Physics of Life Reviews 53 (2025) 281–293

Contents lists available at ScienceDirect

Physics of Life Reviews

journal homepage: www.elsevier.com/locate/plrev

Review

Physiological noise: a comprehensive review on informative randomness in neural systems ☆

Andrea Scarciglia [a,b,*], Claudio Bonanno [c], Gaetano Valenza [a,b,*]

[a] Department of Information Engineering, School of Engineering, University of Pisa, Italy
[b] Bioengineering and Robotics Research Center E. Piaggio, School of Engineering, University of Pisa, Italy
[c] Department of Mathematics, University of Pisa, Italy

ARTICLE INFO

Communicated by Jose Fernando Fontanari

Keywords:
Stochastic processes
Dynamic noise
Output noise
Kalman filter
Stochastic differential equations
Cardiovascular system
Neural activity
Noise estimation

ABSTRACT

Noise is often regarded as mere interference in the analysis of biomedical signals. Nonetheless, stochasticity plays a critical and informative role in the dynamics of complex systems, particularly in neurocardiovascular and neural systems. This review provides a comprehensive exploration on informative randomness in physiological contexts, tracing the evolution of noise research from its foundations on Brownian motion to its applications in neural systems, including the neuroautonomic regulation of cardiovascular dynamics. Key distinctions are made between output (measurement) noise and dynamic (intrinsic) noise, which directly influence the system behaviors at various levels. Several physiological noise identification techniques, such as stochastic differential equations, Bayesian methods, and Kalman filters, are evaluated in real-world scenarios. Special emphasis is placed on the role of physiological noise in multiscale neural systems, such as brain dynamics, neuronal communication, and heart-brain interactions, highlighting how it shapes complex functions. Furthermore, physiological noise is presented as a potential clinical biomarker, offering insights into the underlying structure and health of neural systems. Future research is encouraged to investigate multivariate noise estimation methods and their implications for understanding causality and systemic interactions in neurocardiovascular networks.

1. Introduction and key terminologies

Physiological systems, particularly those related to neural and cardiovascular functions, are often characterized by a degree of randomness that is intrinsic to their dynamics. Traditionally, noise has been viewed as an undesirable interference in the analysis of biomedical signals, but this perspective has evolved over time. Stochastic processes - random, time-dependent fluctuations - are now recognized as critical biological and physiological components that provide valuable insights into the underlying mechanisms of physiological systems.

☆ The research leading to these results has received partial funding by the European Commission Horizon 2020 research and innovation programme under grant agreement No. 101017727 of the project EXPERIENCE and by the Italian Ministry of Education and Research (MIUR) in the framework of the FoReLab project (Departments of Excellence).

* Corresponding authors at: Department of Information Engineering, School of Engineering, University of Pisa, Italy.
E-mail addresses: andrea.scarciglia@phd.unipi.it (A. Scarciglia), gaetano.valenza@unipi.it (G. Valenza).

https://doi.org/10.1016/j.plrev.2025.04.001
Received 9 April 2025; Accepted 10 April 2025

Available online 14 April 2025

This review aims to provide a comprehensive exploration and formal definition of physiological noise, emphasizing its informative role in neurocardiovascular and neural systems. In neurocardiovascular systems, for example, noise can reflect the intricate interplay between the autonomic nervous system's sympathetic and parasympathetic branches, which regulate heart rate and blood pressure. Similarly, in neural systems, noise can manifest in synaptic transmission and neuronal firing, contributing to variability in signal propagation and response.

1.1. Historical background of noise in complex systems

The concept of noise, intended as stochastic process, takes its roots in 1905, when Einstein *invented* it as a mathematical tool to prove the existence of atoms, revealing also the atom's simple complexity [1].

Before Einstein, scientists like Lavoisier, Dalton and Avogadro were trying to understand the behavior of chemical reactions through atoms theory, while Clausius, Maxwell and Boltzmann revolutionized the concept of heat, relating it to the kinetic energy of atoms as formulated in the thermodynamics as we know it today. The latter scientist, in particular, was the first to describe the collisions of atoms in gases introducing stochasticity and providing an equation where the probability density of position and velocity of the atoms evolves through time, irreversibly converging to a Maxwellian distribution.

In his work [2], Einstein predicted a Brownian motion, i.e. the random patterns of particles suspended in a medium (a liquid or a gas), as an observable phenomenon with the aim of proving the existence of atoms, by introducing stochastic components. He derived the governing probability distribution for the small Brownian particles, with a spread proportional to the square root of time, and he indicated how to measure Avogadro's number from a stochastic quantity. In particular, he recognized that the mean kinetic energy of the suspended particles is the same as the mean kinetic energy of the atoms.

Later, the mathematics behind Einstein's idea was simplified and generalized by the physicist Langevin [3], who gave birth to the field of stochastic differential equations becoming the first in history to use Newton's equations with a random force. In particular, he derived Einstein's equation for the description of the Brownian motion starting from the deterministic Newton's equations of a ball going through a fluid with a friction - the Stokes law - and adding another irregular, stochastic force due to the collisions of the surrounding molecules.

Other scientists like Smoluchowski, Ornstein, Rice, Wiener, Kolmogorov, Itô and Stratonovich have improved the mathematics of noisy processes, allowing the formal definition of differential equations contaminated by noise.

1.2. Key terminologies

To facilitate a clear understanding of this review, it is important to define several key terms used throughout the paper.

Random variable Z is a measurable function from the sample space Ω to the real numbers $\mathbb{R}$ (or in general to a measurable space). This function is responsible for the association of a numerical value with each outcome in Ω.

Stochastic or random processes: In probability theory, systems evolving over time that present uncertainty or randomness can be described through mathematical models called *stochastic or random processes*. These objects are indeed used for modeling phenomena where the future states are not fully determined by its initial state like the deterministic processes (see the Dynamical System definition below), but are influenced by probabilistic factors. More formally, a stochastic or random process is a collection of random variables $Z(\omega,t):\Omega\times\mathcal{I}\to\mathbb{R}$ defined on the same probability space $(\Omega,\mathcal{F},p)$. In this context, Ω is the space of realizations, $\mathcal{F}$ is the associated sigma-algebra, and p is the probability measure defined on the events space Ω. The index t represents the continuous time variable and belongs to the uncountable set $\mathcal{I}$, typically defined as an interval in $\mathbb{R}$. When time is discretized, the time index is denoted by a sample n, and $\mathcal{I}$ becomes a subset of $\mathbb{N}\cup\{0\}$. For a fixed $\bar{\omega}\in\Omega$, the function $Z(\bar{\omega},t):\mathcal{I}\to\mathbb{R}$ is called realization or sample path, which is a single outcome of a stochastic process - the same definition applies for discrete-time stochastic processes. Fig. 1 shows exemplary time-continuous and time-discrete stochastic processes.

Noise and Stochasticity: they refer to random fluctuations that can either obscure or reveal critical information about system behavior. Noise is often classified into two types: (1) *output noise*, which arises from measurement inaccuracies or environmental interference, and (2) *dynamic noise*, which is inherent to the system's internal processes and can influence its orbit over time.

Dynamical System (X,T,μ) is a triple formed by a set $X\subset\mathbb{R}^m$, called state or phase space, and a map $T:X\to X$ which defines the dynamics on X; μ is a probability measure on X which is preserved by the map T. For an initial state $x\in X$, the sequence of all its iterates through the map T represents an orbit of the systems.

Physiological Systems: In this review, physiological systems refer to complex biological systems, such as the cardiovascular system and neural networks, where noise plays an informative role in both normal and pathological processes. These systems exhibit nonlinear behavior and are often influenced by a combination of deterministic and stochastic factors.

