescales above trivial

¹³ Numbers vary from 2 to 4 ms (Abeles, 1991; Ham et al., 2008; Marom and Shahaf, 2002; Nakanishi and Kukita, 1998).

lower boundaries? Perhaps at these microscopic levels, phenomenology may be reduced to elementary reaction rates, discrete and identifiable timescales “to think about”?

5. Single neuron timescales and their molecular origin

5.1. Neuronal excitability: origins of the lower boundary

Let us, then, consider a phenomenon that is (arguably) the most well understood elementary level of behaviorally relevant neural process: the action potential. Specifically, we ask “What is the timescale of a single action potential?” To be concrete, the question is about the time from action potential initiation until *all* the involved processes, including the refractory period, fully relax; that is, until a new action potential may be initiated, and the membrane response (in that new action potential) does not indicate any trace of the previous one. We start by looking at the lower temporal boundary of a single action potential thus defined. It is somewhere in the order of 5–10 ms (including refractory period). This was already obvious a century ago, when [Adrian and Zotterman \(1926\)](#) observed the “all-or-none” impulse of cellular voltage responses in their classical paper, probably the first documentation ever of recorded neuronal spikes. Twenty six years following [Adrian and Zotterman's](#) seminal observation came [Hodgkin and Huxley \(1952\)](#) with their voltage clamp measurements and phenomenological model of excitability, setting the ground for our present understanding of the origin of the action potential timescale, in terms of dynamic ionic conductances. In this formalism, as well as in its later extensions, the flow of ions down electrochemical gradients is modulated by the probability of membrane ionophores (‘ionic channel’ proteins) to reside in a conductive state. Non-linearity arises from the voltage dependent reaction rates governing the transitions of these ionic channels between different conductive and the non conductive states. From below, Hodgkin and Huxley formalism teaches us, the timescale of an action potential is bounded by membrane capacitance and by the physical density of the ionic channels that carry the currents. From above, the timescale of an action potential is bounded by interactions between exciting and restoring forces, mediated through ionic channel kinetics. Give or take, these boundaries put us within a fairly narrow range, around 10 ms. Beyond that range, we are assured by the Hodgkin–Huxley model, the action potential is over and done with; that is—a new action potential may commence with no appreciable memory effect.

Given the “all-or-none” nature of the neuronal spike, and the built-in machinery that resets the neuron after a well-defined short time window, it was very difficult *not* to appeal to metaphors and concepts from the (then) emerging science of digital machines. Indeed, the excitement from the results of [Adrian, Zotterman, Hodgkin, Huxley](#) and other eminent physiologists that contributed to the understanding of membrane excitability in those days, was immense; and rightly so. What could be more appealing to the wider community of scientists in the second half of the past century than a possible link between brain, behavior and the various aspects of digital sciences (information and communication, signal processing, computation, and related paradigms and concepts)? Numerous abstracted models were formulated, describing the dynamics and function of extended neural systems (up to the levels of brain and behavior) in terms of interacting little memory-less machines that carry digital-like information. In fact, the Hodgkin and Huxley formulation was so successful, that most of these large-scale models did not use it at all: Many scientists considered the canonic Hodgkin and Huxley model as being too “realistic”; interested in behavioral timescales, if we are assured by the canonic model that the history of binary-like membrane activity evaporates within 10 ms, why bother with the computa-

tional load of the so many coupled differential equations of Hodgkin and Huxley? Integrate and fire or versions of it are certainly sufficient under these conditions.

More important, the timescale of the Hodgkin and Huxley model suggested that longer-term memory should not be looked for at the level of membrane excitability or action potential generation; rather, the relevant levels in that respect are synaptic efficacy, network topology (connectivity) or network dynamics. There can be no stronger, straightforward and successful application of the timescale concept than that, right? But as explained in what follows, the above picture is an erroneous interpolation and misinterpretation of the Hodgkin and Huxley model: the timescale of neuronal excitability is not fixed. Hodgkin and Huxley bounded the action potential transient from below at the 10 ms range by well understood physical constraints. But from above, the relaxation from a single action potential (i.e. refractory period) is temporally unbounded.

