

Connecting neural dynamics and computation across spatial and temporal scales

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Abstract

Neural dynamics are remarkably diverse, even at the level of isolated neurons. How can we characterize these dynamics systematically, and begin to build theories of how they combine to determine collective dynamics and signal processing in networks? Here we review a general approach of characterizing complex, nonlinear dynamics of neurons in terms of filters that describe how neurons transform their inputs into spike trains, with an emphasis on findings from cortex and thalamus. This reveals distinct “prototypes” of neural dynamics with different computational roles. We then review general results on how computational differences at the single neuron level can drive distinct patterns of collective dynamics and collective signal processing in networks.

Keywords: computational neuroscience, modeling, neural coding, adaptation, dynamical systems, bursting, statistical models

From conductances to computation

Biophysical modeling, starting from the pioneering work of Hodgkin and Huxley (Hodgkin and Huxley, 1952), aims to derive differential equations that describe the dynamics of voltage variations in response to current inputs. These equations incorporate the dynamics of activation and inactivation of the multiple types of ion channels that a neuron contains; in the relatively simple case of the Hodgkin-Huxley model, this includes activation of potassium channels and activation and inactivation of sodium channels. While this powerful modeling approach has helped to delineate quantitatively how different ion channel types contribute to the behavior of neurons, the transformation from current input to voltage or spiking output is expressed in a very complex and often non-intuitive way through the nonlinear interactions of a potentially large number of dynamical variables. It is further often notoriously difficult to precisely fit such a model to data. Computational approaches have addressed these issues in two ways. First, one can develop simpler dynamical models with fewer degrees of freedom-- or lower dimensionality-- that capture the essence of the behavior of the full system. Second, one can use data-driven approaches to extract statistical models for how the system transforms its inputs to outputs (Aljadeff et al., 2016; Kass et al., 2018). This latter type of model captures the coding properties of the neuron by explicitly expressing the features of the input that are associated with neural firing. Ideally, one hopes to connect such a coding model to the underlying biophysical mechanisms.

Determining models for computation

A key ingredient of a model that expresses the effective computation of a neuron or circuit is its *filter*. To describe this, consider the system receiving an arbitrary time-varying input, $I(t)$, and producing an output as a series of action potentials. If a neural system were purely linear, one would be able to express the resulting voltage as the convolution of this input with a filter, or kernel, $k(t)$:

$$V(t) = V(0) + \int_0^t k(\tau)I(t - \tau)d\tau. \quad (1)$$

Spiking neurons are clearly not linear as they produce action potentials. However, one can still make use of the linear filtering concept by characterizing the stimulus that drives the system toward an action potential in terms of an effective kernel. In this case, the firing rate $r(t)$ can be expressed as a function of the input analogously to (2):

$$r(t) \approx r_0 + \bar{r} \int_0^t k(\tau)I(t - \tau)d\tau, \quad (2)$$

where $\bar{r}$ sets the scale of the stimulus-driven variations. The kernel or filter $k(t)$ in this expression can be found using a method called reverse correlation. If the system is driven by a randomly varying input that samples a wide variety of possible inputs (typically Gaussian white noise), one can compute the *spike-triggered average* by averaging the stimulus segments preceding a spike over trials, resulting in a time-varying function $k(t)$, Figure 1A. In general, the linear approximation of Eq.(2) is insufficient to provide a good approximation to the firing rate as it cannot capture neural dynamics such as rectification (firing rates cannot be negative) and saturation (firing rates cannot increase arbitrarily with the size of the input). As a fix, one can incorporate a nonlinearity into this description:

$$r(t) \approx \bar{r} g(k * I(t)), \quad (3)$$

where we will use the following shorthand for convolution:

$$k * I(t) = \int_0^t k(\tau) I(t - \tau) d\tau.$$

Here $g(\cdot)$ is a nonlinear function, the mean rate $\bar{r}$ again sets an overall scale, and we from now on consider $r(t)$ relative to the baseline rate r_0 for simplicity. In Eq.(3), one can regard the filter k as a "feature" of the input to which the system is sensitive, extracting some important component of the input, s , by convolution: $s(t) = k * I(t)$. The function g then acts as a "threshold" or more general input/output function that mediates the sensitivity of firing to that stimulus component.

This well-known formulation is known as a "linear/nonlinear" (LN) model, Figure 1B,C, and has been used to characterize many neural systems. While very powerful and general, the model of Eq.(3) has several shortcomings that limit the accuracy with which it can represent the behavior of neurons. The first is that while one observes spiking through voltage fluctuations, this is just one observable of a high dimensional set of dynamical conductance variables, as we discussed for the Hodgkin-Huxley system. Thus one might expect that the linear kernel k that governs the approach of the system to spiking threshold needs to take into account the contributions of those unobserved variables in bringing a neuron to threshold. This can be done by allowing the kernel to have more than one dimension. A convenient way to estimate these additional driving factors of the input is to characterize the set, or ensemble, of stimuli that triggers spikes in more detail. So far we have used only the average; if we also consider the covariance of these stimulus samples, we can derive a set of features from the principal components of the set of spike-triggering stimuli that are most predictive of spikes, Figure 1A,C. This is known as *spike-triggered covariance* (STC) analysis, where one computes the covariance matrix of the set of spike-triggering stimuli. The eigenvectors of this matrix whose corresponding variance is most different from that of non-spike-triggering stimuli define a set of filters, k_1 to k_n , where the number n of relevant dimensions is hopefully small (typically ranging from 2 to 8 in published examples). This results in a model of the form

$$r(t) \approx \bar{r}g(k_1 * I, k_2 * I, \dots, k_n * I), \quad (4)$$

a straightforward generalization of Eq.(3), Figure 1C.