Due to the ubiquitous presence of noise in various scientific fields, numerous studies have explored and investigated this topic from an application and/or methodological standpoint. The content of the following sections is based on the findings of selected papers retrieved from the *Scopus* database using the following queries:

1 ("dynamical noise" OR "dynamical noise levels") AND ("time series" OR "estimation" OR "quantification" OR "detection" OR "determination")
2 ("chaotic time series" OR "chaotic dynamical systems") AND ("noise level" OR "noise" OR "dynamical noise" OR "noise level estimation") AND ("estimating" OR "estimation" OR "determination" OR "quantification")
3 ("process noise covariance estimation" OR "process noise estimation")

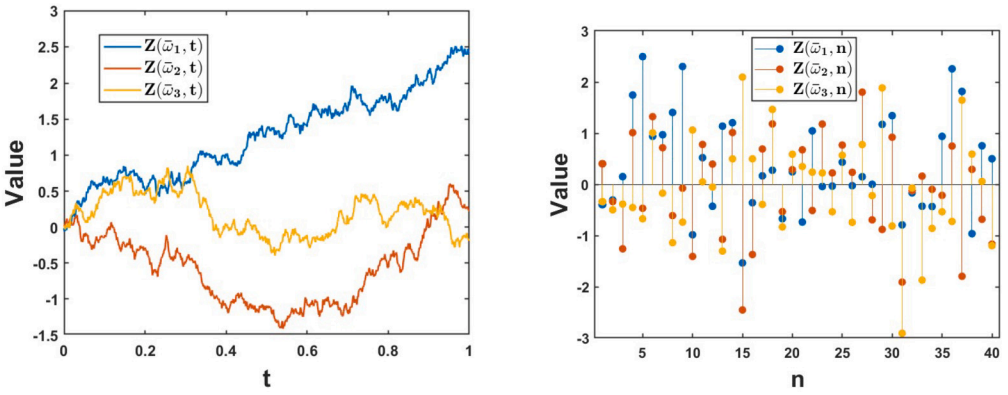

Fig. 1. Exemplary realizations of random processes. The left panel shows three realizations (depicted by different colors) of a continuous-time random variable, where the index set $\mathcal{I} = [0, 1]$; the right panel, instead, shows three exemplary realizations (denoted by different colors) of discrete-time random variables for 40 samples.

Subsequently, only papers published in journals were selected, excluding articles in which dynamical noise was not directly estimated or investigated.

2. Formal definition and types of noise in physiological systems

2.1. Noise as a stochastic process

Given that physiological data collection and analysis involve a sampling process, and for the sake of clarity, we will focus on discrete-time stochastic processes and dynamical systems. The time index is defined as n varying in $\mathcal{I} = \mathbb{N} \cup 0$ unless stated otherwise. However, the following discussion can also be generalized to continuous-time processes and dynamical systems. Noise may be characterized by a collection of random variables $Z(\omega, n) : \Omega \times \mathcal{I} \to \mathbb{R}$ defined in the same probability space $(\Omega, \mathcal{F}, p)$, letting n vary in the index set $\mathcal{I}$.

Before proceeding with the discussion, we introduce the following notation: an infinite sequence is denoted as $\{a_n\}_{n\geq 0}$, where the elements a_n may represent either discrete-time stochastic processes or deterministic sequences, such as the orbit of a dynamical system. For simplicity, we abbreviate this notation as $\{a_n\}_n$, unless stated otherwise. A sequence with a finite number of samples, N, is represented as $\{a_n\}_{n=0}^{N}$.

Noise is commonly categorized by "color", which refers to its frequency characteristics. In this context, the noise process is considered wide-sense stationary (WSS). This implies a constant mean and an autocovariance that is a function solely of the time lag, enabling its characterization through the power spectral density (PSD), which reveals the distribution of power over the frequency spectrum. To illustrate, white noise comprises wide sense stationary, non-correlated samples, with constant PSD across the frequencies [4]. Pink/blue noise [5,6] is characterized by a linearly decreasing/increasing PSD in the logarithmic scale. Brownian noise [7] exhibits a power spectral density that decays at a rate of 6.02 dB per octave, except at zero frequency. It can be considered the integral of white noise. When the noise PSD scales like $1/f^{\alpha}$ as a function of the frequency, the exponent α may characterize colored noise. In particular, for $\alpha = 0$ the noise is white, for $\alpha = 2$ is Brownian, and for $\alpha = 1, -1$ is pink/blue, respectively.

By considering noise as a random process at a fixed time n, it can be characterized as a random variable with its probability density or mass function. Common continuous distributions include Gaussian and uniform distributions, while common discrete distributions are represented by their discrete counterparts. Due to its stochastic nature and lack of time-punctual predictability, quantities such as mean, median, variance, and other statistical measures are often used for its characterization. When the noise process is stationary - meaning the joint probability distribution remains unchanged under time shifts - and ergodic — where the statistics (e.g., mean, covariance) can be estimated from a single long-term realization, comprising nearly all process states and ensuring convergence to the intended statistical moment (e.g., mean, covariance) — it becomes sufficient to average the process samples over time instead of using different realizations at a fixed time. These characteristics are captured by treating noise as independent and identically distributed (IID) random processes, where the components are identically distributed and mutually independent. It can be shown that such processes are wide-sense stationary and ergodic in terms of both mean and covariance.

2.2. Output/measurement noise vs. dynamical noise

System's output may be affected by two kinds of noise: output/measurement or dynamical noise. The former can occur during the process of measuring a system's state and it can be due to, e.g., sensor inaccuracies, environmental interference or random fluctuations in the measurement process, affecting the observed measurements and introducing errors in the estimated state. The dynamical noise, instead, arises from inherent uncertainties or fluctuations *within* the system itself and it may significantly affect a deterministic system's orbit.

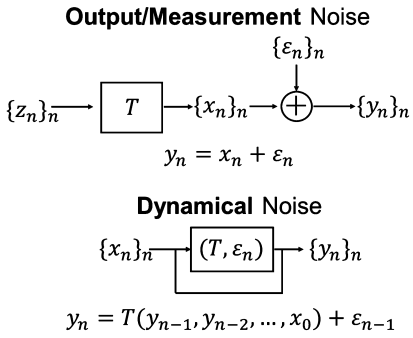

Fig. 2. Schematic representation of Output and Dynamical noises. Lock diagram of noise interactions with the underlying dynamics in the case of output noise (upper panel) and dynamical noise (lower panel). In the former, the noisy process $\{\varepsilon_n\}_n$ is added to an unperturbed orbit; in the latter, each noise sample ε_n is integrated into the dynamics, significantly altering the output.

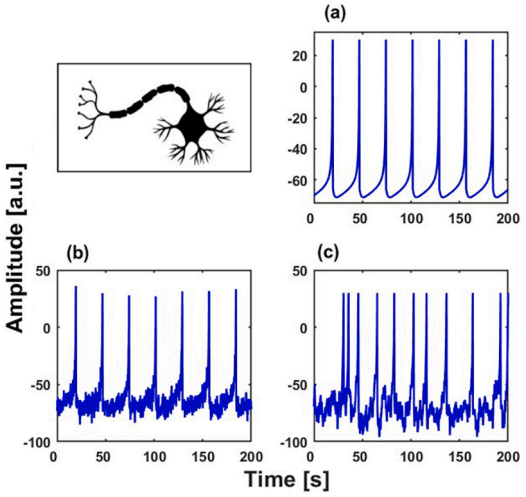

Fig. 3. Neural signals affected by dynamical and output noise. Exemplary neural dynamics (tonic spiking simulated using the Izhikevich model [8]) in the case of no noise (a), and with additive (b) and dynamical (c) noise whose samples ε_n are pairwise uncorrelated (white noise) with Gaussian distribution of mean 0 and $\sigma = 10$[a.u.].

Formally, let $\{x_n\}_{n\geq 0}$ be an orbit of a dynamical system (X, T, μ) starting from an initial state x_0, whose elements satisfy $x_{n+1} = T(x_n)$ for all n. A random process $\{\varepsilon_n\}_{n\geq 0}$ is said to be *output noise* for an orbit $\{x_n\}_{n\geq 0}$ if it produces an orbit of the following form:

$$y_n = x_n + \varepsilon_n$$

for all n.

On the other hand, a random process $\{\varepsilon_n\}_{n\geq 0}$ is said to be *dynamical noise* for an orbit $\{x_n\}_{n\geq 0}$ if it acts in the following way:

$$x_n = T(x_{n-1}) + \varepsilon_{n-1} \tag{1}$$

for all n, i.e. at each step a stochastic term is introduced and integrated in the system.

A schematic representation of these two noises and their interactions with the dynamics is represented in Fig. 2, while exemplary neural time series are illustrated in Fig. 3.

