

Biophysics of nerve tissue

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1 Preface

Location:	House 6, Lecture Hall - Campus Nord
Time:	Tue., 16:00-18:00
Contact:	https://itb.biologie.hu-berlin.de/~schleimer
Practical:	1 week end of semester

1.1 Content Summary

Nerve tissue is comprised of excitable cells, supporting cells and a surrounding bath. This seminar lecture reviews the biophysical basics of excitability, including the stochastic processes that govern voltage-gated ion-channels in nerve membranes. The composition of ion channels, among other factors, determines the functional properties of action potential pulses, which are analysed using dynamical systems theory. The statistics of pulse trains is derived from the microscopic level of ion-channel fluctuations. This will also serve the understanding of a self-consistent description of macroscopic neural-network dynamics.

1.2 (Dis)claimer

This scriptum shall evolve. It will have flaws (didactic ones and outright errors) but you, the reader, student, search bot, provide the selective pressure to improve it. Please write to the lecturer if you find fault of any kind with it.

Although written in a somewhat formal fashion the book is by no means a text in applies mathematics. It completely lacks the mathematical rigor to meet such standards. The choice of wrapping statements in definitions, observations and propositions arose from the need to be able to easily refer to them and to render the logical buildings blocks of some arguments easier to identify and follow through the text. Let's see how that worked out ...

2 Overview

There are many different lectures on “the biophysics of computation”, or “computational neuroscience”. The topic by now is so vast, that only a small non-exhaustive subset of the subject can be discussed within the temporal confinement of a lecture. This one is no different.

The idea here is to approach questions like “What is a nerve impulse?” or “Are there different types of excitability?” from a mathematical and a biophysical angle.

From the biophysical point of view, one has to address the many building blocks of nervous systems: There is needs to understand the biophysics of *lipid sheets* and the chemical gradient across them. *Voltage-gated ion channels* swimming in the membrane should be understood, including their stochastic dynamics. What is going on in the *extracellular medium* might be a topic. And of course what are the consequences of wiring neurons in *networks* via synapses or gap-junctions. Also the enormous *energetic demands* of nerve tissue are important factors in understanding its structure and function.

Many of these *components of nervous systems* derive from *preadaptations*, meaning precursors have been around long before the first nervous system emerged some 600 Myr ago. This is certainly true for excitability, which is found in single celled *Paramecium* and even bacteria. Synaptic components like the SNAR complex is present in fungi and some of the transmitters are used in bacterial communication.

Naturally, there is a risk of getting overwhelmed by these beautiful details. To explain the complexity of nervous systems *ab initio* seems a mindbogglingly difficult task. Yet, there are already *all-atom simulation of ion channels in the membrane*. Still, before and during discussing the structural aspects it is insightful to ask what are the exigences of a nervous system. Not in any teleological sense, theoretical biology is over that, but from an evolutionary standpoint. One may even formulate certain *desiderata*, without claiming that brains were design by anyone.

2.1 Levels of explanation

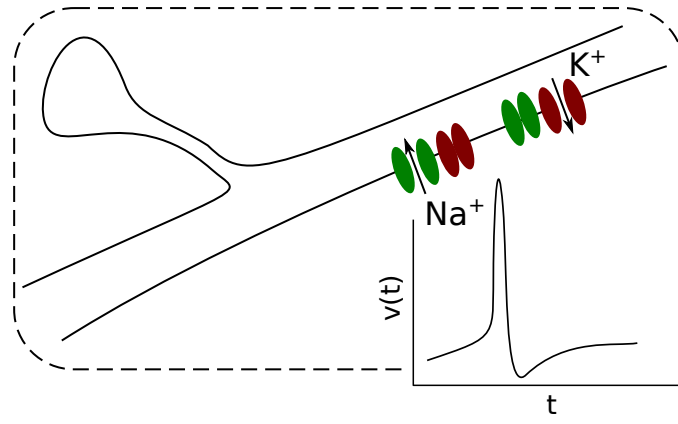
If by attending the lecture or goint through its notes the amount of confusion becomes unbearable Tinbergen’s *levels of analysis* might help

	Diachronic view of historical sequence	Static view of current form
Proximate cause	Ontogeny	Mechanism
Ultimate cause	Phylogeny	Function

While, categories and schemes like the above are of utility in structuring ones thoughts about nature, they should not be taken as dogmatic fences that do not allow you to think, speculate outside of them. Nature is to beautiful to get involved into dogmatic fights over reified wordings, leave them to the humanities.

Roughly one might associated certain disciplins of applied math that can be utilised in the four categories from above.

	Diachronic view of historical sequence	Static view of current form
Proximate cause	Control theory	Dynamical systems, Stochastic processes
Ultimate cause	Information theory, Optimisation	Filter theory, Triggered ensembles



Nerve cell in a bath and an action potential in the inset.

3 The Floquet theory of the action potential

3.1 Periodic event

Of many natural systems we observe only some drastically obvious events, while the underlying complex evolution of all state variables is hidden. The malatonin falling level below threshold (in the *suprachiasmatic nucleus*) causes a “waking-up event”. Results the complex regulatory network causing gap phase 1 → synthesis → gap phase 2 → mitosis transition result in clearly visible cell division events. Sadly, extinction events can be the results of changes in complex foodwebs, the dynamics of which is not completely determined. Action potentials are no different. The dynamics involves charging the cell membrane and the nonlinear kinetics of several ion channels, but the electric impulse is an clearly detectable event (with a glass electrode at least).