5.2. Above the lower boundary

A first hint to the possible problematics involved, comes from something that already [Adrian, Zotterman, Hodgkin and Huxley](#) knew, and practically every present day physiologist knows: the uniqueness of the milliseconds timescale of an action potential is valid *only* if the system is perturbed, observed and analyzed within a time window of milliseconds. Widening the temporal observation window exposes longer time scales. When [Adrian and Zotterman](#) pressed the sensory endings of the plantar surface of the cat's hind foot over seconds, the observed timescale of action potential dynamics was at the range of seconds. They clearly showed that the probability of evoking an action potential is strongly dependent upon the history of evoked action potentials; in other words, the timescale of an action potential (already in [Adrian and Zotterman's](#) data) is history-dependent over, at least, three orders of magnitude, milliseconds to seconds.

Of course, Hodgkin and Huxley were fully aware of these slower temporal scales. In their classical 1952 paper, in a subsection titled “Slow changes” [Hodgkin and Huxley 1952, \(p. 541\)](#), Hodgkin and Huxley clearly state that they limited their temporal observation window, and hence their equations to “... cover only the short-term responses of the membrane...”. Recall our discussion on the impact of the experimental design on the resulting measure, and consider the (now) standard experimental manipulation that Hodgkin and Huxley have used in order to obtain a number that designate the timescale of, for instance, the “refractory period”.¹⁴ Two above threshold depolarizations (S1 and S2) of identical amplitudes are applied, separated by a break with varying duration (Δt) at the scale of milliseconds; if at a given Δt the response to S2 is identical to that of S1, the system is said to completely recover; Hodgkin and Huxley showed that when Δt is in the order of 10 ms, the system completely relaxes from previous activity. But there is another timescale hidden here, which is enforced by the experimentalist: this is the interval (ΔT) allowed between successive introductions of pairs of above-threshold stimuli. What experimentalists usually do, when interested in exposing the lower temporal limit of refractoriness, is to set ΔT “long enough” to ensure stability of the system's response to S1. Indeed, the duration of ΔT that is required to ensure response stability in such pair-pulse paradigms is tens of seconds up to minutes. If one does not wait “long enough” much slower timescales of the excitability process are surfaced. [Adrian and Zotterman](#) have used the term *adaptation* to denote these slower dynamics involved in the machinery of excitability, dynamics that has since been documented, generalized and thoroughly analyzed in practically every

¹⁴ See figure number 20, p. 534, in [Hodgkin and Huxley \(1952\)](#).

neuronal context. It is scale invariant already at the level of the single neuron. Recent examples of scale invariant single neuron adaptation are found in publications of Bialek, Fairhall and their colleagues (Fairhall et al., 2001; Lundstrom et al., 2008, and references therein); those who care for the history of the field might be interested in reading older reports (Chapman and Smith, 1963; Thorson and Biederman–Thorson, 1974).

But slower adaptation dynamics, even if scale invariant, does not contradict the notion of action potential (in and by itself) having a well-defined timescale. A critical reader out-there might justly say that “the timescale of an action potential, in and by itself, might still be ca. 10 milliseconds, while *other* processes, initiated by that action potential (for instance, a rise in intracellular calcium concentration), take longer to relax. If these *other* slower processes reflect back onto the action potential machinery, this might explain the above mentioned ubiquitously observed history dependence of excitability”. This is true, and there are far reaching implications to that loaded remark on our ability to apply the timescale concept and, in fact, to attempt modeling the phenomenon in a biologically meaningful setting. It is related to what Irwin Levitan calls the “lonesome channel” misconception (Levitan, 2006); we will come back to this point later. But let us answer the critical reader by examining the timescales involved in the action potential machinery, in and by itself, detached from other cellular mechanisms that reflect back onto it. Modern technologies allow such measurements; all that is required is to measure the relaxation kinetics of individual “lonesome” ionic channels residing (or reconstituted) in an isolated patch of membrane. Many such studies were conducted in the past 30 years, and the picture that emerges is as clear as one can ask for: individual channels that are the molecular machines underlying the generation of the action potential, demonstrate a wide range of relaxation time scales, from sub-milliseconds to many minutes; for review see (Marom, 1998; Ulbricht, 2005). Thus, even if one looks at the processes that are intrinsic to the machinery of action potential generation, many timescales are involved, distributed over orders of magnitude.