2.3. Physiological noise

Since we are interested in the role of noise in physiological processes as an intrinsic and fundamental component which contains information about the dynamics that cannot be deduced from its past history, it is convenient to assume that the model under study is corrupted by dynamical noise. In this context, the orbit x_n defined above may refer to a neural time series recording.

Remaining as general as possible, we assume that the dynamical noise is modeled by a sequence of IID random variables $\{\varepsilon_n\}_n$, where each $\varepsilon_n \sim \mathcal{N}(0, \sigma^2)$ (i.e. it is Gaussian with zero mean and fixed standard deviation) that it also involved into the dynamics according to eq. (1).

Formally, let us consider a physiological system as a discrete metrical and measure-preserving dynamical system (X, T, μ). Here, X is a compact subset of $\mathbb{R}$, and T is any differentiable map function with bounded derivative, which preserves the probability measure μ. A typical noise-free output of this system is represented as $w_n = T(w_{n-1}, w_{n-2}, ..., w_0)$, where $w_i \in X$ for all positive integers i.

Under the previous setting, we define the *Physiological Noise* as the dynamical noise $\{\varepsilon_n\}_n$, whose samples ε_n, in fact, modify physiological dynamics at each step according to the equation:

$$x_n = T(x_{n-1}; x_0) + \varepsilon_{n-1}, \tag{2}$$

where $x_i \in X$ for all positive integers i, where the map T considers the past history of the system, from the sample x_{n-1} up to the initial condition $x_0 = w_0$, here denoted by $(x_{n-1}; x_0)$. A finite physiological time series contaminated by physiological noise $\{\varepsilon_n\}_n$ can be denoted as $\{x_n(\varepsilon)\}_{n=0}^{N}$ - this notation can be extended to any time series. From the best of our knowledge, without any specific information or assumption on T, it is not possible to estimate the noise ε_n formally.

3. Physiological noise in the neuro-cardiovascular system

The cardiovascular system, part of the circulatory system, carries blood throughout the body, supplying nutrients, immune cells, and waste products to maintain homeostasis and organ function [9,10]. It consists of the heart, an anatomical pump, and blood vessels (veins, arteries, and capillaries). Blood flows through the heart's four chambers: the upper atria and lower ventricles, separated by valves. The heart pumps deoxygenated blood to the lungs for oxygenation (pulmonary circulation) and oxygen-rich blood to the body (systemic circulation). The right heart pumps deoxygenated blood to the lungs via the pulmonary arteries, while oxygenated blood returns to the left heart and is pumped into the body via the aorta. The heart's pumping action, driven by electrical signals in the myocardium, occurs in two phases: diastole (ventricles fill with blood) and systole (ventricles contract and eject blood) [11].

Heartbeat dynamics, along with processes like respiration and blood pressure regulation, are controlled by the sympathetic and parasympathetic limbs of the autonomic nervous system (ANS) [12]. The sympathetic nervous system (SNS), responsible for the "fight or flight" response, increases heart rate and blood pressure. The parasympathetic nervous system (PNS), active in "rest and digest" functions, decreases heart rate and blood pressure [13]. The ANS, under central nervous system control (including the hypothalamus and brainstem), transmits signals via preganglionic and postganglionic neurons located in autonomic ganglia.

The parasympathetic system originates in the brainstem and sacral spinal cord, regulating non-cardiopulmonary processes (e.g., digestion, urination) and cardiopulmonary functions (e.g., heart rate reduction) through the vagus nerve. The SNS originates in the thoracic and lumbar spinal cord, preparing the body for action by increasing heart rate, dilating bronchioles, and redistributing blood flow to essential organs.

The SNS and PNS function complementarily; one system's activity typically reduces the other's role. Their dynamic, nonlinear interaction modulates cardiac responses through bidirectional augmentation, where vagal signals enhance the heart rate response to sympathetic stimulation and vice versa [14]. This interaction influences heart rate variability (HRV), which reflects the balance between sympathetic and parasympathetic activities and is modulated by factors like blood pressure and respiration [15].

Even though the ANS does not transmit signals to every organ of the body, the nonlinear interactions between the two systems can deliver nonlinear neural information to the targeted organ. This is the case of the autonomic outflow to the heart where the sympathetic and parasympathetic branches, through their continuous dynamic interaction, modulate the cardiac response by means of the so-called bidirectional augmentation [14]: a tonic vagal signal enhances the gain of the transfer function that links dynamic vagal stimulation to heart rate, and vice versa. This bidirectional enhancement is influenced by cytosolic adenosine 3, 5-cyclic monophosphate, which is a key element in the biological foundation of the nonlinear autonomic regulation of heartbeat dynamics. [16]. In other words, the parasympathetic and sympathetic activity effects on heart rate are not purely antagonistic, but they are effect of not simply additive combined sympathetic and vagal stimulation [17], revealing nonlinear and dynamical interactions [16], i.e. simultaneous nervous systems changes accordingly to the physiological and pathological stresses in the cardiovascular system.

Since cardiovascular dynamics exhibit both nonlinear and complex behaviors, it is important to discuss the role of noise or stochastic fluctuations and their potential biological origins in cardiac physiology.

While there is no scientific proof of the specific biological dynamics underlying stochasticity in the neurocardiovascular system, related physiological noise likely arises from the nonlinear interaction between the sympathetic and parasympathetic nervous systems. Indeed, autonomic control is the main source of cardiovascular complexity and, consequently, stochasticity [18]. Specifically, a physiological interpretation of cardiovascular dynamical noise could be linked to the production of hormones or neurotransmitters released by components of the ANS, which innervate all body organs and systems. Since the central-autonomic network also controls cardiac activity, this stochasticity may influence the dynamics of the brain and body as a whole, including interconnected networks [19,20].

Norepinephrine, a hormone produced by the sympathetic nervous system, may serve as a physiological source and mediator of neurocardiovascular noise. This hormone may enhance neural control in the prefrontal cortex, particularly during decision-making tasks, by reducing underlying noise [21]. Additionally, norepinephrine system activity appears to correlate with the $1/f^{\alpha}$, $\alpha = 1$, pink noise spectrum of the nervous system [22], suggesting the possibility that neurocardiac noise fluctuations could be modulated by cognitive states.

Furthermore, other chemicals resulting from parasympathetic activity, such as acetylcholine, cytosolic adenosine 3,5-cyclic monophosphate, and other mediators of postjunctional interactions between the sympathetic and vagal systems, influence the combined neural control of heartbeat, potentially contributing to neurocardiovascular noise [16].

Physiological noise in cardiovascular dynamics may be monitored by processing series of heartbeat dynamics, referred to as HRV series. These series may be extracted from the electrocardiogram (ECG) and provide valuable insights into the parasympathetic and sympathetic activities of the ANS [15]. HRV reflects physiological variations in the time intervals between heartbeats, typically measured as changes in the beat-to-beat interval. It is also referred to as "cycle length variability", "R–R variability" (with R denoting the peak of the QRS complex on the ECG, and R–R indicating the interval between successive R peaks), and "heart period variability". The RR interval is used to calculate HRV. The HRV series is most commonly derived from the ECG, which is considered the gold standard for HRV measurement because it directly reflects cardiac electrical activity. R-peak identification in the ECG is commonly performed using the Pan-Tompkins algorithm [23]. In certain conditions (e.g., resting state), HRV series can also be derived from photoplethysmogram signals.

4. Physiological noise in the neural system

The nervous system is a complex network responsible for transmitting signals between different parts of the body, coordinating various physiological functions and behaviors. It is composed of specialized cells, primarily neurons and glial cells, organized into two main divisions: the central nervous system (CNS) and the peripheral nervous system (PNS). The following sections provide an overview of these components, including the structures of neurons and glial cells, as well as a more detailed look into the CNS and PNS, highlighting their respective roles in maintaining the body's functionality.

Neurons: Neurons are the building blocks of the nervous system, responsible for transmitting electrical and chemical signals [24]. These excitable cells consist of a soma, which houses the cell's nucleus and metabolic machinery, dendrites that receive input from other neurons, and a single axon that transmits signals away from the cell body [25]. The axon can extend for long distances, transmitting impulses to target cells like muscles or glands. At the end of the axon, synaptic boutons release neurotransmitters, enabling communication between neurons at the synapse. The axon is often insulated by a myelin sheath, which increases signal transmission speed by allowing action potentials to jump between the nodes of Ranvier. This efficient communication system underlies all nervous system functions, from simple reflexes to complex cognitive tasks.