3.2 Pulse-based communication

Why do nervous system use pulses, called action potentials or spikes to communicate? In fact, not all do. The information picked up by your photo receptors is processed by cells in the retina (amacrine cells, horizontal cells) still as graded potentials, which are then recoded into a impulse based representation. Conversely, the visusal system of flys starts out with pulses representation and converts it to graded potentials upstream. Last but not least, the small nervous system of nematode *C. elegans* (302 neurons) seemed to operate entirely on graded potentials. No spikes had been reportet for a long time. But in 2018 someone found Ca^{2+} based spikes in one of their neurons.

One of the differences between passive graded potential and an active action potential is that the latter does not suffer from the same kind of siganl degradation over long distances. There could be active more or less graded potentials, but these are less temporally precise as a short pulse and it turns out that many computations rely on on exactly this temporal precession.

A neurobiological “dogma” states that action potentials follow the *all-or-nothing* principle (E.D. Adrian and Zotterman 1926). Fortunately, the jelly fish *Aglanta digitalae* does not care much for dogmas and encodes its swimming patterns in different action potential shapes. So its not really a dogma or even a principle. But most action potentials really are very stereotypical events, hence its a common property. The all-or-nothing property can be construed to mean that the exact shape of the action potential does not matter¹ and that information is instead stored in the exact spike times or the frequency of their occurence.

This can be formalised to mean that the voltage evolution ought to be represented by a shifted pulse wave form

$$(1) v(t) = \sum_k A(t - t_k) = A(t) * \sum_k \delta(t - t_k),$$

where t_k are the spike times, which need to be defined later.

It also means that the action potential $A(t)$ should be stable under perturbations, but that inputs ought to be able to shift the occurrence of spikes in time. In mathematical terms, these *desiderata* read

- i) The action potential must be *stable* in amplitude,
- ii) yet *neutrally stable* in phase.

¹Actually it does, if you bring energetic considerations into baring.

To wit, (ii). just means that stimulus induced phase shifts should neither decay nor blow up.

3.3 Tonic spikes are limit cycles

The mathematical object that suffices the *desiderata* (i) and (ii) are limit cycles. They are closed orbits in phase space. Naturally, the state space need to be at least two dimensional for it to contain a limit cycle. What are the state variables? The membrane voltage, $v(t)$, typically in millivolts sounds like a reasonable one, at least that is what electrophysiologist measure. The conformational state of the ion channels also changes with time, $c_k(t)$, and so do ion concentration, say $[K^+]_o$. The exact governing equations are going to be derived in the following chapters. For now, denote a vector of state variables as

$$\vec{x} = \begin{pmatrix} v \\ c_1 \\ c_2 \\ [K^+]_o \\ \vdots \end{pmatrix}.$$

A general differential equation could have the following structure

$$(2) \quad \dot{\vec{x}} = \vec{F}(\vec{x}, \vec{\alpha}) + \vec{\eta}(\vec{x}, t)$$

\vec{F} is the time independent (homogeneous) flow field. $\vec{\eta}$ is a (often assumed small), possibly time dependent (inhomogeneous) perturbation to the system. $\vec{\alpha}$ are system's parameter. Parameters could be cell size and other fixed properties, but also a constant applied bias current. The change of solutions in response to variations in system's parameter will be studied later.

In the absence of perturbations, $\vec{\eta} = 0$, Eq. (2) becomes a *homogeneous ordinary differential equation*

$$(3) \quad \dot{\vec{x}} = \vec{F}(\vec{x}, \vec{\alpha}).$$

We are interested in the cases in which, at least for cerctain parameter values $\vec{\alpha}$, \exists a P -periodic *limit cycle* solution, with $\vec{x}_{lc}(t) = \vec{x}_{lc}(t + P)$, also known as *periodic orbit*. This solution is identified as the action potential if it suffices the requirements of amplitude-stability and time-shiftability (i) and (ii).

3.4 Limit cycle stability

Stability of is probed by studying small perturbation to an invariant set solution. Our invariant set is the limit cycle (periodic orbit) \vec{x}_{lc} . Assuming there was a *small* perturbation to the system the solution can be decomposed as

$$(4) \quad \vec{x}(t) = \vec{x}_{lc}(t) + \vec{y}(t)$$

with $\forall t : \|\vec{y}(t)\| < \epsilon$ some "small" perturbation to the orbit. What small, *i.e.*, ϵ is we do not want to say now, maybe later, lets see ...

Assuming the perturbation was transient (only in initial conditions) and the system is homogeneous again we plug the Ansatz of Eq. (4) into Eq. (3) and get

$$\frac{d}{dt} \vec{x}_{lc}(t) + \dot{\vec{y}}(t) = \vec{F}(\vec{x}_{lc}) + \underbrace{\nabla \vec{F}(\vec{x}_{lc})}_{\mathbf{J}(\vec{x}_{lc}(t))} \cdot \vec{y}(t)$$

The *Jacobi matrix* evaluated on the limit cycle can be written as a function of time $\mathbf{J}(t) = \nabla \vec{F}(\vec{x}_{lc}(t))$. Note that since the limit cycle solution is P -periodic, so is $\mathbf{J}(t) = \mathbf{J}(t + P)$.

Identifying the limit cycle solution above we are left with the *first variational equation* of Eq. (3)

$$(5) \quad \dot{\vec{y}}(t) = \mathbf{J}(t)\vec{y}(t).$$

Hence, one needs to study of linear system with periodic coefficients. One solution of Eq. (5) can be guessed, let us try the time derivative of the orbit, $\frac{d\vec{x}_{1c}}{dt}$

$$(6) \quad \frac{d}{dt} \left(\frac{d\vec{x}_{1c}}{dt} \right) = \frac{d}{dt} \vec{F}(\vec{x}_{1c}) = \nabla \vec{F}(\vec{x}_{1c}) \frac{d}{dt} \vec{x}_{1c} = \mathbf{J}(t) \frac{d\vec{x}_{1c}}{dt}.$$

So it is a solution alright, and it happens to be a P -periodic solution. This solution is called the *Goldstone mode*. But for arbitrary initial conditions not all solutions should be periodic.