“Still,” our critical reader from above might insist, “this picture, complicated as it may be, does not contradict the applicability of the timescale concept above the lower boundary of 10 milliseconds. There is nothing problematic in the fact that a process relaxes with more than one timescale: multi-exponential relaxation is a ubiquitous feature in nature, and so does the application of several timescales to account for the rich temporal dynamics of the kind described above. Thus, to account for the multiple timescale adaptation or memory effects at the level of membrane excitability (in and by itself), all that is required is to add more processes to the model, with relaxation kinetics in the appropriate orders of magnitude”.

Indeed, the exponent spook is not so easily dismissible. Aided by experimental techniques that continuously become more advanced, new timescales are exposed, leading to interpretations that are expressed in terms of an ever-increasing number of degrees of freedom. Concordantly, present variants of the canonical Hodgkin and Huxley model (that was originally limited to cover only the short term responses of the membrane), may include dozens of coupled differential equations, each of which (ideally) takes care of one timescale, extending from milliseconds to seconds and minutes. While serving as an inexhaustible source for high-resolution physiological experiments and computer simulations, I will show below, and in Sections 7.1–7.2, that these timescale-based “spaghetti” models (e.g. Brette et al., 2007, pushed to the limit in Markram, 2006) are combinatorially intractable; their physiological meaning becomes dubious when the arsenal of intracellular modulatory and gene expression regulation is considered seriously.

In my view, a *coup de grâce* to dreams of describing the dynamics of single neuron excitability, above the lower temporal boundary, in terms of uniquely defined timescales, comes from systematic analyses of ionic channel kinetics over extended temporal windows. These analyses reveal that aside from the fact that the range of measured timescales of excitability seems to be unbounded from above, the reported timescales are inseparable from each other in the boundaries. This is reflected as a power-law relation between reported molecular reaction rates that govern the dynamics of ionic channels, and the intensity of their past activation (Toib et al., 1998; Marom, 1998; Melamed-Frank and Marom, 1999; Ellerkmann et al., 2001; Manevitz and Marom, 2002; Jones, 2006; Uebachs et al., 2006). Various aspects of ionic channel activity mechanisms were shown to be scale invariant, but the case of sodium channel availability is most instrumental for our discussion: Voltage-dependent sodium channels serve as the major path through which sodium ions flow down their electrochemical gradient, from the extracellular space into the neuron. This flux is the exciting force during the generation of action potentials in practically every neuron. The availability of the channels to participate in action potential generation is dissipated by past activity; the latter causes channels to become unavailable for further activation. The timescale of recovery from unavailability sets limits on the capability of subsequent stimuli to evoke action potentials. From below, the timescale (τ_r) of recovery from unavailability is bounded at about 10 ms; this is the process of recovery from inactivation described in the canonical Hodgkin and Huxley formalism. But above this lower boundary, unless constrained by the experimental design, the timescale of recovery scales with the duration (T_a) of neuronal activity, following a power law function: $\tau_r \propto T_a^D$, over five orders of magnitude (milliseconds to hundreds of seconds) (Toib et al., 1998; Ellerkmann et al., 2001).

A mechanistic view of these results is given in Section 7; at this point let us just restate the upshot of the above: *there are no uniquely defined timescales to be put into timescale-based models of excitability in order to describe even the most basic functional feature of a neuron—the probability of a response to a given input in a long, physiologically realistic, series of stimuli*. Indeed, the lesson from our journey across levels of organization, from behavior through neural assemblies to single neurons and proteins, suggests that dreams on all-encompassing microscopic timescale-based descriptions, aimed at explaining the temporal richness of macroscopic levels, should be abandoned. Other approaches are called for.

6. Temporal manifold: a semantic digression

The temporal complexity described so far, comes in different flavors and the language used is unavoidably loose. As we have seen, the picture that emerges is of temporal lower boundaries that are fairly well-explained in biophysical terms; above these lower boundaries, temporal scale invariance is ubiquitous.¹⁵ All this is nested in a hierarchy of organization levels: temporal complexity of proteins nested in that of neurons, which is in turn nested within assemblies and then behavior. One may describe this temporal complexity in a spectral language using terms such as $1/f^\alpha$ or (less committing) “broad spectrum” with “cutoffs” and some “peaks”, etc. But in the neurosciences, spectral terminology is traditionally associated with analyses of changes around steady state; it does not necessarily (and certainly not fully) capture the nature of relaxation (dissipation or perturbation) experiments. In the present text, I have used terms borrowed from chemical kinetics: “multiple timescales” or “multiple rates”, “broadly distributed

¹⁵ Notwithstanding sparse “coloring”.

reaction rates” and “timescale free kinetics”, “scale invariance”, etc. While more tightly connected to relaxation experiments, this language is ambiguous compared to the operational nature of the spectral language. There seems to be no escape from the poverty of language in attempting a compact description of the richness encountered when temporal domains are experimentally unfolded in biology. As of this point I use the term *temporal manifold* as a more general shorthand to represent the complex temporal picture that emerges in the analysis of behavior and neural systems, including the temporal boundaries from below and the scale invariance above these lower boundaries.