Glial cells: Glial cells, or neuroglia, play essential support roles within the nervous system, contributing to homeostasis, protecting neurons, and forming the myelin sheath that insulates axons [26,27]. They are non-excitable and do not transmit electrical signals but are crucial for the overall health and efficiency of neural networks. In the CNS, oligodendrocytes form myelin, astrocytes regulate the environment around neurons, microglia serve as immune cells, and ependymal cells produce cerebrospinal fluid. In the PNS, Schwann cells myelinate peripheral neurons, and satellite cells provide support in ganglia. Without glial cells, neuronal communication would be less efficient, and neurons would be more vulnerable to damage.

Central nervous system (CNS): The CNS consists of the brain and spinal cord, which are protected by the skull, vertebrae, and meninges. The spinal cord serves as the primary communication pathway between the brain and the rest of the body, divided into 31 segments corresponding to different nerve pairs that control sensory and motor functions. The spinal cord's gray matter contains neuron cell bodies, while the surrounding white matter is made of myelinated axons that transmit signals up and down the spinal cord [28,29].

The brain, the central organ of the CNS, processes sensory information and coordinates motor control. It is divided into the cerebrum, cerebellum, and brainstem. The cerebrum, the largest part of the brain, governs cognitive functions, emotions, and voluntary movement and is divided into four lobes (frontal, parietal, temporal, and occipital), each specialized for different tasks. The cerebellum, located at the back of the brain, fine-tunes motor actions, ensuring smooth and coordinated movement. The brainstem connects the brain to the spinal cord and regulates vital functions like heart rate and breathing [30,31].

4.1. Neural activity monitoring for physiological noise identification

Neural activity monitoring techniques, including but not limited to calcium imaging, electroencephalography (EEG), and functional magnetic resonance imaging (fMRI), provide valuable insights into brain function. These methods generate time series related to neural spiking activity (ion current), neural electrical activity, and brain metabolic activity, respectively. Estimating physiological noise in each time series can offer insights into the stochasticity of the neural system at different scales.

Calcium imaging: Calcium imaging is a technique that measures real-time changes in calcium ion concentrations ($[Ca^{2+}]$) within living cells, allowing the study of cellular activity and communication [32,33]. Calcium indicators, which fluoresce in the presence of Ca^{2+}, are used due to calcium's role in processes like neurotransmission and muscle contraction. This method enables the observation of electrical activity in neuronal circuits during ongoing behavior, as action potentials are accompanied by fast Ca^{2+} flows.

Key steps include choosing and loading calcium indicators (chemical or genetically encoded) [34], stimulating cells using chemical, electrical, or optogenetic stimuli, and detecting fluorescence with advanced microscopy techniques [35]. Data collection captures dynamic fluorescence changes, and the analysis involves quantitative measurements of calcium levels, kinetics, and spatial distribution. These measurements provide insight into neuronal activity, muscle contraction, or signaling pathways [33,36].

EEG signals: EEG is a non-invasive method for recording the brain's electrical activity in real time, providing insights into neural dynamics [37–39]. EEG signals originate from the electrical activity of neurons, particularly pyramidal neurons in the cerebral cortex. When groups of neurons fire synchronously, their combined electrical fields form dipoles, generating weak signals that travel through the brain, skull, and scalp to be detected by electrodes.

EEG electrodes, placed using standardized systems like the 10-20 system, capture signals typically in the microvolt range. These signals are amplified and filtered to remove non-neural noise (e.g., from muscles or eye movements). EEG measures the brain's oscillatory activity across different frequency bands, with slower waves like delta indicating deep sleep and faster waves like beta and gamma linked to active cognition. Despite its limited spatial resolution, EEG is valuable for studying real-time brain function in health and disease.

fMRI signals: fMRI detects brain activity through hemodynamic responses to neuronal activity. When neurons are active, they consume more oxygen, leading to an increase in local blood flow to meet metabolic demands [40]. fMRI signals are based on differences in the magnetic properties of oxygenated versus deoxygenated blood. As neurons consume oxygen, the local changes in blood oxygenation levels alter the magnetic resonance signal, which is captured by the MRI scanner [41].

fMRI provides a detailed map of brain regions engaged during specific tasks by tracking these hemodynamic changes. While it has high spatial resolution, fMRI captures brain activity indirectly and is less sensitive to rapid neural events compared to techniques like EEG.

4.2. Stochasticity in neural dynamics

According to different neural system scales, there are several physiological sources contributing to the presence of noise in the nervous system.

At the cellular level, neuronal variability can exhibit statistical features such as mean and variance that resemble random processes, though not necessarily being purely stochastic. This variability differs across repeated neuronal activity recordings and among individual neurons. While multiple factors influence neuronal trial-to-trial variability, including changes in the internal states of neurons and networks, noise is often considered the primary contributor to this variability [42].

The presence of stochasticity in neurons may account for the variation in the timing of action potentials, even when neurons are driven by identical time-varying stimuli over repeated trials [43,44].

Possible biochemical and biophysical sources of cellular noise include the functioning of ion pumps, synaptic vesicle fusion, the diffusion and binding of signaling molecules to receptors, and the production and degradation of proteins. Membrane potential fluctuations, even in the absence of synaptic inputs, are influenced by electrical noise, specifically channel noise-random currents caused by the opening and closing of voltage- or ligand-gated ion channels. This channel noise affects action potential timing, propagation along the axon, and trial-to-trial variability [45]. Additionally, noise or stochasticity becomes more relevant when neurons decrease in size, as their weakened firing mechanism is increasingly contaminated by an higher noise activity and interference.

Large-scale effects of small biochemical reactions, concentrations, and electrochemical fluctuations in cells may arise from the amplification of nonlinear neuronal activity.

Other sources of electrical noise include shot noise and thermal noise, which are approximately three orders of magnitude smaller than channel noise in central nervous system neurons. Furthermore, *cross-talk* noise occurs due to variations in the activity of nearby neurons, which result from significant changes in extracellular ion concentration following electrical signaling and the spillover of neurotransmitters between unrelated synapses [46].

At the synaptic level, many neocortical cells experience *synaptic background noise*, a multitude of signals from thousands of synapses, which contain meaningful structure on a large scale but also include microscopic sources of true noise from each synapse [47].

Synaptic noise arises spontaneously due to miniature postsynaptic currents, generated by the random release of neurotransmitter vesicles [48]. This randomness is driven by stochastic processes within the synaptic transmission machinery, including the spontaneous release of intracellular Ca^{2+}, noise in synaptic Ca^{2+} channels, random initiation of vesicle-release mechanisms, and spontaneous vesicle fusion with the membrane. Other contributors to synaptic noise include fluctuations in the number of neurotransmitter molecules released per vesicle, random diffusion of these molecules, and noise in synaptic receptor channels, especially when few receptors are present [49,50]. Receptor protein numbers and densities can also vary randomly over time due to thermodynamic noise affecting protein expression and degradation processes.

In motor and sensory systems, stochasticity is inherently involved through thermodynamic or mechanical noise [51]. In chemical sensing (e.g., smell and taste), noise arises from the random arrival rates of molecules at receptors due to diffusion and the receptors' limited capacity to count signaling molecules accurately [52]. In vision, noise is introduced by the absorption of photons at photoreceptors, governed by a Poisson process, which sets a physical limit on contrast sensitivity, particularly in low-light conditions when fewer photons are available. In movement, noise is produced by interactions with the environment, as well as by human skeletal muscles and muscle fibers [53,54].

5. Physiological noise estimation techniques

In this section, we list the methods used to estimate dynamical noise from an observable time series. Therefore, these methods may provide a quantitative measurement of physiological noise in neural systems when applied to time series.