Def: Floquet Ansatz According to Floquet theory the solution to Eq. (5) can be written in the form of a P -periodic similarity matrix² and an matrix exponential

$$(7) \quad y(t) = \mathbf{R}(t)e^{t\mathbf{\Lambda}}.$$

For the proof please consult (Chicone 2006), here we are just going to work with this as an Ansatz. The constant matrix $\mathbf{\Lambda}$ is called the *Floquet matrix*.

Recall the matrix exponential

Def: Matrix Exp Let $\mathbf{A} \in \mathcal{O}^{n \times n}$ then $\exp \mathbf{A} = \sum_{k=0}^{\infty} \frac{1}{k!} \mathbf{A}^k$ A useful corollary of this definition is that the eigen vectors of an exponentiated matrix are the same as those of the original and eigenvalues become exponentiated. If λ_i, \vec{w}_i are the eigenvalue, eigenvector pairs of the matrix \mathbf{A} , *i.e.*, $\mathbf{A}\vec{w}_i = \lambda_i\vec{w}_i$ then by using this identity k -times

$$(8) \quad e^{\mathbf{A}}\vec{w}_i = \left(\sum_{k=0}^{\infty} \frac{1}{k!} \mathbf{A}^k \right) \vec{w}_i = \sum_{k=0}^{\infty} \frac{1}{k!} \lambda_i^k \vec{w}_i = e^{\lambda_i} \vec{w}_i$$

Inserting the Floquet Ansatz into Eq. (5) yields

$$\dot{\mathbf{R}}e^{t\mathbf{\Lambda}} + \mathbf{R}(t)\mathbf{\Lambda}e^{t\mathbf{\Lambda}} = \mathbf{J}(t)\mathbf{R}(t)e^{t\mathbf{\Lambda}}.$$

Which by multiplying with $e^{-t\mathbf{\Lambda}}$ results in a dynamics equation for similarity matrix \mathbf{R} .

$$(9) \quad \dot{\mathbf{R}} = \mathbf{J}(t)\mathbf{R}(t) - \mathbf{R}(t)\mathbf{\Lambda}.$$

Remember that \mathbf{R} was invertable so one can also derive an equation for the inverse

$$(10) \quad \frac{d}{dt} \mathbf{R}^{-1} = -\mathbf{R}^{-1} \dot{\mathbf{R}} \mathbf{R}^{-1} = \mathbf{\Lambda} \mathbf{R}^{-1}(t) - \mathbf{R}^{-1}(t) \mathbf{J}(t).$$

3.4.1 Eigensystem of the Floquet matrix

The Floquet matrix, $\mathbf{\Lambda}$, is constant, though not necessarily symmetric. Hence it has an orthonormal left and right eigensystem

$$(11) \quad \mathbf{\Lambda} \vec{w}_i = \mu_i \vec{w}_i \text{ and } \vec{z}_i \mathbf{\Lambda} = \mu_i \vec{z}_i \text{ with } \vec{z}_i \cdot \vec{w}_j = \delta_{ij}.$$

The μ_k are called Floquet exponents, for reasons becoming obvious below. One can now define a “rotated” eigensystem

Def. 1 (“Rotated” eigensystem and Floquet modes)

The rotated eigensystem of a spike is $\vec{W}_i(t) = \mathbf{R}(t)\vec{w}_i$ and $\vec{Z}_i(t) = \vec{z}_i \mathbf{R}^{-1}(t)$. For which *ipso facto* obeys

$$(12) \quad \forall t : \vec{Z}_i(t) \cdot \vec{W}_j(t) = \delta_{ij}.$$

$\vec{W}_i(t)$ and $\vec{Z}_i(t)$ are also called the *Floquet modes*.

If we project the eigenvectors on the Eqs. (9) and (10) and use this definitions we get

$$(13) \quad \frac{d}{dt} \vec{W}_k = (\mathbf{J}(t) - \mu_k \mathbf{I}) \vec{W}_k(t)$$

and

$$(14) \quad \frac{d}{dt} \vec{Z}_k = (\mu_k \mathbf{I} - \mathbf{J}^\dagger(t)) \vec{Z}_k(t).$$

²For now this means that its an invertable matrix; $\forall t : \exists \mathbf{R}^{-1}(t)$

As a final test of what has been achieved by introducing the new time-dependent coordinate system of the right and left Floquet modes, project the general solution $y(t)$ from Eq. (7) on the the adjoint Floquet modes, $Z_k(t)$:

$$\vec{Z}_k(t) \cdot \vec{y}(t) = \vec{z}_k \mathbf{R}^{-1}(t) \mathbf{R}(t) e^{t\Lambda} = \vec{z}_k e^{t\Lambda} = \vec{z}_k e^{t\mu_k}.$$

Along these rotating basis one observes a simple exponential contraction or expansion depending on the sign of the Floquet exponents. The magnitude of the Floquet exponents is the rate of convergence in units of 1/Time. What if a Floquet exponent is zero? In fact, by comparing Eq. (6) and (13) one may observe that the Goldstone mode is always a solution to the