The following section reviews studies showing that the wealth of biological structure, even at the most elementary level, is sufficient to explain the observed temporal manifold. I then suggest that, given this temporal manifold, approaches that are *not* timescale-based are wanted. I discuss modeling strategies that have been applied to account for the temporal manifold of neural systems at different levels of organization, from channels to networks and behavior.

7. Mechanisms, models and impacts of the temporal manifold

7.1. The origin of the temporal manifold: lessons from protein dynamics

The manifestation of the temporal manifold at the level of membrane channel proteins, provides a unique opportunity to analyze the phenomenon in a reduced and physically well defined setting. What can we learn about the mechanism underlying the temporal manifold at this microscopic level? The first and most fundamental observation is that these channels undergo sharp transitions between uniquely defined conformations; these are widely known as channel “states”, and anyone familiar with traces of single channel recordings will accept that fact. Of the immense space of possible states within which ionic channel proteins operate, present day technology supports direct observation of only few states in sufficient resolution. In fact, in most cases that are relevant to our discussion, only two are observable: the *non-conductive* and the *conductive* states. The existence of all the other states is inferred by their impact on the statistics of transitions between the observable states. We have all reasons to assume that transitions between those other hidden states are also describable in terms of movements between well-defined configurations. This being the case, a Markovian architecture with an immense number of hidden states seems to me a most pragmatic choice to envision the underlying physics. This picture is supported by every bit of information revealed in studies of protein dynamics and structure. Let us go deeper into the biophysics of ionic channels. It will prove useful as a concrete example for the mechanistic nature of processes underlying the temporal manifold in biology.

Our discussion now focuses on ionic channels that participate in the generation of neural action potentials, but it is generalizable to other kinds of ionophores (channels and receptors). It is instructive to think of the space of channel states as being composed of two subsets that are separated by a somewhat blurred margin. The *first* subset is small; it includes the conductive state and the few non-conductive states that are entailed by the canonical Hodgkin and Huxley formalism. This small subset is temporally compact in the sense that the involved states are strongly coupled by rapid transition rates with a characteristic time scale at the range of milliseconds. I refer to this subset as the *available set of states*; from anywhere within this subset, in the presence of an activator (membrane voltage or chemical ligand) channels may become conductive, and hence available for carrying ions and participating in the generation of membrane potential transients in general, and action potentials in particular. The structure and dynamics

underlying the key transitions within the set of available states are well-understood and thoroughly described in the literature over the past 20 years or so; they amount to the closest thing a biologist may hope for when seeking for *causal* relations between microscopic (protein level) physical constraints and macroscopic (action potential) lower temporal boundaries.

The *second* subset of states is temporally extended. This is the *unavailable set of states*; it is composed of an immense number of non-conductive states that are coupled by transition rates with time scales ranging from milliseconds to many minutes and beyond. It turns out that in the presence of an activator, most ionic channels of excitable membranes are pushed from the available set to the unavailable set as a function of their probability to be in the conductive state. In graph language, the conductive state of the available set may be viewed as a *node* through which the channel may connect to the unavailable set. Thus, with little poetic license, the following scene may be imagined: In the absence of an activator, the channel protein explores within the available set, residing mostly in non-conductive states. Enabled by the presence of an activator (membrane voltage or chemical ligand), the probability of the channel to change to the conductive state, still in the available set, increases. Once in the conductive state, the path to the unavailable set is unfolded; the channel eventually takes this path. When the activator disappears, the probability per time unit of the channel to flow back from the unavailable into the available set increases. This latter probability, often called “recovery” rate, translates to a timescale that we have referred to as τ_r in Section 5.2.