Nonlinear estimation methods: The methods presented in this section exploit nonlinear and chaotic dynamical system theory. In many of the following quantifiers and methods, the first step is to reconstruct the embedded phase-space X_{emb} from a given time series $\{x_n\}$ of length N in a m-dimensional space, following Taken's embedding theorem [55], according to

$$X_{\text{emb}} = [\vec{\mathbf{x}}_1, \dots, \vec{\mathbf{x}}_{N-m+1}],$$

where $\vec{\mathbf{x}}_j$ is the transpose of the vector $[x_j, \dots, x_{j+m-1}]$, with $j = 1, \dots, N-m+1$. The main tools are:

- The correlation integral (or sum), firstly proposed in [56] and extended in [57], a mathematical quantity used to characterize the complexity of a dynamical system by quantifying the density of points in the phase space. Given a finite orbit $\{x_n\}$, the idea is to count the number of pairs of points in the reconstructed m-dimensional phase space X_{emb} of the system that are within a certain distance r of each other. The correlation integral $C_m(r)$ is defined by

$$C_m(r) = \frac{2}{N(N-1)} \sum_{i \neq j} \theta(r - d_{ij}),$$

  where N is the total number of data vectors, d_{ij} is a distance between the vectors $\vec{\mathbf{x}}_i$ and $\vec{\mathbf{x}}_j$ of the phase space X_{emb} and $\theta(x)$ is the Heaviside step function, which is equal to 1 if x is positive and 0 otherwise.
- The correlation dimension D_2 [56], an index that reflects the fractal nature of a set of points in the phase space X_{emb}, measuring the scaling behavior of the correlation integral $C_m(r)$ with respect to the distance r, according to the scaling law

$$C_m(r) \propto r^{D_2},$$

  independently on the embedding dimension m.
- The correlation entropy [57,58], which measures the average information content per data point in the reconstructed m-dimensional phase space X_{emb} of the system. It is closely related to the correlation dimension and can be calculated from the correlation integral. It is formally computed as:

$$K_2 = \lim_{r \to 0} \lim_{N \to \infty} \lim_{m \to \infty} \frac{\ln C_m(r)}{m},$$

  where N is the total number of points, and $C_m(\varepsilon)$ is the correlation sum for an embedding dimension m.
- Lyapunov exponents, which measure the sensitivity of a dynamical system to initial conditions [59]. They quantify how rapidly nearby orbits diverge from each other over time. If the system is described by $x_{n+1} = T(x_n)$, the Lyapunov exponents measure the behavior of the quantities

$$\frac{1}{n} \ln \left\| \frac{\partial T^n(x_0)}{\partial x} \cdot v \right\|$$

  as $n \to \infty$, where $T^n(x_0)$ is the n-th iterate of the map applied to the initial condition x_0, and v is a vector applied at x_0.
- Recurrence plots, a powerful tool that visualizes the times at which the state of a dynamical system revisits the same or a similar state, offering insights into the system's behavior over time [60]. Formally, after embedding the series in a m dimensional space X_{emb}, recurrence plots are represented by a square matrix R where the element $R(i,j)$ is 1 if the states $\vec{\mathbf{x}}_i$ and $\vec{\mathbf{x}}_j$ are within a specified threshold distance r, and 0 otherwise, as defined by:

$$R(i,j) = \begin{cases} 1, & \text{if } ||\vec{\mathbf{x}}_i - \vec{\mathbf{x}}_j|| \leq r \\ 0, & \text{otherwise} \end{cases}$$

Unless specified otherwise, the following methods assume that the observable time series x_n is generated by a perturbed dynamical system

$$x_n = T(x_{n-1}) + \varepsilon_{n-1}$$

where the map T defines the system model, and ε_n represents realizations of a stochastic Gaussian white noise variable $\mathcal{N}(0, \sigma)$. The term "noise estimation" refers to the quantification of the σ value.

In [61], the authors present a noise estimation technique based on the functional dependence between the coarse-grained entropy $K_2(r)$ and the threshold r, as well as the correlation dimension, which incorporates the noise standard deviation within the time series. A similar method is proposed in [62], where the authors suggest a correction to the embedding dimension estimate in noisy regimes.

The work in [63] also offers an estimation of the dynamical noise in the correlation integral and the K_2 entropy, utilizing geometric considerations on how noise distributes in the reconstructed phase space along the attractor - a subset of the phase space to which the dynamics converge after a transient period.

Other noise estimation methods specifically designed for estimating measurement or output noise in chaotic time series, but also applicable to infer dynamical noise levels, are also presented here. The main noise identification procedure is found in [64], where the noise level in time series is determined by linking the scaling properties of the correlation integral to a Gaussian noise functional involving the first two moments of the Gaussian noise distribution. This method was further refined in [65,66] to detect higher levels

of noise by computing a similar estimator of the correlation integrals and sums using the L^∞ norm, instead of the Euclidean L^2 norm in the phase space, in order to reduce the effects of the attractor's curvature. A further refinement of this noise level estimation is provided in [67] through the correlation dimension and noise level estimations using the linear maximum likelihood procedure or the linear least-squares method [68], which reduces large estimation errors. In [69], noise estimation is achieved by representing Schreiber's Gaussian functional in terms of confluent hypergeometric functions of the first kind, and by developing a linear least-squares algorithm based on a truncated version of the functional, which reduces computational costs.

Another approach to noise estimation in time series involves measuring the noise drift of the largest Lyapunov exponent [70,71], a nonlinear index of orbit divergence in a dynamical system [72].

Probabilistic approaches: Other methods for noise identification are purely based on probability theory. In particular, they rely on Bayes' theorem, which retrieves the noise level σ as the most likely value given the model and data distribution. These methods also employ Monte Carlo simulation techniques, which use random numbers to estimate numerical results (such as statistical mechanics quantities), and probability density function estimations.

The Bayesian probabilistic approach is used to detect and distinguish output or measurement noise from dynamical noise, provided that there is a reliable fit or approximation of the underlying deterministic model [73]. This method has also been applied for time series forecasting in regimes dominated by dynamical noise [74]. In [75], the power of dynamical noise was identified and distinguished from measurement noise in Hénon and Ikeda maps, revealing that the probability density function of time series samples corrupted by dynamical noise resembles a Cauchy distribution. This method further exploits the scaling properties of correlation entropy, which primarily depends on the distribution of additive noise contaminating a given time series and appears to be independent of the dynamical noise distribution. Similarly, the Markov Chain Monte Carlo Bayesian approach described in [76] enables dynamical denoising by providing an iterative estimation of the dynamical noise within the series.

Stochastic differential equations and Langevin processes: Dynamical noise levels can also be formalized and quantified within the framework of continuous-time stochastic differential equations. In this context, a general form of a noise-drifted process can be expressed using Langevin diffusion processes:

$$dx(t) = f(x(t))dt + \sigma dB(t)$$

where $x(t)$ represents the multidimensional state of the system at time t, $f(x(t))$ is the deterministic force acting on the system, σ is a constant that determines the strength of the random fluctuations (noise level), and $dB(t)$ is a Wiener process, which is a continuous-time random walk with independent increments. The first term on the right-hand side of the equation represents the deterministic evolution of the system, while the second term accounts for random fluctuations.

In [77], a model-free noise quantification method for both output and dynamical noise was proposed through the reconstruction of Langevin processes. This approach utilizes the Kramers-Moyal coefficients [78] and conditional moments [79], applied to sufficiently long time series. Within the Langevin framework, measurement noise interferes with dynamical noise detection by introducing estimation drifts, generating offsets in the process. A similar effort to distinguish output noise from dynamical noise was undertaken through statistical tests in [80], specifically for the Van der Pol oscillator.

In contrast, the authors of [81] provided an estimation of dynamical noise levels, scaled from 0 to 1, within the Wiener process framework by employing the time series dimension (TSD) [82], a technique used to measure the fractal dimension of attractor segments in phase space. Their method relies on an analytical relationship between the TSD and the levels of dynamical noise.

Kalman filters and extensions: Dynamical noise can be referred to as process noise. In this framework, dynamical systems are typically represented as:

$$\begin{cases} x_{k+1} &= f(x_k, t_k) + w_k \\ y_k &= g(x_k, t_k) + v_k \end{cases} \tag{3}$$

where x_k are the n-dimensional state vectors and y_k are m-dimensional observation vectors. The functions f and g define, respectively, the underlying model and the observation function, which represents what can actually be measured. The terms w_k and v_k are samples of noisy distributions: the former arises from process (dynamical) noise since it interacts with the system's dynamics, while the latter is associated with output/measurement noise. Both noise samples are assumed to be drawn from white noise distributions, with covariances Q_k and R_k, respectively.