Note that if $\mu_0 = 0$,

$$(15) \quad \vec{W}_0(t) = \frac{d}{dt} \vec{x}_{1c}(t)$$

is the Goldstone mode, and from Eq. (12)

$$(16) \quad \vec{Z}_0(\phi) \cdot \frac{d}{dt} \vec{x}_{1c}(\phi) = \vec{Z}_0(\phi) \cdot \vec{F}(\vec{x}_{1c}(\phi)) = 1$$

W.l.o.g, let the Floquet exponents of a stable limit cycle be ordered such that

$$0 = \mu_0 \geq \mu_1 \geq \dots \geq \mu_{n-1}$$

What are left Floquet modes useful for? Here is an example. First, rewrite Eq. (14) for $k = 0$ in the form

$$\left(\frac{d}{dt} + J^\dagger(t)\right) \vec{Z}_0 = 0$$

Say one is interested in the change of the period of a limit cycle oscillator w.r.t. a parameter change. By rescaling time

$$\frac{d\vec{x}_{1c}}{dt} - P(\alpha) \vec{F}(\vec{x}_{1c}, \alpha) = 0$$

Taking the total derivative (and chain rule) one finds

$$\frac{\partial}{\partial \alpha} \frac{d\vec{x}_{1c}}{dt} - \frac{\partial P}{\partial \alpha} \vec{F} - P \frac{\partial \vec{F}}{\partial \alpha} - P \nabla \vec{F} \frac{\partial \vec{x}_{1c}}{\partial \alpha} = 0$$

The derivatives of the first term can be exchanged. Now project the equation from the left onto the zeroth Floquet mode

$$-\frac{\partial P}{\partial \alpha} (\vec{Z}_0 \cdot \vec{F}) - P (\vec{Z}_0 \cdot \frac{\partial \vec{F}}{\partial \alpha}) + \vec{Z}_0 \cdot \left(\frac{d}{dt} - PJ(t)\right) \frac{\partial \vec{x}_{1c}}{\partial \alpha} = 0$$

The last term can be rewritten by transposing the operator

$$\vec{Z}_0 \cdot \left(\frac{d}{dt} - PJ(t)\right) \frac{\partial \vec{x}_{1c}}{\partial \alpha} = - \underbrace{\left(\left(\frac{d}{dt} + PJ^\dagger(t)\right) \vec{Z}_0\right)}_{=0} \cdot \frac{\partial \vec{x}_{1c}}{\partial \alpha}$$

Hence

$$(17) \quad \frac{\partial P}{\partial \alpha} = -P(\vec{Z}_0 \cdot \frac{\partial \vec{F}}{\partial \alpha})$$

4 Spikes event time series and isochrons

4.1 Spike times and Isochrons

There is still a lack of a formal definition of the spike time t^{sp} in Eq. (1). Electrophysiologists typically envision a voltage threshold, but these would only exist if the voltage dynamics was a one dimensional equation, which it is not. In fact, it can not be if true limit cycles are to exist. In the general state-space of action potential dynamics there may exist a generalised *threshold manifold*. A reasonable alternative definition would take the (local) peak/maximum of the voltage

$$v(t^{\text{sp}}) = v_{\text{max}}.$$

Again, a definition based on properties of the state variables and it also leaves all other dimensions undefined. The general problem seems to be to *uniquely associate time with states*. If the dynamics was restricted to only on the limit cycle this is easy. As the maximum voltage value is only reached once per spike it also implies unique values for the other state variables, which can be called the *spike boundary condition*: \vec{x}_{sp} . Most importantly it also implies a unique time indices at which such events occur, $\vec{x}_{\text{lc}}(t^{\text{sp}}) = \vec{x}_{\text{sp}}$. The normalised time index of points on the limit cycle is also called the phase, $\phi \in [0, 1)$ s.t. $\vec{x}_{\text{lc}}(P\phi) = \vec{x}_{\text{lc}}(P(\phi + 1))$. Given synaptic bombardment, intrinsic noise and other perturbations the dynamics, however, may be temporarily not exactly on the limit cycle. The simple idea is that the time phase of any point in the basin of attraction of a limit cycle can be defined as the phase it converges back to when asymptotically approaching the limit cycle. To make this precise, first define the flow:

Def. 2 (*Flow of an ODE*)

For a given initial condition $\vec{x}_0 \in B \subset \mathbb{R}^n$, where B is the basin of attraction of the limit cycle, the *flow* or *trajectory* induced by the ODE in Eq. (3) is denoted as $\vec{x}(t; x_0)$.

Numerically, the flow can be evaluated by forward-integration of the ODE starting at a given initial value.

Def. 3 (*Asymptotic phase*)

For point $\vec{y} \in B$, in the basin of attraction of the limit cycle solution of Eq. (3), the *asymptotic phase*, ψ , is defined as

$$(18) \quad \psi(\vec{y}) = \operatorname{argmin}_{\psi} \lim_{t \rightarrow \infty} \|\vec{x}(t - \psi P; \vec{y}) - \vec{x}_{\text{lc}}(t; \vec{x}_{\text{sp}})\|.$$

Note that the limit cycle solution was initiated at time $t = 0$ at the spike boundary condition. Based on the asymptotic phase, the concept of isochrons can be introduced (Winfree 1974; Osinga and Moehlis 2010) as the *level sets* of constant phase:

Def. 4 (*Isochrons*)

The *isochron* manifolds, $\mathcal{I}(\phi)$, are the level sets of the asymptotic phase variable

$$\mathcal{I}(\phi) = \{\vec{y} \in B : \psi(\vec{y}) = \phi\}.$$

An isochron defines a $n - 1$ dimensional manifold of points that converge to the same asymptotic phase on the limit cycle.