The beauty of this approach is that one can now examine the form of the filters k_i and interpret them in terms of the computation that the circuit properties and biophysics of the neural system generates. For single neurons, three typical types of filters emerge. The most typical is a **leaky integrator**, Figure 2A. Such a filter sums over recent inputs but with a weight that decreases as one looks further into the past. This is the filter one would expect from a simple passive membrane RC circuit, the dynamics that form the basis for the leaky integrate-and-fire neuron model. Such a filter has a decay timescale τ that defines the window of integration of a neural system. To first approximation, cortical neurons are often well fit by such filters, with time constants on order of tens of milliseconds. Other specialized neuron types have very different time constants. For example, neurons in brainstem auditory sound localization circuits need to be extremely temporally precise in order to deliver temporally synchronous information arising from the two ears; such neurons have filters with time constants on the order of 1 or 2 milliseconds (Slee et al., 2005).

Another typical type of filter is a **differentiator**, Figure 2B. Such a filter takes inputs from the recent past, smoothed in a window of a certain size, and subtracts the weighted inputs from further back in time. Such a filter is therefore bimodal, with positive and negative lobes. It turns out that the Hodgkin-Huxley neuron is best described as a differentiator (Agüera y Arcas et al., 2003), meaning that *changes* in the input most reliably drive spiking.

A third type of filter is a **resonator** (Izhikevich, 2007), Figure 2C. Such a filter contains a fluctuation at a certain frequency; thus by computing the convolution between this filter and the input, one can find moments in time at which that frequency dominates. An example of this occurs in rat barrel cortex, where cortical neurons are sensitive to a certain frequency (Maravall et al., 2007). In this case, covariance analysis shows that there are two primary filters, essentially a sine wave and a cosine wave at the same frequency. These two filters are then nonlinearly combined to predict that firing occurs at an arbitrary phase in this cycle.

While we have discussed this approach primarily in terms of temporal variations in the stimuli driving neurons (which might be injected current, or whisker movement, or light intensity), these methods are easily generalized to other stimulus dimensions such as spatial structure for visual neurons (Rust et al., 2005) or frequency content (Theunissen et al., 2000), leading to spatial, spatiotemporal or spectrotemporal filters.

History dependence

While the filter-based models described above are powerful, synaptic inputs or applied stimuli are not the only determinants of spiking, as neuronal excitability at a given time is also critically

dependent on spiking history. At a minimum, this is due to refractoriness arising from the (de)inactivation and (de)activation dynamics of voltage-gated sodium and potassium channels. Functionally, the neuron cannot spike or will spike with lower probability immediately after an action potential, thus limiting the firing rate (absolute refractory period) and rendering the neuron less sensitive to additional inputs (relative refractory period). Longer timescale activity dependence arises from longer timescale channel dynamics, including the calcium-dependent activation of potassium channels controlling afterhyperpolarization (AHP) or slow inactivation of potassium and sodium channels. Inputs can also trigger persistent increases in excitability, e.g. through calcium dynamics that support intrinsic bursting or NMDA plateau potentials (see, e.g. chapters by Budde in Section 2 and by Palmer in Section 3).

Such history-dependent behavior cannot be captured in the purely feedforward, stimulus-selective models of Eqs.(1-3). Instead, the instantaneous probability of spiking given presentation of an input stimulus must be modulated by a feedback term reflecting the neuron's internal state. Without such a representation, feedforward models predict many "false positive" spikes and erroneously high output firing rates. Furthermore, neglecting interspike interactions influences the estimation of stimulus features (Agüera y Arcas et al., 2003; Mease et al., 2014b).

This issue can be addressed using the *generalized linear model* (GLM), Figure 1D, a widely used statistical model that incorporates multiple inputs using linear filters and combines them through a single nonlinear function. GLMs are often autoregressive, that is, one can include a filter that acts on the previous output of the system. In our context, one can define a spike history filter, $h(t)$, which filters the history of the system's activity and alters the probability of subsequent spiking accordingly. The history and stimulus filters are fit simultaneously in order to best capture both stimulus encoding and interspike interactions. Unlike the models described above, GLMs use a prespecified nonlinearity and are fit using maximum likelihood methods. An alternative method to capture history dependence is to include it in an LN model as an additional factor entering the nonlinearity that is calculated directly from the interspike interval distribution (Mease et al., 2014b). In this case, the probability of spiking at any given time is a function of both the stimulus components $s_1, \dots, s_n$ and the time to last spike.

Diverse computations across cell types

Neurons across the brain differ considerably in terms of the synaptic receptor types with which they are driven and the ion channels that they express, leading to distinct dynamics of excitation and post-stimulus refractoriness. While one could model these differences using complete sets of differential equations describing channel dynamics in the Hodgkin-Huxley formalism, one can also use the methods as we have discussed to analyze the effective computations of neurons, and to attempt to link these computational differences to underlying biophysical and circuit mechanisms.

GLMs incorporating stimulus and spike-history selectivity can capture a diverse range of dynamical behaviors realized by neurons. Izhikevich (Izhikevich, 2007) showed that one can simulate a wide range of firing properties using dynamical models consisting of just 2 variables, an equation for the voltage incorporating an intrinsic nonlinearity combined with a threshold to approximate the generation of a spike, along with a feedback variable that provides history dependence:

$$\begin{aligned}\frac{dV}{dt} &= -aV + bV^2 - cW + I(t), \\ \frac{dW}{dt} &= dV - eW,\end{aligned}\tag{5}$$

along with a reset condition on V and W once V exceeds some threshold. Different settings for the parameters a - e produce many firing behaviors including tonic, phasic, and burst spiking, and also bistable spiking initiated and terminated by brief inputs, resonance, and type I and II FI curves. GLMs are able to capture all of these regimes (Weber and Pillow, 2017). Moreover, simple changes to either $k(t)$ or $h(t)$ can shift neuronal dynamics between distinct dynamical regimes. The GLM fits are also able to capture the extremes of both highly precise spike timing and highly variable, i.e. “super-Poisson,” spike trains seen *in vivo*.