In an elegant theoretical study (Millhauser et al., 1988a,b), Glenn Millhauser and colleagues have postulated that the immensity of the unavailable set, when considered in terms of extended chains of Markov processes, gives rise to scale invariance of τ_r . Fluctuation and relaxation (dissipation) experiments under well controlled conditions corroborate this postulate (Liebovitch et al., 1987; Liebovitch and Tóth, 1990; Marom, 1998; Toib et al., 1998; Melamed-Frank and Marom, 1999; Ellerkmann et al., 2001; Manevitz and Marom, 2002; Jones, 2006; Uebachs et al., 2006). Furthermore, numerical analyses suggest that the minimal number of states, within the unavailable set, that is required in order to produce *effectively* scale invariant kinetics is surprisingly small (Marom, 1998; Lowen et al., 1999; Lundstrom et al., 2008; Marom, 2009). The nice thing about the result of Millhauser and his colleagues is that it ties together the temporal manifold phenomenon to modern views of protein dynamics, without forcing us to abandon the pragmatism of the Markovian architecture: proteins are known to exist in an immense space of possible states, few of which are stable, and fewer are “active” (e.g. conducting ions, affecting the surroundings). This is sufficient to account for well defined lower temporal boundaries, with invariance at slower temporal ranges.

7.2. Entailed dimensionality of all too concrete models

Note the following two critical points, entailed by the above picture: (i) nested within the cellular milieu, the “lonesome” channel (or receptor) protein is under chemical modulation at various timescales; consider, for instance, the many documented effects of phosphorylation, acidity, calcium or magnesium concentrations, to name but a few. In the picture drawn above, these modulations are translatable to added states and rates in the available and unavailable sets. Viewed as such, these modulations cannot be put aside in endeavors to construct timescale based models, especially if long term dynamics are intended. On the other hand, when considered in terms of added states and rates, these modulations make timescale based models combinatorially large. (ii) Molecular and genetic analyses show that the number of

different proteins that function as conducting paths for a single ionic species can be large. The case of potassium channel proteins is remarkable; around 100 different genes coding for these channels were identified so far. Many of these gene products operate in different ranges of lower temporal boundaries. Moreover, any one given channel is built of subunits that may be contributed by products of different genes. There are also “channel auxiliary subunits” that contribute to temporal lower boundaries. Of course, all these dimensions may be translated to states and rates that are embedded in the available and unavailable sets. But what can one say about the timescales of potassium conductance in a given neuron, when its membrane contains such a multitude of ionophores that operate as potassium channels? Ten states or less are sufficient to produce an effective scale invariance; the combinatorics mentioned here amounts to a practically countless number of states.

Not everyone is panicked by the above entailed dimensionality. We have already mentioned (Section 5.2) the tendency in recent years, to model neuronal excitability by accounting for all possible measurable variables and parameters. The measurement techniques become increasingly precise, computers become increasingly strong, and as pointed out elsewhere (Marom, 2009), the present state-of-the-art brings to mind Borges’ comment on naive reductionism.¹⁶ But there are alternatives to this infinite regress approach. We do not have to detail ourselves to death like Ireneo Funes, “the Memorious”¹⁷ whose world was filled with an ever-growing immense set of contiguous particulars. For “To think is to Ignore (or forget) Differences, to Generalize, to Abstract”.¹⁸ As shown below, much work can and needs to be done in that direction *vis-à-vis* behavior and neural timescales.

7.3. Lessons from abstracted approaches

Within the standard elementary reaction $x \rightleftharpoons y$ picture, the rates α and β are defined by the differential equation: $dx/dt = -\alpha x + \beta y$, leading to exponential relaxation with a uniquely defined timescale, $1/(\alpha + \beta)$. In biology, these reaction rates, which are also called rate “constants”, are usually not really constant. Rather, they are under modulation of a system variable that is not entailed by anything within the $x \rightleftharpoons y$ reaction; if the modulator is kept constant, the rates α and β are also assumed constant. Indeed, the dependencies of reaction rates on modulating system variables are routinely used as means to couple between elementary reactions and the dynamics of the larger system. The upshot of the temporal manifold, however, is that even when the modulating system variables are kept constant, α and β change as complex functions of the time spent in x and y , respectively. This is what we take from the power-law of forgetting and other psychophysical performance measures at the behavioral level, all the way down to reaction rates at the level of single membrane proteins (channels and receptors). Thus, in essence, the question that a modeler has to deal with, when attempting formulation of the temporal manifold is: How to impart time (history) dependence upon a reaction rate in and by itself; that is - no external modulator may be used for controlling the value of the reaction rate. In Rosen’s language, the issue at hand boils down to entailing α and (or) β from within the $x \rightleftharpoons y$ process (Rosen, 1991).