Based on the isochron one can now define a spike as a crossing of the flow/trajectory with $\mathcal{I}(0)$.

Note: There are several other ways to define a phase (Hilbert transform, linear interpolation between spikes, ...). In principle, there should be monotonous mappings between each other.

4.2 Neutral dimension and phase shifts

An alternative to studying the high dimensional set of coupled nonlinear biophysical equations is to find an (approximately) *input/output(I/O)-equivalent* equation for the phase evolution like in *Fig. 1*. In the figure the phase is plotted as modulo 1. However, it is also convenient to consider the freely evolving phase since this is related to the *spike count* process,

$$N(t) = \lfloor \phi(t) \rfloor.$$

The k^{th} spike time is then defined as

$$\phi(t_k^{\text{SP}}) = k.$$

A spike-train can be written as

$$(19) \quad r(t) = \sum_k \delta(t - t_k^{\text{SP}}) = \sum_k \delta(\phi(t) - k).$$

Def. 5 (*I/O-equivalent phase oscillator*)

An I/O-equivalent phase oscillator produces with its threshold crossing process the same spike times $\{t_k^{\text{SP}}\}_k$ as a particular conductance-based model (Lazar 2010).

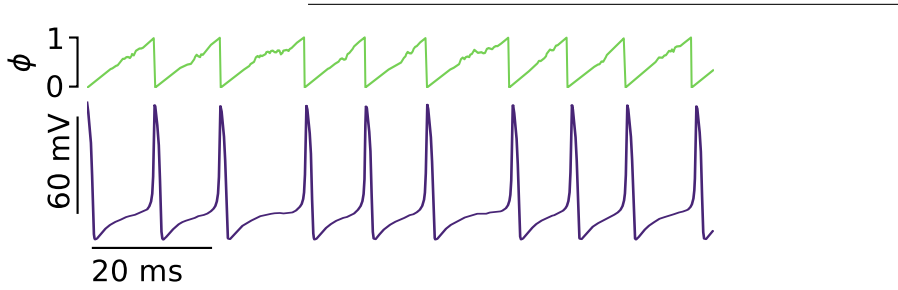


Fig. 1

The phase equation turns the spiking neuron into a one-dimensional level-crossing process with equivalent spike times. The phase is plotted modulo 1.

The evolution of the phase of Eq. (2) is given by the chain rule as

$$\frac{d\phi}{dt} = \nabla \phi(\vec{x}) \cdot \frac{d\vec{x}}{dt}.$$

To first order this is

$$(20) \quad \frac{d\phi}{dt} = \nabla \phi(\vec{x}_{1c}) \cdot \frac{d\vec{x}_{1c}}{dt} = \nabla \phi \cdot \vec{F}(\vec{x}_{1c}) + \nabla \phi \cdot \vec{\eta}(\vec{x}_{1c}, t).$$

The geometric interpretation of the phase gradient, $\nabla \phi$, is that it points perpendicular to the isochrons towards the steepest change of the asymptotic phase variable ϕ .

4.3 The empirical infinitesimal phase response curve

Def. 6 (*empirical PRC*)

Given a short δ -pulse of amplitude ϵ , delivered at a certain phase, ϕ , (time point) in the inter-spike interval of a tonically firing neuron the *linear* phase response is defined as

$$\text{PRC}(\psi) = \lim_{\epsilon \rightarrow 0} \frac{1}{\epsilon} \frac{P_0 - P_\epsilon(\psi)}{P_0}.$$

The underlying assumption of interpreting PRC is that it is a function, $\text{PRC}(\psi) : [0, 1) \mapsto \mathbb{R}$, that maps phase or time of occurrence of a perturbation to a persistent measurable phase shift. (Please appreciate how idealised and “noise free” these definitions are.) The convention is that a prolongation of interval corresponds to a phase delay, while shortening means phase advance.

The perturbed period can be written as the original period minus the phase shift converted back to time (by multiplying with the unperturbed period)

$$P_\epsilon = P_0 - \Delta\phi P_0.$$

Given that the time evolution of $\phi(t)$ has been perturbed at some time point $\psi P_0 < P_0$, The phase shift can be measured at the spike time of the unperturbed system as

$$\Delta\phi = \phi(P_0) - 1.$$

The empirical PRC in *Def. 6* can then be expressed as

$$\text{PRC}(\psi) = \frac{1}{\epsilon} \frac{P_0}{P_0} (1 - (\phi(P_0) - 1) - 1) = \frac{1}{\epsilon} (\phi(P_0) - 1).$$

Apply the identify operator of functions (convolution with a δ -function) on the left and the fundamental theorem of calculus on the right hand side then to first order

$$\epsilon P_0 \int_0^{P_0} \text{PRC}(\phi(t)) \delta(\psi - \phi(t)) dt = \int_0^{P_0} (\dot{\phi} - \frac{1}{P_0}) dt$$

This step is not really allowed, but for well behaved integrals we can identify the integrands to see

$$\dot{\phi} = \frac{1}{P_0} + \epsilon \text{PRC}(\phi) \delta(\psi - \phi).$$

One can bring this equation in agreement with the phase evolution in Eq. (20), if one identifies

$$\nabla\phi(\psi) = \text{PRC}(\psi) \text{ and } \nabla\phi(\psi) \cdot \vec{F}(\psi) = \frac{1}{P_0} = f_0.$$