Closely related methods have recently been applied to the Allen Institute’s large-scale database of physiological responses sampled from many neuron types in mouse primary visual cortex, to extract cellular dynamics and cluster or categorize them (Teeter et al., 2018). This analysis found functional categories that overlapped with multiple genetically defined cell types. Thus inspired, statistical methods have recently been designed that are tailored to the problem of identifying cell types based on stimulus filters and spike-history filters, and to test hypotheses that there are indeed distinct clusters of these filters’ properties. These combine GLM model fitting with hierarchical clustering into a single “simultaneous” modeling step (Zdeblick et al., 2023).

Thalamic computation

Thalamic relay neurons are a fascinating example of how complex intrinsic encoding can be revealed in the LN framework. Due to the presence of both fast spike-generating currents as well as depolarizing currents with slow dynamics – the transient low-threshold calcium current I_T and the hyperpolarization activated cation current (HCN) - thalamic relay neurons show bistable behavior controlled by resting membrane potential (see Chapter by Budde in Section 2). In brief, the voltage-dependent (in)activation of I_T leads to bursting, a well-characterized hallmark of thalamic excitability. At mean hyperpolarized membrane potentials, depolarizing input evokes

transient, relatively stereotyped calcium plateaus or “low threshold spikes” that in turn are sufficient to bring the membrane potential near or above the voltage threshold for sodium channels, resulting in high-frequency bursts of sodium action potentials. However, after this brief period of depolarization, I_T inactivates, ending the burst of APs until the neuron remains at hyperpolarized membrane potential sufficient to deinactivate I_T . In contrast, during prolonged depolarization, I_T is largely unavailable and more regular, lower-frequency “tonic” spiking occurs. Within the LN framework, this complex burst-tonic behavior manifests in dramatic changes in filter shape reflecting the kinetics and voltage-dependencies of these currents (Samengo et al., 2013; Elijah et al., 2015; Mease et al., 2017; Zeldenrust et al., 2018).

In the case of neurons from the higher-order somatosensory thalamus in rodents, a particularly complex picture emerges (Mease et al., 2017). As Figure 2D illustrates, in tonic mode, the stimulus filter is narrow (~10 ms) with a largely integrating shape, reminiscent of filters measured for cortical neurons. However, in burst mode, the filter is elaborated into a compound waveform comprising 1) a much broader (~200 ms) biphasic, differentiator waveform, summed with 2) a very narrow (~3 ms) additional filter. The broad filter shape reflects the requirement for I_T to first be deinactivated (initial hyperpolarizing phase) in order to then activate with relatively slow kinetics (subsequent depolarizing phase); the relative contribution of each lobe depends on the mean membrane potential determined by the DC input. The similarity of slowly changing stimuli to this filter sets the size of the evoked calcium spike and concomitantly, the duration (~spike count) of each burst event. Most strikingly, the presence of the very narrow feature means that during burst mode, high-frequency stimuli can control the exact timing of spikes within a burst.

In sum, this complex arrangement of intrinsic properties allows higher-order thalamic neurons to simultaneously encode information with distinct timescales in burst onset time, burst duration, and interspike intervals within a burst. The driving excitatory inputs to these neurons are largely strong, precise projections from cortical layer 5 neurons suggested to carry information in a particularly dense code (see Chapter by Palmer in Section 3, Chapter by Mease and Groh, Section 4), integrated with several sources of inhibition and excitation on widely varying time scales (see Chapter by Acsady in Section 2). How intrinsic thalamic processing further sculpts and distributes these representations is not yet understood, but the multiple feature selectivity could allow information from distinct presynaptic sources to be combined at the single neuron level.

Computation on multiple timescales

As the discussion above has indicated, ion channel dynamics at the single neuron level as well as short and long-term synaptic plasticity imbue individual neurons and neural circuits with diverse computational properties that can span multiple timescales. One aspect of this is reflected in

alternate ways of describing a neuron's output: on one hand, neurons are often characterized in terms of their firing rate vs current input, or f-I curves, which quantify responses to the mean input; on the other, one may characterize the details of fluctuations that tend to trigger individual spikes as discussed above. In both cases, these descriptions depend on the statistics of the stimuli used to sample the model. The shape of f-I curves can be altered by the variance of noise added to the mean input (Chance et al., 2002; Higgs et al., 2006), while LN models are also influenced by the properties of the stimulus. In general, the computation of a neural system can be considered as nonstationary, depending intimately on the potentially time-varying statistics of the input and the history of its own recent behavior. This nonstationarity is often called *adaptation*, a term that incorporates a wide variety of phenomenology (Whitmire and Stanley, 2016; Weber and Fairhall, 2019; Weber et al., 2019).

A classic form of adaptation is a change in firing rate in response to a stimulus that is stepped to a new value and held fixed; generally the firing rate will show a rapid response to the change in the stimulus, then gradually relax toward a resting value. While this decay is regarded as an adaptation to a steady state input, a similar adaptation of firing rate also occurs in response to a change in the variance or contrast of an input. As the previous discussion will have made clear, such behavior is just one of several possibilities for systems in which the computation can be described through the temporal filters of Figures 1 and 2, in this case a differentiator, whereby a change in the stimulus drives a large response that then decays away.

One can also evaluate the effect of a change in stimulus condition by fitting an LN model of the system, which, as discussed above, describes how the instantaneous firing rate depends on the recent stimulus input. In many systems, the properties of the LN model, both the filter/s and the nonlinearity, depend on the statistical properties of the input—its mean, variance/contrast, or even higher order properties of the stimulus such as correlation structure (Hosoya et al., 2005; Sharpee et al., 2006), Figure 3A,B. These changes may be almost instantaneous, suggesting that they arise from intrinsic nonlinearity, or may take time to develop, suggesting changes in circuit wiring.