I find it useful to group the approaches that have been applied in that context in two classes: *constant-rates* and *scaled-rates*. The two classes of abstract approaches qualitatively differ in the domain to

which the manifold is imparted, that is - spatial (*constant-rates*) or temporal (*scaled-rates*), representing two antipode solutions to the problem in a time-space tradeoff: Consider the $x \rightarrow y$ reaction. If one insists on using *constant* rates, the only way to enrich the temporal dynamics (without using an external modulator) is by subdividing state x to more distinct coupled entities. On the other hand, if one allows the reaction rate leading from $x \rightarrow y$ to change as a function of, for instance, time spent in x , options for complex temporal dynamics are unconstrained, without adding more states.

In fact, the *constant-rates* approach follows the logic of the exponent spook (see Section 3) in order to generate a temporal manifold by adding states. Note that the idea here is not to incorporate states that represent actual spatial configurations of the natural system; this is what those interested in concrete all-encompassing timescale based models aim at (see Section 7.2). Rather, the idea is to design a model, composed of a minimal number of states (coupled by constant reaction rates), that is capable of producing an *effective* temporal manifold. The approach relies on the generalized lesson taken from protein dynamics, where the temporal manifold, observed in fluctuation analyses or relaxation experiments, emerges from a multitude of system states. While the *constant-rates* model may be concretized in idioms of different (but related) conceptual frameworks (for instance, multiscaled randomness (Hausdorff and Peng, 1996), multiple independent autoregressive processes (Granger, 2001), Markov chains (Millhauser et al., 1988a,b; Liebovitch, 1989; Nadler et al., 1996; Manevitz and Marom, 2002; Gilboa et al., 2005), distributed relaxation process (Thorson and Biederman-Thorson, 1974)), to name but few, the abstract picture is similar: history of activity is encoded in terms of coordinates in a space of states. In that picture, observed timescales reflect the distance between the present system’s state and a given functional state; a distance that may be expressed in terms of (e.g.) energy or number of transitions from the present state to the functional state.

Using various realizations of the *constant-rates* approach, researchers reconstructed the temporal manifold in an impressive array of model systems, at different levels of organization: For instance, Lowen et al. (1999) extended the microscopic version of the Hodgkin and Huxley formalism to account for the temporal manifold of neuronal spike times; they did that by elongating the chain of non-conductive states of the individual channel. They show that a macroscopic temporal manifold emerges, in the statistics of spike times, which is absolutely impossible if the temporal manifold at the microscopic channel level is not taken into account. Others (Soen and Braun, 2000; Gilboa et al., 2005; Drew and Abbott, 2006) took a similar path, albeit in a more abstract fashion, to analyze non-exponential history dependent spiking dynamics. Fairhall and colleagues (2008) have used a *constant-rates* model to account for adaptation in neocortical neurons; the timescale of adaptation in these neurons depends on the timescale of changes in stimulus statistics. They show that this temporal manifold may be reconstructed using a *constant-rates* model with only few states, provided that the rate constants are properly adjusted. Moreover, following the footsteps of Chapman and Smith (1963), Fairhall and colleagues pointed to the fractional nature of adaptation thus considered, suggesting that the firing rate of a neuron may encode the history of slowly varying input by means of fractional order differentiation, weighing the history using a function that decays as a power law in time. French and Torokkeli (2008) also arrive at a conclusion that the temporal manifold of adaptation may be reconstructed using a *constant-rates* model with properly adjusted few states. They have reconstructed the temporal manifold of adaptation by accounting for multiple timescales of channel activity in mechanoreceptor neurons. There are many examples for implementation of *constant-rates* models at the more macroscopic

¹⁶ “On Exactitude in Science”, J. L. Borges, *A Universal History of Infamy*, Penguin Books, London, 1975; translated by Norman Thomas de Giovanni

¹⁷ “Funes, His Memory”, J. L. Borges, *Collected Fictions*, Penguin Books, London, 1998; translated by Andrew Hurley.