4.4 Constant phase shift and adjoint equation

The assumption underlying the experimental procedure described in *Def. 6* is that the phase shift stays constant in time, say $\Delta\phi$. Without perturbation there is not long-term shift of the phase. Hence it must be the perturbation off the limit cycle which causes the phase shift. The phase change must be due to the $\Delta\vec{x}(t)$ and is given by

$$\Delta\phi = \nabla\phi \cdot \Delta\vec{x}(t) = \text{const. From } \frac{d\Delta\phi}{dt} = 0 \text{ one gets}$$

$$0 = \frac{d}{dt} \nabla\phi \cdot \Delta\vec{x} + \nabla\phi \cdot \frac{d}{dt} \Delta\vec{x}$$

Again the evolution of $\Delta\vec{x}(t)$ can be linearised if it is small

$$0 = \frac{d}{dt} \nabla\phi \cdot \Delta\vec{x} + \nabla\phi \cdot \mathbf{J}(t) \Delta\vec{x} = \left(\frac{d}{dt} \nabla\phi + \mathbf{J}^\dagger(t) \nabla\phi \right) \cdot \Delta\vec{x}$$

Such that by Fredholm’s alternative

$$\frac{d}{dt} \nabla\phi = -\mathbf{J}^\dagger(t) \nabla\phi$$

This is the same ODE as for the zeroth left Floquet mode, rendering them identical up to scaling.

5 The continuum limit of a membrane patch

Motivation and aim

In this lecture ion channels are introduced as stochastic devices floating in the membrane of a nerve cell. It should motivate why the analysis techniques and models introduced in this lecture need to deal with fluctuations and noise. (Nerve) cells produce stochastic processes on several levels:

1. The ion channels in their membrane stochastically jump between conformations, governed by *Master equations*.
2. On a more macroscopic level their membrane voltage fluctuations show properties of coloured noise, well described by diffusion processes and *stochastic differential equations*.
3. The trains of action potentials they emit from *point processes*.

In the stationary state these processes can be subjected to *spectral analysis*.

Note that in 1952, the first equations describing membrane voltage dynamics were the deterministic rate equations by Hodgkin & Huxley (Hodgkin and Huxley 1952). Only in 1994 Fox and Lu derived these equations from the continuum limit of an ensemble of stochastic ion channels (Fox and Lu 1994). Essentially, this was achieved by doing a *diffusion approximation* in the thermodynamic limit of many ion channels.

Finally, in 1998 the structure of a K^+ ion channel from *Streptomyces lividans*, which is nearly identical to *Drosophila*'s shaker channel was discovered using X-ray analysis (Doyle 1998).

Since then the nuances of applying diffusion approximations to neurons have been investigated (Linaro, Storace, and Giugliano 2011, Orio and Soudry (2012)) and reviewed (Goldwyn et al. 2011, Goldwyn and Shea-Brown (2011), Pezo, Soudry, and Orio (2014)).

5.1 Empirical assertions about ion channels

Observation 1 (*Concerning the ion channels of excitable membranes*)

- i) Ion pores show different degrees of *selectivity* to ionic species. Understanding of the mechanisms of the ionic filter was achieved by structural analysis (Doyle 1998). Potassium channels conduct K^+ 1000 fold more than Na^+ and allow for conduction rate of 10^8 ions per second.
- ii) In single channel patch experiments ion channels show *discrete levels of conductivity*, which look like a Telegraph process.
- iii) Independent ion channels (no cooperativity or spatial heterogeneity)
- iv) Membrane bound proteins like many others change conformation on various triggering signals:
 - a change in pH
 - a change in the surrounding electric field
 - mechanical pressure
 - ligand binding

To relate measured voltage changes to ion flux across the membrane note that according to Kirchoff's law and electro neutrality

$$C \frac{dv}{dt} = \frac{F\Omega}{A} \left(\frac{d[\text{Na}^+]_i}{dt} + \frac{d[\text{K}^+]_i}{dt} + \frac{d[\text{Cl}^-]_i}{dt} \right)$$

The currents are assumed to follow Ohms law:

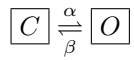
$$\frac{F\Omega}{A} \frac{d[\text{K}^+]_i}{dt} = \gamma N_K (E_K - v)$$

where γ is the unitary conductance and N is the total number of open pores.

5.2 First-order rate kinetics

Starting with a hypothetical ion pore of which there is a fixed total concentration, $[\text{Pore}] = \text{const}$. The pore an open conformation, O , in which, say only K^+ , ions can pass and a closed states, C , which blocks ion flow completely:

Def. 7 (*Two-state ion-channel*)



Based on the *law of mass-action*, the corresponding first-order rate equation is

$$\frac{d[O]}{dt} = \alpha[C] - \beta[O] = \alpha([\text{Pore}] - [O]) - \beta[O]$$

The second equality is by *conservation of mass* $[O] + [C] = [\text{Pore}] = \text{const}$.

has the typical structure of its stochastic counterpart the Master equation of a birth-death process.

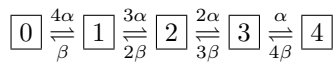
Hodgkin and Huxley normalised the equation by defining $n(t) = \frac{[O]}{[\text{Pore}]}$.

$$\frac{dn}{dt} = \alpha(1 - n) - \beta n = \left(\frac{\alpha}{\alpha + \beta} - n \right) (\alpha + \beta) = (n_\infty - n) / \tau$$

Under a voltage-clamp experiment, for each voltage level this equation predicts an exponential charge up to a level n_∞ with the time constant τ that could be fitted.

Hodgkin and Huxley discovered that their measured traces could not be fitted well by the above equation.

Def. 8 (*A tetrameric K^+ pore*)



5.3 The ion channel as a Markov model

Instead of writing down heuristic macroscopic laws for channel concentrations, one can attempt to derive them from microscopic dynamics of single pores. For this the state diagram in *Def. 7* is reinterpreted as the state of a single molecule.