Gain modulation

Gain modulation refers to changes in the slope of an input/output function, which can be influenced by other properties of the input (Ferguson and Cardin, 2020). For example, as mentioned, the slope of an f-I curve may be changed by the variance of added noise (Chance et al., 2002; Higgs et al., 2006). In the LN model picture, the slope or offset of the nonlinear function g in Eq.(3) may depend on stimulus properties. Gain-scaling adaptation is a special case in which the nonlinearity g adapts to maintain the same dynamic range independent of the overall fluctuation range, σ , of the stimulus (Brenner et al., 2000), Figure 3B, which in general is time-varying (Fairhall et al., 2001). In this case, Eq.(3) above becomes

$$r(t) \approx \bar{r}g(s(t)/\sigma(t)), \quad (6)$$

where the filtered stimulus $s(t)$ is normalized by its local amplitude or envelope $\sigma(t)$. Such a coding scheme maintains the same information encoded per spiking event, regardless of the stimulus amplitude, preventing the system from saturating when the overall stimulus range is large, or of failing to resolve small fluctuations when the input “goes quiet”.

This property has been observed in several systems, including the fly H1 neuron (Brenner et al., 2000; Fairhall et al., 2001), the retina (Baccus and Meister, 2002), and barrel cortex (Maravall et al., 2007; Diaz-Quesada and Maravall, 2008). While it can arise as a circuit property, it can also emerge from quite simple mechanisms at the level of single neurons, according to the balance of voltage-gated sodium (Na_v) and potassium (K_v) channels. For example, in the Hodgkin-Huxley model, increasing the Na_v/K_v maximal conductance ratio both shifts selectivity from differentiation to integration (Lundstrom et al., 2008b) and supports gain-scaling behavior (Hong et al., 2008). In developing neurons in the mouse sensorimotor cortex, gain scaling emerges as a function of the Na_v/K_v conductance ratio that increases with age until reaching a stable value: “young” neurons with low Na_v/K_v with limited spiking do not gain scale, while comparatively “mature” neurons with higher Na_v/K_v show gain scaling (Mease et al., 2013). This behavior can be reproduced using both conductance-based and exponential leaky integrate and fire models (Mease et al., 2013).

In the example of thalamic relay neurons described in the previous section, using reverse correlation to parse stimulus selectivity into coding channels with distinct timescales also reveals distinct adaptation motifs for each channel. While the slow encoding channel driving calcium low-threshold spikes is sensitive to global stimulus variance, the fast encoding channel driving timing of sodium APs within bursts shows gain-scaling behavior, i.e. sensitivity to high-frequency inputs adjusts according to overall stimulus gain (Mease et al., 2017). Thus, in burst mode, fluctuations matching the selectivity of the slow channel unlock a transient window of gain invariant encoding of fast inputs (see chapter by Mease and Groh in Section 4).

Long timescales of adaptation

While the model above demonstrates that one can capture time-varying instantaneous coding properties with an LN model with time-varying components, the mean firing rate also tracks the variations in stimulus conditions on long timescales, i.e. $\bar{r}(t)$ is some function F of the slow-varying mean or variance, e.g. $\bar{r}(t) = F(\sigma(t))$. Spike-frequency adaptation is an example of this, Figure 3C. It has long been observed that some neural systems adapt to step changes in input mean or variance with a multiple time constant or even power-law decay (Drew and Abbott, 2006; Pozzorini et al., 2013). Power law decay can be a reflection of another type of computation: fractional differentiation, observed in both fly visual neurons (Fairhall et al., 2000)

and cortical layer 5 sensorimotor neurons (Lundstrom et al., 2008a). This intriguing computation is a generalization of differentiation. While a differentiator responds only to change in the input, a fractional differentiator is a “soft” differentiator, giving an enhanced response to change, but settling to a steady state in response to a maintained input that has a unique value. The same operation also leads to a frequency-independent phase shift in response to a sinusoidal input. While first demonstrated *in vitro*, such a phase-shifted response was observed *in vivo* both in thalamic ventral posteromedial (VPM) nucleus and in layer 5 barrel cortical neurons responding to vibrissa motion (Maravall et al., 2007; Lundstrom et al., 2010). Cortical neurons showed a much larger phase shift, indicating that the vibrissa input may have been cascaded through multiple fractional differentiations in its passage through the neural circuitry.

Multiplexing

Thalamic neurons have been demonstrated to convey information in spike patterns (Reinagel and Reid, 2000). In particular, the two firing modes, tonic firing and bursting, shaped by the unique channel dynamics of thalamic neurons, have long been proposed to act as distinct channels of information transmission (Sherman and Guillery, 2002). As we have discussed, these two modes of firing are associated with different stimulus features, Figure 2D, and show distinct adaptation properties (Mease et al., 2017; Zeldenrust et al., 2018). The ability of neurons to communicate through multiple symbol types is a form of multiplexing, whereby the same channel can convey distinct types of information (Oswald et al., 2004; Alenda et al., 2010; Estebanez et al., 2012; Naud and Sprekeler, 2018). The concept of temporal multiplexing can also be applied to the adapting neural codes as described above. For example, one may have a neural response to a fast-varying signal modulated by an overall amplitude σ given by

$$r(t) = \bar{r}(\sigma(t))g(s/\sigma(t)), \quad (7)$$

whereby the slowly varying rate $\bar{r}$ encodes the envelope σ on slow timescales while fast variations drive individual spikes according to the normalized LN model, $g(s/\sigma)$, conveying information about different stimulus properties on different timescales (Alenda et al., 2010, Lundstrom et al., 2008a).