The primary goal is typically to estimate the states x_k given the measurements y_k. This procedure also acts as a denoising technique, as it mitigates the effects of noise on the observed data.

In [83], Kalman proposed a filter that allows one to retrieve the states x_k if the functions f and g are linear, provided that the process and measurement noise covariances are properly tuned. The filter operates in real-time, recursively, and works through a two-phase process: a prediction phase and an update phase. In the prediction phase, the Kalman filter generates estimates of the current state variables along with their uncertainties. In the update phase, once the next measurement is observed, these estimates are refined using a weighted average.

The Kalman filter has since been extended to handle nonlinear systems (Extended and Ensemble Kalman filters) [84,85], while still requiring knowledge of the system's equations and noise levels. Some variants of the Kalman filter (known as Unscented filters) have been applied when no prior knowledge of the model is available [86].

Nevertheless, the challenge of tuning the noise covariance matrices Q_k and R_k, which are critical to state estimation, remains. Two main common approaches determine noise covariances R_k and Q_k: a "divide-and-conquer" strategy, where observation noise is estimated in the lab and process noise is tuned based on normalized estimation error squared (NEES) and the normalized innovation error squared (NIS) [87]; and auto-tuning algorithms like maximum likelihood, Bayesian inference, and Kalman smoothing [88–90]. However, lab-based methods may not reflect real-world sensor behavior, while auto-tuning can face numerical instability and struggles with nonlinear filters [87,91]. Moreover, these procedures may affect the accuracy of state estimation, potentially causing the filter to diverge when large errors exist in the process noise covariance matrix.

Many techniques for estimating both the state and process noise are variations of adaptive Kalman filters, which can adjust their parameters to account for changes in system dynamics or measurement noise characteristics. This adaptability is especially useful for systems that are non-stationary or have uncertainties that evolve over time.

For instance, the process noise covariance (or dynamical noise level) has been estimated in [92] through adaptive filters, where dynamical constraints are also imposed on the noise; in [93], an adaptive Unscented Kalman filter was used; in [94], an adaptive filter based on reinforcement learning was proposed; and in [95], a filter for noise estimation was applied online, achieved by comparing expected and observed event rates using the golden section search optimization algorithm. A moving-window version of the extended Kalman filter has also been proposed [96], which has been used for modeling process noise in structural damage detection. Other noise estimation methods include iterative low-rank matrix approximation [97], Bayesian probabilistic theory [98], stochastic approximation [99], and adaptive cubature information filters [100].

Additionally, a further extension of the Kalman filter, known as the Kalman-Takens filter, has been proposed to address the lack of a model and the need for *a priori* noise tuning [101]. This filter reconstructs the system in a higher-dimensional space based on Taken's embedding theory [55], provided there is a sufficient number of time series samples. This approach bridges nonlinear analysis tools and classical signal processing filtering techniques. Moreover, it eliminates the necessity for the process and measurement noise matrices Q_k and R_k to recover the system's states. Instead, noise covariances can be estimated independently through adaptive techniques that iteratively adjust the noise matrices from an initial random guess. This method has also proven effective for dynamical noise reduction when compared with classical Kalman filters.

In [102], a statistical estimator for linearly autocorrelated noise is proposed. Impulsive noise, defined as instantaneous disturbances or artifacts, is detected in [103] using nonlinear prediction or adaptive Kalman filters [104].

Model-free noise estimation methods: Taking inspiration from the aforementioned works, we have developed a model-free dynamical noise estimation algorithm, particularly suitable for physiological time series [105,106]. The method leverages the well-known nonlinear Approximate Entropy quantifier [107], which is an estimator of the Kolmogorov-Sinai entropy for finite time series, characterizing dynamical systems. These quantities measure the complexity of a dynamical system in terms of the predictability of a current state given the past history of the system. Alternatively, in an information-theoretic context, they can be interpreted as the average amount of information required to characterize a system's state.

If $\{x_n\}_n$ is a time series of length N and m is the embedding dimension, the approximate entropy of $\{x_n\}_n$ with embedding dimension m and tolerance r is defined as:

$$\mathrm{ApEn}(\{x_n\}_n, m, r) = \Phi^m(r) - \Phi^{m+1}(r)$$

where

$$\Phi^m(r) = \frac{1}{N-m+1} \sum_{i=1}^{N-m+1} \ln C_m^i(r)$$

and $C_m^i(r)$ denotes the empirical probability to find any m-dimensional vectors $\vec{\mathbf{x}}_j$ close to a fixed $\vec{\mathbf{x}}_i$ of the embedded phase space, within a distance r.

The noise estimation method is theoretically based on the divergence of the Approximate Entropy when the tolerance radius r is comparable to the noise level σ. When the dynamical noise $\{\varepsilon_n\}_n$ is assumed white and Gaussian $\mathcal{N}(0,\sigma)$, the following closed-form expression has been proposed [106] for a perturbed time series $\{x_n(\varepsilon(\sigma))\}_n$, whose stochastic part is determined only by the parameter σ:

$$\log(\sigma) \approx \mathrm{ApEn}(\{x_n(\varepsilon(\sigma))\}_n, m, r) + \log(r/\sqrt{\pi}), \tag{4}$$

relating the dynamical noise level σ, and hence its complete characterization, to the entropy quantifier. The method does not require system model estimation and is not limited to white Gaussian noise distributions.

The associated algorithm is based on plotting the Approximate Entropy (ApEn) quantifier as a function of the radius parameter r, and then identifying the radius where the ApEn function exhibits the same differential behavior as the logarithmic Gaussian function in (4).

6. Conclusions and future research directions

Noise has been pivotal to the advancement of applied sciences. Beyond the traditional view of noise as a source of interference in signal acquisition or experimental reproducibility, a more recent perspective considers noise as an integral part of dynamical systems.

From a physiological standpoint, noise is not only a process linked to a single system but also a strategic component for the balance and proper functioning of various processes. Indeed, physiological noise - dynamical noise in physiological systems - plays a crucial role, particularly in neural system dynamics, as it continuously alters the system's behavior. Identifying and potentially removing this noise remains a challenging task, especially when the underlying dynamics are unknown. Current approaches to identifying intrinsic noise primarily rely on dynamical systems frameworks, complexity quantifiers developed in the latter half of the last century, probability theory and calculus (notably the Bayesian approach), and stochastic differential equation processes. These methods often require an analytical understanding of the observed phenomenon, such as in state-space models where the Kalman filter is used for noise estimation and removal, assuming the model is known or can be reasonably approximated.

Signals with relatively unknown governing dynamics include neurocardiovascular variability series (HRV), EEG signals, neural activity time series from calcium imaging, spike potentials, and fMRI recordings. These represent the activities of the cardiovascular system, cerebral cortex, and neural and brain functions, respectively. As discussed, noise in these systems is crucial for both function and modeling, influencing processes at different scales - from ion exchange within cells to neuronal communication, spiking activity, and the regulation of sympathetic and parasympathetic activity.