¹⁸ See footnote 17.

level. For instance, Kelso's group have used the *constant-rates* approach to model, in terms of multiple autoregressive processes, the statistics of timing errors in human coordination (Ding et al., 2002); Anderson (2001) have used a *constant-rates* model in order to reconstruct the rate of forgetting in saving experiments.

In contrast to the *constant-rates* approach, *scaled-rates* models express the temporal manifold in non-Markovian terms, where past activity is registered by changes in the rates themselves. Given an elementary process $x \rightarrow y$, the *scaled-rates* approach formulates the transition rate from x to y as $\alpha(\tau)$, a function of the residency time (τ) in x . Some biophysicists are vexed when seeing the term “non-Markovian” in print. Note, however, that at this point we are not interested anymore in the underlying mechanism of the temporal manifold, phrased in an over-reduced manner; I would hope that our discussion above (Section 7.1) made that point clear. Instead, we are interested in how the manifold may be expressed in biophysical models. In that context, the term “non-Markovian” is figurative, designating a high-level approach to describe a microscopic process that might as well be Markovian, or not.

Lowen and his colleagues incorporated the temporal manifold into models of membrane excitability using the *scaled-rates* approach. They rephrased the FitzHugh planar representation of the Hodgkin and Huxley formalism by imparting dynamics onto the rate “constants” that govern the state transitions (Lowen et al., 1999). Specifically, they have used a power-law form to describe rate retardation as a function of τ , reconstituting a whole range of temporal manifold manifestations that were previously documented in neuronal measurements; these include broad inter spike interval histograms, firing rate estimates, power spectral density of spike counts and scaling of spike count correlations over different timescales. Drew and Abbott took an even more abstracted path to realize the temporal manifold in a *scaled-rates* model (Drew and Abbott, 2006). They have reasoned a linear system with a stimulus $s(t)$ leading to response $r(t)$ that is modulated by a subtractive feedback $I(t)$ such that $r(t) = s(t) - I(t)$. The subtractive feedback $I(t)$ is a power-law integrator of the output. Doing so, Drew and Abbott reconstructed a power-law adaptation in response to constant, pulsed and oscillating inputs. Furthermore, they were able to model the temporal manifold of a larger-scale psychophysical sensory phenomenon—the tilt aftereffect, a scale invariant recovery process from the impacts of an observed image on the perception of the image that follows (Greenlee and Magnussen, 1987).

One good reason to bother with formulation of an abstract model is the hope that it leads up to a mathematical construct that dramatically reduces the dimensionality of the problem at hand. This, in turn, allows for analyses and uncovering of principles that are otherwise masked by the details. Indeed, the contribution of low-dimensional abstractions to deep understanding of dynamical systems in general, and aspects of neural sciences in particular, is indispensable. Fitzhugh's planar representation of the Hodgkin and Huxley high-dimensional model (Fitzhugh, 1961) is a most lucid example to the power of this approach; its impact on present day understanding of the principles of neuronal excitability (as well as excitability in other types of cells) is immense. No doubt that the dimensionality of the above mentioned *constant-rates* and *scaled-rates* abstract models is significantly reduced compared to “realistic” models of the kind described in Section 7.2. Yet, so far, abstract models were used as means for reconstruction of the temporal manifold phenomenon in a mathematical language, rather than means for in-depth analyses. As I read it, this state of art reflects (at least partly) the lack of mapping to a comprehensive and mathematically solid theoretical framework that caters to analysis of the temporal manifold in behavioral and brain sciences; *a framework that lets temporal scales be entailed by (rather than*

entailing the) dynamics of the system and its interactions with environmental constraints.