The sensitivity of thalamic firing properties and thus feature selectivity to a shift in the mean input, as discussed previously, provides a mechanism by which corticothalamic feedback (see (e.g. Chapter by Brown Section 5) and subsequent feedforward inhibition from thalamic reticular nucleus (Chapter by Pinault in Section 4) can dynamically modulate feedforward processing. Such feedback can control thalamic tonic/burst mode and adaptation to peripheral sensory inputs in a frequency-dependent manner (Mease et al., 2014a; Crandall et al., 2015), sharpen thalamic spatial and temporal receptive fields (Chapter by Briggs Section 4) and gate information transmission to cortex by controlling thalamic synchrony. Moreover, naturalistic patterns of corticothalamic

feedback increase dynamic range of input encoding by promoting interleaved tonic and bursting modes (Wolfart et al., 2005)

More generally, this intrinsic ability to sculpt feature selectivity based on mean input could contribute to network-level and behavioral effects linked to changes in thalamic excitability. For example, the enhancement of cortical sensory response precision by thalamic hyperpolarization which increases bursting (Borden et al., 2022), and conversely, locus coeruleus' neuromodulatory boosting of thalamic tonic spiking, which enhances sensory coding and discrimination (Rodenkirch et al., 2019).

The generation of spike patterns in response to inputs is a combination of channel, synaptic and circuit mechanisms that span milliseconds to seconds. While it is sometimes possible to separate the timescales of short fluctuations and slower timescale variations in statistical properties such as mean or variance in order to write down models such as Eq.(7), more generally one might consider adaptive dynamics to simply encode stimulus variations on slower timescales, as in the case of fractional differentiation, which can modulate fast encoding (Weber and Fairhall, 2019). One approach to capture encoding on multiple timescales is to fit filters that span a wide range of temporal scales. This analysis has been performed using intracellular recordings from cortical neurons from three different sensory areas, visual, somatosensory and auditory cortices (Latimer et al., 2019). By using a random sequence of punctate stimuli, responses were fit using multidimensional GLMs in which filter outputs were combined nonlinearly. This method extracted a set of filters that spanned an order of magnitude in time, from short filters describing local features to filters integrating over almost a second of stimulus history, making explicit how long timescale stimulus statistics modulate spike rates. These methods could be generalized to model how combinations of feedforward and feedback inputs dynamically influence information processing.

Computation from dynamics

To relate neurons' computational properties to the underlying biophysical mechanisms, one would like to be able to derive filters directly from the underlying dynamical equations. In the case in which the underlying equations are themselves linear, as for, e.g., resistor-capacitor circuit models of dendritic trees or cell bodies, this process is direct: the equations can be solved explicitly in terms of a filter that exactly describes responses to inputs (Gabbiani and Cox, 2010). For nonlinear, spiking neurons, the observed voltage is only one of many underlying dynamical variables that interact nonlinearly to contribute to excitation. Thus, the filter of a linear/nonlinear model arises as a linearized approximation to the nonlinear dynamics that drive the voltage to threshold (Agüera y Arcas et al., 2003). The filter is therefore modulatable according to the regime in which the system is operating (Famulare and Fairhall, 2010) -- for example, as a DC input shifts the mean subthreshold voltage, as shown above for thalamic neurons (Figure 2D), or an increased input variance explores a different range of the

subthreshold dynamics (Hong et al., 2007). It should also not be surprising that the probability of firing can often be better accounted for by contributions from multiple stimulus filters that help to capture the influence of unobserved activation and inactivation variables (Agüera y Arcas et al., 2003; Hong et al., 2007). For some simplified model neurons, analytical expressions for the mean firing properties can be derived which allow one to directly link the filtering properties of the model neuron with the parameters of its dynamical equations (Hong et al., 2007; Famulare and Fairhall, 2010) (Brunel et al., 2001) (Lindner et al., 2005; Trousdale et al., 2012).

From computation in neurons to computation in networks

How do the dynamical properties of single cells scale up to describe how signals are processed across neural networks? Here, we review modeling and theoretical approaches to this problem. These reveal how distinct dynamics, expressed in terms of input-output filters of single cells, drive distinct dynamics at the network level – and how connectivity can systematically reshape neuronal dynamics to tune signal processing at the network level.

Many modeling studies have addressed the question of information propagation in feedforward networks, Figure 4a, in which neurons in the first layer are driven with a signal which then flows through the network. The nature of single neuron coding in individual layers strongly influences the network output, including the synchrony of firing in subsequent layers (Vogels and Abbott, 2005; Ratté et al., 2013), and the ability of the network to transmit different timescales of input drive through multiple layers (van Rossum et al., 2002; Lundstrom et al., 2010; Gjorgjieva et al., 2014). For example, without the gain scaling properties described above, single neurons are relatively insensitive to the rapid fluctuations local to each neuron and tend to fire synchronously to common large amplitude inputs (van Rossum et al., 2002; Lundstrom et al., 2010; Gjorgjieva et al., 2014). With gain scaling, each neuron becomes sensitive to fast input fluctuations, efficiently conveying local information but losing the ability to transmit slowly varying population-wide input variations as the signal propagates through the network (Figure 4b).

Next, we describe a general approach to understanding signal processing in recurrent neural networks. Once again, we begin with the most basic approximation of individual neurons above, in which they are described by linear (or linearized) input-output filters. These individual neurons may produce outputs described as either continuous rates, or as spikes emitted stochastically according to these rates (Sejnowski, 1976; Lindner et al., 2005; Ostojic and Brunel, 2011; Trousdale et al., 2012). Specifically, as illustrated in Figure 4c, we ask: when such a network receives an input signal $I(t)$, how do its single neuron properties – the filters $k(t)$ – combine with recurrent reverberations of neural outputs according to a connectivity matrix W to produce the network wide response $R(t)$?