The discussion so far has primarily focused on the effect of dynamic noise in one-dimensional or univariate series. For future research, developing methods to estimate dynamic noise in multivariate series is of great interest. Since the stochastic component of the signal is intrinsic and not merely a disturbance, identifying and correlating these noises across different sources could reveal new connections that have previously been overlooked or obscured. This is especially relevant when the assumption of purely deterministic or purely stochastic systems excludes the possibility of their coexistence. Monitoring physiological noise in multivariate signals can uncover new functional properties of the system under observation. In this context, the estimation of noise covariance matrix between systems may pave the way towards novel stochastic connectomics maps, offering insights into multisystem physiological processes and their outcomes. Finally, noise estimation in multivariate systems could also help correct potential biases when determining causality between systems.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Cohen L. The history of noise [on the 100th anniversary of its birth]. IEEE Signal Process Mag 2005;22(6):20–45.
[2] Einstein A. Über die von der molekularkinetischen Theorie der Wärme geforderte Bewegung von in ruhenden Flüssigkeiten suspendierten Teilchen. Ann Phys 1905;4.
[3] Langevin P, et al. Sur la théorie du mouvement brownien. C R Acad Sci Paris 1908;146:530–3.
[4] Kuo H-H. White noise distribution theory. CRC Press; 2018.
[5] Szendro P, Vincze G, Szasz A. Pink-noise behaviour of biosystems. Eur Biophys J 2001;30:227–31.
[6] Ulichney RA. Dithering with blue noise. Proc IEEE 1988;76(1):56–79.
[7] Gillespie DT, et al. The mathematics of Brownian motion and Johnson noise. Am J Phys 1996;64(3):225–39.
[8] Izhikevich EM. Which model to use for cortical spiking neurons? IEEE Trans Neural Netw 2004;15(5):1063–70.
[9] Marieb EN, Hoehn K. Human anatomy & physiology. Pearson Education; 2007.
[10] Noble A, Johnson R, Thomas A, Bass P. Systems of the body series: the cardiovascular system; 2010.
[11] Buja LM, Butany J. Cardiovascular pathology. Academic Press; 2022.
[12] Sinski M, Lewandowski J, Abramczyk P, Narkiewicz K, Gaciong Z. Why study sympathetic nervous system. J Physiol Pharmacol 2006;57(Suppl 11):79–92.
[13] Koopman FA, Stoof SP, Straub RH, Van Maanen MA, Vervoordeldonk MJ, Tak PP. Restoring the balance of the autonomic nervous system as an innovative approach to the treatment of rheumatoid arthritis. Molec Med 2011;17:937–48.
[14] Tahsili-Fahadan P, Geocadin RG. Heart–brain axis: effects of neurologic injury on cardiovascular function. Circ Res 2017;120(3):559–72.
[15] Valenza G, Citi L, Saul JP, Barbieri R. Measures of sympathetic and parasympathetic autonomic outflow from heartbeat dynamics. J Appl Physiol 2018;125(1):19–39.
[16] Sunagawa K, Kawada T, Nakahara T. Dynamic nonlinear vago-sympathetic interaction in regulating heart rate. Heart Vessels 1998;13:157–74.
[17] Levy MN. Brief reviews: sympathetic-parasympathetic interactions in the heart. Circ Res 1971;29(5):437–45.
[18] Karavaev A, Ishbulatov YM, Ponomarenko V, Bezruchko B, Kiselev A, Prokhorov M. Autonomic control is a source of dynamical chaos in the cardiovascular system. Chaos, Interdiscip J Nonlinear Sci 2019;29(12).
[19] Valenza G, Sclocco R, Duggento A, Passamonti L, Napadow V, Barbieri R, et al. The central autonomic network at rest: uncovering functional mri correlates of time-varying autonomic outflow. NeuroImage 2019;197:383–90.
[20] Valenza G, Passamonti L, Duggento A, Toschi N, Barbieri R. Uncovering complex central autonomic networks at rest: a functional magnetic resonance imaging study on complex cardiovascular oscillations. J R Soc Interface 2020;17(164):20190878.
[21] Aston-Jones G, Cohen JD. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. Annu Rev Neurosci 2005;28(1):403–50.
[22] Pertermann M, Mückschel M, Adelhöfer N, Ziemssen T, Beste C. On the interrelation of 1/f neural noise and norepinephrine system activity during motor response inhibition. J Neurophysiol 2019;121(5):1633–43.
[23] Pan J, Tompkins WJ. A real-time qrs detection algorithm. IEEE Trans Biomed Eng 1985;3:230–6.
[24] Carnevale NT, Hines ML. The NEURON book. Cambridge University Press; 2006.
[25] Friedman A. Introduction to neurons. In: Tutorials in mathematical biosciences I; 2005. p. 1–20.
[26] Parpura V, Heneka MT, Montana V, Oliet SH, Schousboe A, Haydon PG, et al. Glial cells in (patho) physiology. J Neurochem 2012;121(1):4–27.
[27] Jessen KR. Glial cells. Int J Biochem Cell Biol 2004;36(10):1861–7.
[28] Brodal P. The central nervous system. Oxford University Press; 2010.
[29] Michael-Titus AT, Shortland P. The nervous system, E-book: the nervous system, E-book. Elsevier Health Sciences; 2022.
[30] Mai JK, Paxinos G. The human nervous system. Academic Press; 2011.