Surely, the temporal manifold is a phenomenon that characterizes behavior in a wide range of animate and physical systems; it is by no means unique to behavioral and brain sciences. Can the temporal manifold in behavioral and brain sciences be mapped to another domain of scientific discourse, where such analysis is more tenable? Biased as it may sound, I suggest that a step in that direction was made by pointing at the relations between elementary kinetics in abstract models of the temporal manifold and a standard model used in population dynamics. It turns out that the equation $dx/dt = k(\tau)(1-x)$, that describes a normalized population relaxation process $(1-x) \rightarrow x$ with a transition rate k that scales with the residency time in $(1-x)$, may be expressed in terms of a Logistic-like equation (Marom, 2009). Specifically, it translates to the form $dx/dt \propto (1-x)x^D$, where D is a measurable exponent of the power-law that describes the relations between duration (τ) of residency in $(1-x)$ and transition rate k ; that is $k \propto \tau^{-D}$. To be concrete, $(1-x)$ may represent a pool of items in memory (in which case D is the exponent of the power-law of forgetting; see Section 2.2); at the microscopic level, $(1-x)$ may represent, for instance, the pool of inactive channel proteins (in which case D is the scaling exponent of recovery from inactivation, see Section 5.2). More broadly speaking, D may be thought of as a measure of the complexity of the $(1-x)$ space. The possible connection to population dynamics opens up a whole range of theoretical opportunities for in-depth analysis of the temporal manifold and its interactions with environmental constraints, within a well-established mathematical biology field. This framework caters to analyses in the continuous and discrete time domains and in both elementary (i.e. a single pool of stored elements) and extended (i.e. coupled pools of stored elements) settings.

As a whole, the above reviewed collection of abstract approaches suggests that the temporal manifold is analyzable in terms of mathematically tenable reduced models; models that are based on a small number of experimentally measurable parameters, and with immediate physiological implications on our understanding of function within the temporal manifold. But there is a long way to go in refining present models of the temporal manifold, before meaningful insights on behavior and brain function are gained; insights that may advance us beyond overused sweeping statements on scale invariance of objects in the world that surrounds us and the “matching” invariance of adaptive brain processes.

8. A closing comment

The temporal manifold is a hallmark of behavior and neural activity throughout the range of organization levels, from psychophysics down to single neurons and single proteins: At each of these levels, above lower boundaries that are dictated by fairly well understood physical constraints, there seems to be no uniquely defined timescales that are inherent to the observed system, separable from each other in the boundaries. Rather, observed and reported timescales are the outcome of conditions imposed by the observer through the measuring procedure. This state of the art pulls the rug from under uniquely defined timescale based approaches to analyses of behavior and its underlying neural processes.

Yet, the concept of a uniquely defined timescale is so deeply rooted in the discipline, that for the impacts of the temporal manifold to be thoroughly analyzed, a substantial change in the way we think about an elementary process is required. This is not an easy task. Our reliance on (and search for) uniquely defined timescales in elementary biological processes is tied up with

reductionism, the Holy Grail of modern science. Indeed, the very idea of a process that cannot be reduced to a set of states and well defined transition rates (i.e. timescales), is difficult to digest. But the change will come; we do not have much choice, since every serious attempt to account for behavior and neural dynamics beyond the lower temporal boundaries, *must* consider the temporal manifold. Paradigms are wanted, in which timescales are measured, reported and interpreted as the outcome of the dynamics and the history of activity. Such paradigms are different in essence from most present day approaches in which timescales are enforced upon the system, either as experimental constraints or as parameters that are explicitly incorporated into the equations.

New and promising approaches to the temporal domain in behavioral and brain sciences do start to appear in recent years, phrased in terms borrowed from a range of physics and engineering frameworks, from control theory to complex graphs, non-linear systems and population dynamics. The list of questions that await answers is extensive and includes issues that span the whole range of neuroscience discourse, from development to object representation, adaptation and learning. Nevertheless, there is still a lot of work ahead. Some of it lies on desks of theorists, yet I strongly believe that the burden is mostly on us, experimentalists: We must change our experimental ways in order to uncover the temporal richness of the phenomena that we observe. This entails, mainly, widening temporal observation windows, and becoming more cognizant of the impacts of temporal experimental constraints on the numbers that we deliver at the end of the day. Moreover, we should be aware of (and study the) tradeoffs between scales at which biological mechanisms may be analyzed, and scales of behavioral relevance. *Complexity goes all the way down*; admittedly, this state of affairs is not so convenient for those invested in promoting simple stories. However, failing to acknowledge complexity to the marrow, failing “to Ignore (or forget) Differences, to Generalize, to [properly] Abstract”,¹⁹ may lead us (experimentalists), as well as our fellow theorists, into the quagmire of naive reductionism, inventing “. . . discrete structures further and further down in the scale of things, whole *raison d'être* is to be found entirely within ourselves” (Bridgman, 1927).

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¹⁹ “Funes, His Memory”, J. L. Borges, see footnote 18.

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