The general answer to this question may be expressed in an exact mathematical form (Sejnowski, 1976; Lindner et al., 2005; Ostojic and Brunel, 2011; Trousdale et al., 2012; Ocker et al., 2017). However, the range of possibilities at first appears very complicated to parse, because there are so many possible connectivities W (Pernice et al., 2011; Trousdale et al., 2012; Hu et al., 2014; Ocker et al., 2017). However, it turns out that the impact of a general connectivity matrix on a network's signal processing can often be accurately summarized through a surprisingly small and simple set of connectivity features, or "motifs." These features, illustrated in Figure 4d, begin with the probability that any cell pair is connected. The next motif is the "excess" probability that any chain of three cells is connected, over and above what we would estimate from the connection probability of cell pairs. The next is the excess probability that any chain of four cells is connected, and so forth. These chain motifs define pathways for reverberations of various lengths through the network, and, in the simplest settings, give a complete description of network signal processing through a set of reverberant loops, as schematized in Figure 4E (Hu et al., 2018). The strengths of these loops, in turn, determine whether a network might produce a more vs. less oscillatory response to a network input – or, equivalently, might be selective for a more vs. less oscillatory form of this input (Figure 4F).

While this motif-based approach is attractive in how it simplifies analysis of vast set of possible network configurations, and how it applies to many other metrics of network response beyond that shown above (Pernice et al., 2011; Roxin, 2011; Hu et al., 2014; Martí et al., 2018; Recanatesi et al., 2019), it is part of a much wider landscape of analytical and computational techniques for network dynamics. We highlight in particular the textbook *Mathematical Foundations in Neuroscience* (Bard Ermentrout and Terman, 2010) which, among many others, treats methods that describe the emergence of oscillations using nonlinear methods which profoundly extend the assumptions above.

Recent large-scale realistic modeling efforts incorporating detailed morphological and physiological properties from thalamocortical circuits, e.g. from the Human Brain Project and as described in the chapter by Oberlaender in Section 3, suggest exciting ways to test and expand upon these principles.

Conclusion

Here we have surveyed how computational methods allow us to determine how biophysical properties of neurons influence the fundamental ways in which they respond to their inputs. These methods reveal a range of response types: integrators, which sum inputs over time; differentiators, which identify changes in these inputs; and resonators, which pick out oscillatory features in these inputs. Each of these subserves different computations that are important for thalamocortical processing. Integrators accumulate signals over long timescales. Differentiators can enhance selectivity to coincident, punctate inputs, over and above steadier background inputs

– a major focus of the chapter by Stanley in Section 11. Resonances in single cells interact with feedback delays and synaptic dynamics in networks to produce network-wide oscillations, as developed in detail in the chapter by Golden and Bazhenov in Section 11. The complex thalamic filters act to differentiate slow-varying inputs, but also allow fast fluctuations to precisely control the timing of spikes within a burst, as discussed in the chapter by Mease and Groh in Section 4. The overall shape of stimulus filters, and how this is matched to the temporal statistics of input stimuli, determines whether and when neurons reformat these inputs to spike rates that maximize transmitted information, as described in the chapter by Hirsch and Sommer in Section 11.

Importantly, the mapping of stimuli to responses, even in individual neurons, should not be viewed as a fixed process, but rather as a continuously evolving one, changing in response to the sensory environment as well as local circuit conditions. Above, we have described one fundamental way in which this occurs, via adaptation to stimulus statistics in the single neurons themselves, and discussed how stimulus variations on multiple timescales contribute to the system's probability of response. These factors are, once again, just the tip of the iceberg. Other chapters in this volume detail important impacts of long-term kinetics in synapses, which reshape inputs *en route* to neurons, and underlie important aspects of adaptation across thalamocortical networks. Additionally, modulatory inputs can combine with “driving” stimulus inputs to reshape overall input statistics and hence neural response processing. Neuromodulators broadcast throughout neural networks drive further changes in signal processing in the underlying neurons and networks. As many of the chapters in this section detail, computational methods have already illuminated many ways that these mechanisms can combine to shape thalamocortical processing, and as such have cast light on an exciting road ahead, as many more interactions remain to be discovered.