[31] Vogel H. Nervous system. Cambridge University Press; 2009.
[32] Blinks J, Prendergast F, Allen D. Photoproteins as biological calcium indicators; 1976.
[33] Robbins M, Christensen CN, Kaminski CF, Zlatic M. Calcium imaging analysis–how far have we come? F1000Research, vol. 10. 2021.
[34] Ohkura M, Matsuzaki M, Kasai H, Imoto K, Nakai J. Genetically encoded bright ca2+ probe applicable for dynamic ca2+ imaging of dendritic spines. Anal Chem 2005;77(18):5861–9.
[35] Nguyen JP, Shipley FB, Linder AN, Plummer GS, Liu M, Setru SU, et al. Whole-brain calcium imaging with cellular resolution in freely behaving caenorhabditis elegans. Proc Natl Acad Sci 2016;113(8):E1074–81.
[36] Grienberger C, Konnerth A. Imaging calcium in neurons. Neuron 2012;73(5):862–85.
[37] Da Silva FL. Eeg: origin and measurement. In: EEG-fMRI: physiological basis, technique, and applications. Springer; 2023. p. 23–48.
[38] Jackson AF, Bolger DJ. The neurophysiological bases of eeg and eeg measurement: a review for the rest of us. Psychophysiology 2014;51(11):1061–71.
[39] Cohen MX. Where does eeg come from and what does it mean? Trends Neurosci 2017;40(4):208–18.
[40] Song AW. Diffusion modulation of the fmri signal: early investigations on the origin of the bold signal. NeuroImage 2012;62(2):949–52.
[41] Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. Neurophysiological investigation of the basis of the fmri signal. Nature 2001;412(6843):150–7.
[42] White JA, Rubinstein JT, Kay AR. Channel noise in neurons. Trends Neurosci 2000;23(3):131–7.
[43] Tolhurst DJ, Movshon JA, Dean AF. The statistical reliability of signals in single neurons in cat and monkey visual cortex. Vis Res 1983;23(8):775–85.
[44] Bryant HL, Segundo JP. Spike initiation by transmembrane current: a white-noise analysis. J Physiol 1976;260(2):279–314.
[45] Schneidman E, Freedman B, Segev I. Ion channel stochasticity may be critical in determining the reliability and precision of spike timing. Neural Comput 1998;10(7):1679–703.
[46] Faisal AA, Selen LP, Wolpert DM. Noise in the nervous system. Nat Rev, Neurosci 2008;9(4):292–303.
[47] Fellous J-M, Rudolph M, Destexhe A, Sejnowski TJ. Synaptic background noise controls the input/output characteristics of single cells in an in vitro model of in vivo activity. Neuroscience 2003;122(3):811–29.
[48] Fatt P, Katz B. Some observations on biological noise. Nature 1950;166(4223):597–8.
[49] Calvin WH, Stevens CF. Synaptic noise as a source of variability in the interval between action potentials. Science 1967;155(3764):842–4.
[50] Calvin WH, Stevens CF. Synaptic noise and other sources of randomness in motoneuron interspike intervals. J Neurophysiol 1968;31(4):574–87.
[51] Harris CM, Wolpert DM. Signal-dependent noise determines motor planning. Nature 1998;394(6695):780–4.
[52] Bialek W, Setayeshgar S. Physical limits to biochemical signaling. Proc Natl Acad Sci 2005;102(29):10040–5.
[53] de C Hamilton AF, Jones KE, Wolpert DM. The scaling of motor noise with muscle strength and motor unit number in humans. Exp Brain Res 2004;157:417–30.
[54] Jones KE, Hamilton AFdC, Wolpert DM. Sources of signal-dependent noise during isometric force production. J Neurophysiol 2002;88(3):1533–44.
[55] Sauer T, Yorke JA, Casdagli M. Embedology. J Stat Phys 1991;65:579–616.
[56] Grassberger P, Procaccia I. Characterization of strange attractors. Phys Rev Lett 1983;50(5):346.
[57] Nolte G, Ziehe A, Müller K-R. Noise robust estimates of correlation dimension and k 2 entropy. Phys Rev E 2001;64(1):016112.
[58] Grassberger P, Procaccia I. Estimation of the Kolmogorov entropy from a chaotic signal. Phys Rev A 1983;28(4):2591.
[59] Brin M, Stuck G. Introduction to dynamical systems. Cambridge University Press; 2002.
[60] Faure P, Korn H. A new method to estimate the Kolmogorov entropy from recurrence plots: its application to neuronal signals. Phys D: Nonlinear Phenom 1998;122(1–4):265–79.
[61] Urbanowicz K, Hołyst JA. Noise-level estimation of time series using coarse-grained entropy. Phys Rev E 2003;67(4):046218.
[62] Kugiumtzis D. Correction of the correlation dimension for noisy time series. Int J Bifurc Chaos 1997;7(06):1283–94.
[63] Szpiro GG. Measuring dynamical noise in dynamical systems. Phys D: Nonlinear Phenom 1993;65(3):289–99.
[64] Schreiber T. Determination of the noise level of chaotic time series. Phys Rev E 1993;48(1):R13.
[65] Leontitsis A, Pange J, Bountis T. Large noise level estimation. Int J Bifurc Chaos 2003;13(08):2309–13.
[66] Xu P, Li WK, Jayawardena A. Noise level estimation for a chaotic time series. Int J Bifurc Chaos 2012;22(03):1250052.
[67] Jayawardena A, Penchang X, Sivakumar B. Noise level estimation of chaotic hydrological time series. IAHS Spec Publ 2002;274:297–304.
[68] Jayawardena A, Xu P, Li WK. A method of estimating the noise level in a chaotic time series. Chaos, Interdiscip J Nonlinear Sci 2008;18(2).
[69] Çoban G, Büyüklü AH, Das A. A linearization based non-iterative approach to measure the Gaussian noise level for chaotic time series. Chaos Solitons Fractals 2012;45(3):266–78.
[70] Yao T-L, Liu H-F, Xu J-L, Li W-F. Estimating the largest Lyapunov exponent and noise level from chaotic time series. Chaos, Interdiscip J Nonlinear Sci 2012;22(3).
[71] Yao T-L, et al. Noise-level estimation of noisy chaotic time series based on the invariant of the largest Lyapunov exponent; 2012.
[72] Eckmann J-P, Ruelle D. Ergodic theory of chaos and strange attractors. Rev Mod Phys 1985;57(3):617.
[73] Heald J, Stark J. Estimation of noise levels for models of chaotic dynamical systems. Phys Rev Lett 2000;84(11):2366.
[74] Hirata Y. Reconstructing latent dynamical noise for better forecasting observables. Chaos, Interdiscip J Nonlinear Sci 2018;28(3).
[75] Strumik M, Macek WM, Redaelli S. Discriminating additive from dynamical noise for chaotic time series. Phys Rev E, Stat Nonlinear Soft Matter Phys 2005;72(3):036219.
[76] Kaloudis K, Hatjispyros SJ. A Bayesian nonparametric approach to dynamical noise reduction. Chaos, Interdiscip J Nonlinear Sci 2018;28(6).
[77] Siefert M, Kittel A, Friedrich R, Peinke J. On a quantitative method to analyze dynamical and measurement noise. Europhys Lett 2003;61(4):466.
[78] Moyal JE. Quantum mechanics as a statistical theory. Math Proc Camb Philos Soc 1949;45(1):99–124.
[79] Böttcher F, Peinke J, Kleinhans D, Friedrich R, Lind PG, Haase M. Reconstruction of complex dynamical systems affected by strong measurement noise. Phys Rev Lett 2006;97(9):090603.
[80] Boschi CDE, Ortega G, Louis E. Discriminating dynamical from additive noise in the van der Pol oscillator. Phys D: Nonlinear Phenom 2002;171(1–2):8–18.
[81] Sase T, Ramírez JP, Kitajo K, Aihara K, Hirata Y. Estimating the level of dynamical noise in time series by using fractal dimensions. Phys Lett A 2016;380(11–12):1151–63.
[82] Higuchi T. Approach to an irregular time series on the basis of the fractal theory. Phys D: Nonlinear Phenom 1988;31(2):277–83.
[83] Kalman RE. A new approach to linear filtering and prediction problems; 1960.
[84] Kalnay E. Atmospheric modeling, data assimilation and predictability. Cambridge University Press; 2003.
[85] Bergemann K, Reich S. An ensemble Kalman-Bucy filter for continuous data assimilation. Meteorol Z 2012;21(3):213.
[86] Bilgin N, Olivier A. Joint Bayesian estimation of process and measurement noise statistics in nonlinear Kalman filtering. Mech Syst Signal Process 2025;223:111836.
[87] Chen Z, Biggie H, Ahmed N, Julier S, Heckman C. Kalman filter auto-tuning with consistent and robust Bayesian optimization. IEEE Trans Aerosp Electron Syst 2024;60(2):2236–50.
[88] Bishop CM. Pattern recognition and machine learning. New York: Springer; 2006.
[89] Barratt ST, Boyd SP. Fitting a Kalman smoother to data. In: 2020 American control conference (ACC). IEEE; 2020. p. 1526–31.
[90] Duník J, Kost O, Straka O, Blasch E. Covariance estimation and Gaussianity assessment for state and measurement noise. J Guid Control Dyn 2020;43(1):132–9.
[91] Zhang L, Sidoti D, Bienkowski A, Pattipati KR, Bar-Shalom Y, Kleinman DL. On the identification of noise covariances and adaptive Kalman filtering: a new look at a 50 year-old problem. IEEE Access 2020;8:59362–88.
[92] Stacey N, D'Amico S. Adaptive and dynamically constrained process noise estimation for orbit determination. IEEE Trans Aerosp Electron Syst 2021;57(5):2920–37.

[93] Hu G, Gao B, Zhong Y, Gu C. Unscented Kalman filter with process noise covariance estimation for vehicular ins/gps integration system. Inf Fusion 2020;64:194–204.
[94] Gao X, Luo H, Ning B, Zhao F, Bao L, Gong Y, et al. Rl-akf: an adaptive Kalman filter navigation algorithm based on reinforcement learning for ground vehicles. Remote Sens 2020;12(11).
[95] Martínez-Rey M, Santos C, Nieto R, Losada C, Espinosa F. Online evaluation of the process noise covariance matrix for event-based state estimators. Int J Numer Methods Eng 2019;120(2):195–208.
[96] Lai Z, Lei Y, Zhu S, Xu Y-L, Zhang X-H, Krishnaswamy S. Moving-window extended Kalman filter for structural damage detection with unknown process and measurement noises. Meas: J Int Meas Conf 2016;88:428–40.
[97] Li J, Fan W, Li Y, Yang B, Lu C. Desert seismic noise suppression based on an improved low-rank matrix approximation method. J Appl Geophys 2020;173.
[98] Bilgin N, Olivier A. Joint Bayesian estimation of process and measurement noise statistics in nonlinear Kalman filtering. Mech Syst Signal Process 2025;223.
[99] Bianchi F, Formentin S, Piroddi L. Process noise covariance estimation via stochastic approximation. Int J Adapt Control Signal Process 2020;34(1):63–76.
[100] Jiang H, Cai Y. Adaptive fifth-degree cubature information filter for multi-sensor bearings-only tracking. Sensors 2018;18(10).
[101] Hamilton F, Berry T, Sauer T. Kalman-Takens filtering in the presence of dynamical noise. Eur Phys J Spec Top 2017;226:3239–50.
[102] Leontitsis A. Red noise estimation. Int J Bifurc Chaos 2006;16(07):2111–7.
[103] Itoh K-i. A method for detecting impulsive noises in chaotic time series. IEICE Trans Fundam Electron Commun Comput Sci 1996;79(10):1670–5.
[104] Tang Y, Qian G, Wu W, Chien Y-R. An efficient filtering algorithm against impulse noise in communication systems. J Internet Technol 2023;24(2):357–62.
[105] Scarciglia A, Gini F, Catrambone V, Bonanno C, Valenza G. Estimation of dynamical noise power in unknown systems. IEEE Signal Process Lett 2023;30:234–8.
[106] Scarciglia A, Catrambone V, Bonanno C, Valenza G. Physiological noise: definition, estimation, and characterization in complex biomedical signals. IEEE Trans Biomed Eng 2024;71(1):45–55.
[107] Pincus SM. Approximate entropy as a measure of system complexity. Proc Natl Acad Sci 1991;88(6):2297–301.