Based on *Obs. 1* such single channel dynamics can be described by a finite state Markov model which is mathematically described as a Master equation.

A Markov model represented by a *graph* like *Def. 8* is a special kind of *chemical reaction network* studied in systems biology. The connectivity/topology can be stored in a

Def. 9 (*Stoichiometry matrix*)

The stoichiometry matrix, $\mathbf{N} \in \mathbb{N}^{m \times n}$ describes n reactions (transitions) involving m chemical species (states). It can be decomposed into the educt matrix \mathbf{E} and the product matrix \mathbf{P} by $\mathbf{N} = \mathbf{P} - \mathbf{E}$

The stoichiometry matrix of *Def. 8* would look like

$$\mathbf{N} = \begin{pmatrix} -1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 & -1 & 1 & 0 & 0 \\ 0 & 1 & -1 & 0 & 0 & -1 & 1 & 0 \\ 0 & 0 & 1 & -1 & 0 & 0 & -1 & 1 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & -1 \end{pmatrix}$$

In addition one needs the *rate vector*

$$\vec{v} = [4\alpha, 3\alpha, 2\alpha, \alpha, \beta, 2\beta, 3\beta, 4\beta]^\top$$

to define the complete reaction network for the channel.

To understand the dynamical evolution of occupation propability of different conformational states, take the two-state channel as an example. Define a vector of the probability of being closed and open, $\vec{p} = [p_C, p_O]^\top$, respectively.

In actuality the channels are part of the membrane dynamical system, where α and β depend at least on v and hence are not constant during a spike. One needs an update rule of how to get from the probability of being open at time t to the probability of begin open at time $t + dt$. Given are the rates, so the propabilities of change in an interval of time dt are the rates times the interval length, *e.g.* $dt\beta$. For the two state channel this can be summarised in matrix notation

$$\begin{pmatrix} p_C(t + dt) \\ p_O(t + dt) \end{pmatrix} = \begin{pmatrix} 1 - \alpha dt & \beta dt \\ \alpha dt & 1 - \beta dt \end{pmatrix} \begin{pmatrix} p_O(t) \\ p_C(t) \end{pmatrix}$$

or in vector form

$$\vec{p}(t + dt) = (\mathbf{I} + \mathbf{Q}dt)\vec{p}(t)$$

The infinitesimal limit yields a kind of Kolmogorov forward-equation

$$(21) \quad \frac{d}{dt}\vec{p} = \mathbf{Q}\vec{p}.$$

Def. 10 (*Transition rate matrix*)

The *transition rate matrix* (or infinitesimal generator) is $\mathbf{Q} \in \mathbb{R}^{m \times m}$.

In general the transition rate matrix can be obtained from the graph

$$\mathbf{Q} = \mathbf{N} \text{diag}(\vec{v}) \mathbf{E}^\top.$$

Exercise 1 (*Transition rate matrix*)

Derive \mathbf{Q} of a three state channel

$$\boxed{0} \xrightleftharpoons[\beta]{3\alpha} \boxed{1} \xrightleftharpoons[2\beta]{2\alpha} \boxed{2} \xrightleftharpoons[3\beta]{\alpha} \boxed{3}$$

Note that Eq. (21), though a consistent description of the occupation probabilities, does not give us realisations or sample paths comparable to the traces measured in single-channel patch clamp experiments.

5.4 Sample path of a telegraph process (simulation a jump process)

Given a total number of ion channels N , the goal is to track the actual number of channels in a particular state. Based on reaction rate theory and given a certain reaction rate a , the number k of reaction events in a time window is

$$k \sim \text{Poisson}(a) = \frac{a^k e^{-a}}{k!}.$$

If several reactions can occur and several molecules are involved then (because Poisson distribution is closed under convolution) one has

$$k \sim \text{Poisson}\left(\underbrace{\sum_j N_j a_j}_{\lambda}\right).$$

So the rate of the occurrence of **any** reaction is given by this linear combination of the rates of individual reactions. The waiting time distribution between reactions is exponential with the same rate:

$$p(t) = \lambda e^{-\lambda t}$$

Starting in a particular state $\vec{N} = [N_1, \dots, N_n]$ at time t_0 the life time of staying in that state until $t_0 + t$ is The escape rate of the state is (any reaction occurring)

$$\lambda = \sum_{k=1}^n N_k a_k$$

where a_k are the rate of leaving state k . For example a_3 in the K^+ -channel is

$$a_3 = 2\beta + 2\alpha$$

But **which reaction** did occur? Let j be the reaction (not the state!). For example, there are 8 reactions in the K^+ channel. The probabilities of occurrence associated with any one of them is

$$p(j) = \frac{N_j a_j}{\sum_{k=1}^{N_{\text{reac}}} N_k a_k} = N_j a_j / \lambda$$