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Figure Legends

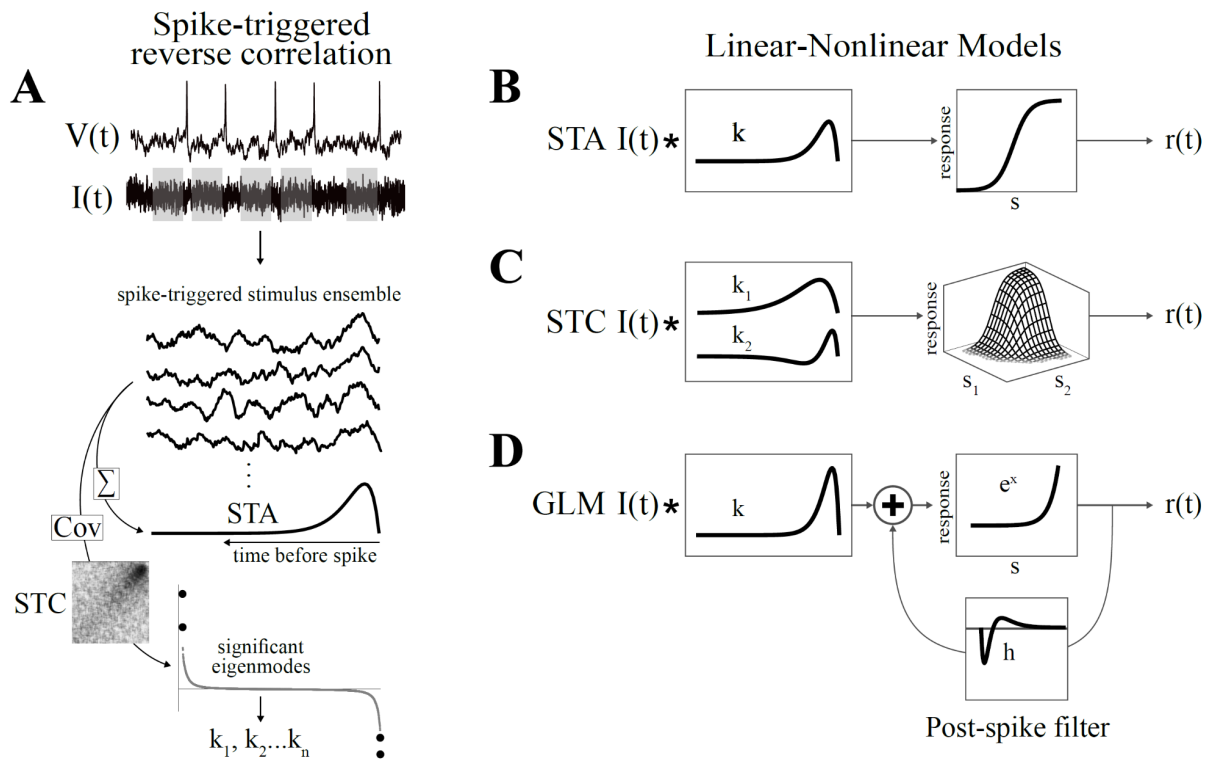


Figure 1. Cascade models for capturing neuronal computation and intrinsic encoding properties. A) Reverse correlation methods: the spike-triggered ensemble comprises the stimuli that precede spikes. From this ensemble one can determine the spike-triggered average (STA) or spike-triggered covariance (STC). B-D) Cascade models for capturing neuronal dynamics and intrinsic encoding properties. B) One-dimensional STA model, with a single linear filter k and a nonlinear function relating the filtered stimulus $s = k \star I$ to the firing output C) n-dimensional model using multiple filters derived from covariance analysis D) GLM point process model in which the filtered stimulus is combined with the filtered spike history and then passed through a nonlinearity.

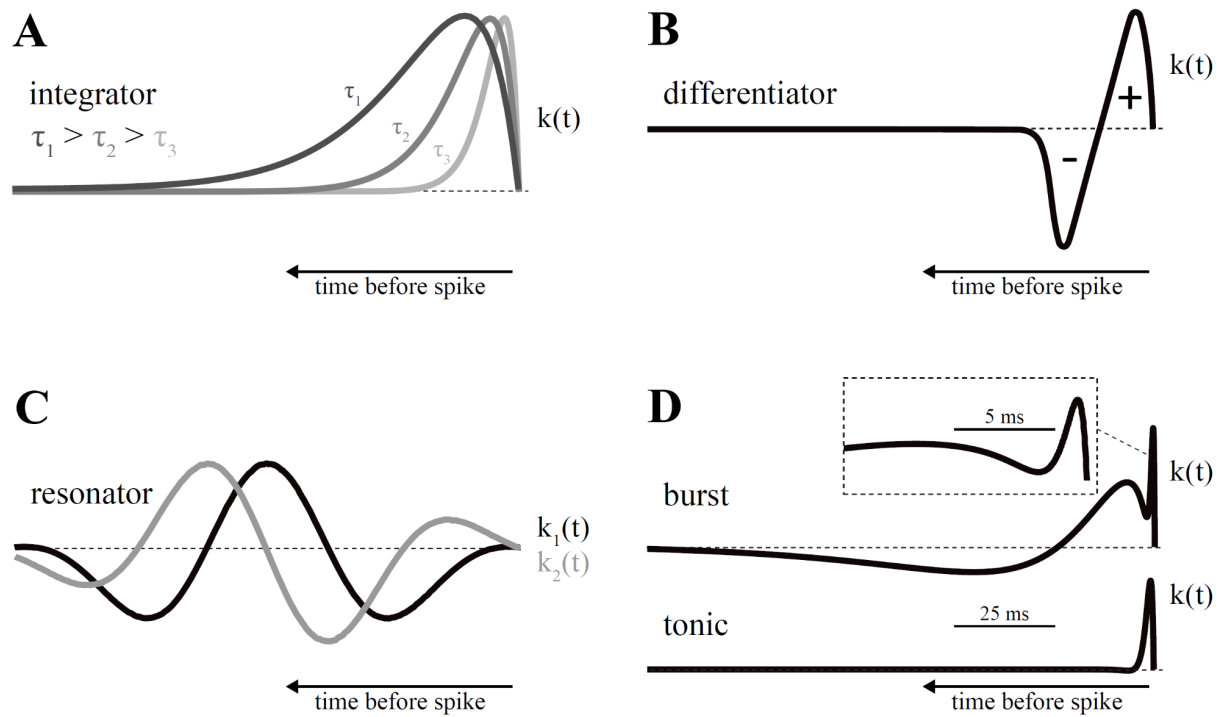


Figure 2. Prototypical stimulus filters for single-neuron feature selectivity. A) Integrators with different time constants. B) A differentiator is a bimodal filter. C) A resonator is sensitive to a certain frequency. Such filters often appear in conjugate pairs (sine and cosine). D) Burst (upper) and tonic (lower) filters for thalamic relay neurons, modified from (Mease et al., 2017).

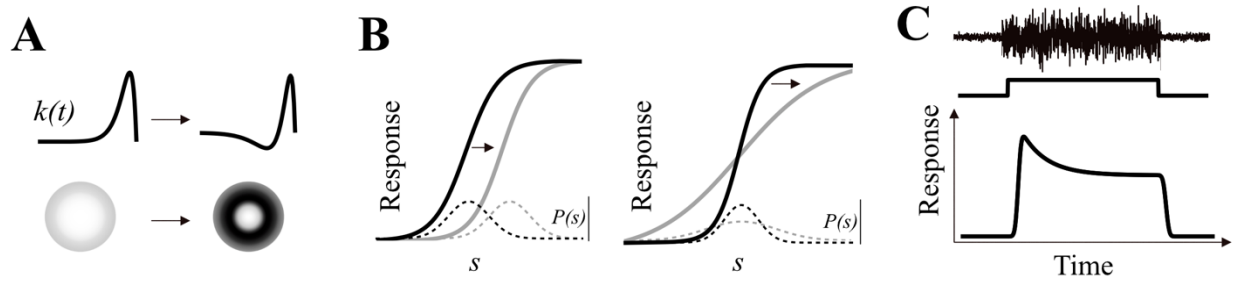


Figure 3. Multiple forms of adaptation. A) Adaptation in cascade models: filters may be changed by the statistics of the input. This can occur for temporal and spatial aspects of the filter. In this example, the filter transforms from integrating to differentiating. B) Adaptation in cascade models: the slope of the input/output relation between stimulus and response may change in offset, or in slope, ie undergo gain modulation. This often occurs in response to changes in the stimulus distribution, shown in dotted lines, where the stimulus distribution may change in mean (left) or variance (right). Such adaptation is a form of efficient coding whereby the system acts to maintain the same rate of information transmission about the new stimulus distribution. C) Spike-frequency adaptation. The firing rate in response to a step change in input often relaxes following the change, both to steps in mean input and in stimulus variance. In some systems, the changes in firing rate can be modeled as fractional differentiation, which acts as a filter on the envelope of the input.

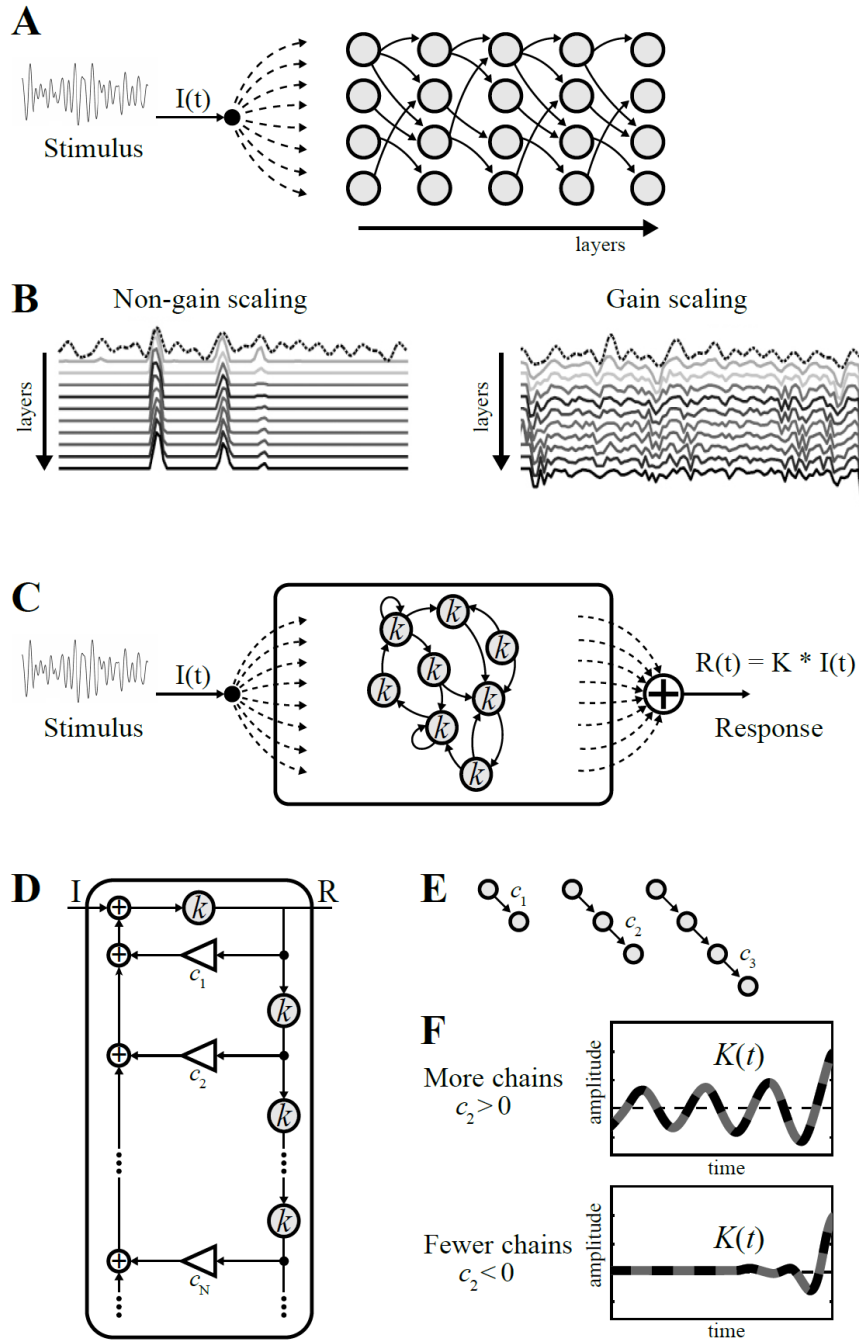


Figure 4. Network transformations. A) Schematic of a feedforward network receiving a stimulus $I(t)$. B) Propagation of signals through a multi-layer feedforward network. A time-varying input is injected into each neuron in the initial layer (dotted trace) but with independent noise added to each neuron. Depending on whether individual cells have gain-scaling or non-gain scaling properties, the network either reliably transmits the peaks of the original common input in a wave-like fashion, or loses the common signal in favor of faithfully propagating the noise fluctuations (or local signals). Adapted from Gjorgieva et al. (2014). C) Schematic of a recurrent network receiving a stimulus $I(t)$; here, individual cells have a stimulus filter k , and the

question is how the network as a whole reshapes these filters to produce a network-wide filter K : the response of the network as a whole is described by the convolution $R(t) = I * K(t)$. D) Network motifs: single connections among pairs of cells, with probability c_1 , length-two chains of connections with excess probability c_2 , and length-three chains of connections with excess probability c_3 . These excess probabilities are referred to as motif cumulants in the literature (Ocker et al., 2017). E) These motifs determine the strength of reverberant loops in the network-wide filter connecting stimulus and response. F) In networks with the same overall number (probability) but more vs. fewer chains can lead to more vs. fewer oscillatory network-wide stimulus filters $K(t)$. (Panels c-f modified from (Hu et al., 2018).)

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