In a computer algorithm one can draw the waiting time for the next reaction simply by generating a uniform random number $r_1 \sim U(0, 1)$ and then

$$\tau \leftarrow \ln(r_1^{-1}) / \lambda$$

The reaction is determined with a second random number $r_2 \sim U(0, 1)$

$$P(j) = \sum_{k=1}^j p(k)$$

$$j \leftarrow \text{argmax}_j P(j) < r_2$$

while

 r1 = rand

 r2 = rand

 tau = ln(1/r1) / a

5.5 Statistical properties

With $p_C = 1 - p_O$ we can express one row of this equation as

$$\dot{p}_O = \alpha p_O - \beta(1 - p_O)$$

or

$$\tau \dot{p}_O = p_O^{(\infty)} - p_O \text{ with } \tau = \frac{1}{\alpha + \beta} \text{ and } p_O^{(\infty)} = \frac{\alpha}{\alpha + \beta}$$

which has solution

$$p_O(t) = p_O^{(\infty)} (1 - e^{-t/\tau})$$

Fourier transformation leads to

$$\tau i\omega \tilde{p}(\omega) = p_O^{(\infty)} - \tilde{p}(\omega)$$

or

$$\tilde{p}(\omega) = \frac{p_O^{(\infty)}}{1 + i\tau\omega}$$

$$|\tilde{p}(\omega)|^2 = \tilde{p}(\omega) \tilde{p}^*(\omega) = \frac{p_O^{(\infty)2}}{1 + (\tau\omega)^2}$$

a Lorentzian spectrum. Inverse Fourier transform yields the covariance function

$$c(\tau) = \langle p_O(t)p_O(t + \tau) \rangle$$

An ionic current produced in the open state would be

$$I^{\text{ion}} = \gamma_{K^+} N_O (E_{K^+} - v)$$

γ_{K^+} and E_{K^+} are the unitary conductance and the Nernst potential respectively. The average such current would be

$$\langle I^{\text{ion}} \rangle = \gamma_{K^+} N p_O (E_{K^+} - v)$$

where N is the total number of channels in the membrane patch under consideration. But what about a particular stochastic realisation of the current, what about the fluctuations around the mean?

If we have N channels than the number of k of them being open is binomially distributed

$$P_O(k) = \binom{N}{k} p_O^k p_C^{N-k}$$

5.5.1 The n -state channel

Let us try to calculate the statistics of the current originating from an n -state channel (just like in the two state case). *Why* would one do this? The idea, later on is to be able to find a continuous stochastic process that we can simulate and analyse easily.

Let $K(t) \in [1, \dots, n]$ be the realisation of the n -state Markov channel. For example a K^+ -channel with four subunits

$$\boxed{0} \xrightleftharpoons[\beta]{4\alpha} \boxed{1} \xrightleftharpoons[2\beta]{3\alpha} \boxed{2} \xrightleftharpoons[3\beta]{2\alpha} \boxed{3} \xrightleftharpoons[4\beta]{\alpha} \boxed{4}$$

For the K^+ channel with $n = 4$ conformations states, of which one is conducting, let us further define

$$G(t) = \delta_{4K(t)} = \begin{cases} 1 & : K(t) = 4 \\ 0 & : K(t) < 4. \end{cases}$$

If there are several conducting states (with possibly different conductance level, one could have *e.g.*, $G = \delta_{2K(t)} + 2\delta_{4K(t)}$).

The single channel current at a voltage clamp $v(t) = v$ is then

$$(22) \quad I(t) = \gamma G(t)(E - v).$$

How does it evolve? Define $p_i(t) = P(K(t) = i)$ and $\vec{p}(t) = [p_1, \dots, p_n]^\dagger$, then

$$(23) \quad \frac{d}{dt} \vec{p} = \mathbf{Q} \vec{p}$$

With formal solution

$$\vec{p}(t) = e^{\mathbf{Q}t} \vec{p}(0) = \underbrace{(e^{\mathbf{Q}t})}_{\mathbf{M}} \vec{p}(0) = \mathbf{M}^t \vec{p}(0)$$

Use the singular value decomposition, $\mathbf{M} = \mathbf{U} \mathbf{\Sigma} \mathbf{V}^\dagger$, the matrix power can be written as $\mathbf{M}^t = \mathbf{U} \mathbf{\Sigma}^t \mathbf{V}^\dagger$. Or (recall Eq. (8))

$$(24) \quad \vec{p}(t) = \sum_{k=1}^n \vec{u}_k \vec{v}_k^\dagger e^{\nu_k t} \vec{p}(0).$$

If Eq. (23) has a stationary distribution in the $t \rightarrow \infty$ limit, then this must correspond to the eigenvalue $\nu_1 = 0$ (let us assume they are ordered). So $\frac{d}{dt} \vec{p}(\infty) = 0 \implies$ for $\vec{p}(\infty) = \vec{v}_1, \exists \nu_1 = 0 : \mathbf{Q} \vec{v}_1 = \nu_0 \vec{v}_1 = 0$. Therefore, the solution can be written as

$$(25) \quad \vec{p}(t) = \vec{p}(\infty) + \sum_{k=2}^n \vec{u}_k \vec{v}_k^\dagger e^{\nu_k t} \vec{p}(0).$$

The average channel current of Eq. (22) is

$$\langle I(t) \rangle = \gamma(E - v) \sum_{k=1}^n p_k(t) \delta_{1k} = \gamma(E - v) (p_1(\infty) + \sum_{k=2}^n u_{1k} v_{1k} p_1(0) e^{\nu_k t}),$$

which if the chain is stable ($\nu_k < 0 : \forall k > 1$) has steady state

$$\langle I \rangle = \lim_{t \rightarrow \infty} \langle I(t) \rangle = p_1(\infty).$$

The steady state covariance $C(\Delta) = \lim_{t \rightarrow \infty}$ in this case is

$$C_t(\Delta) = \langle I(t)I(t+\Delta) \rangle - \langle I \rangle^2 = \gamma^2(E-v)^2 \sum_{j,k=1}^n \delta_{1j} \delta_{1k} p_j(t) p_k(t+\Delta) - \langle I \rangle^2$$

Hence

$$C_t(\Delta) = p_1(t)p_1(t+\Delta) - \langle I \rangle^2 = \sum_{i,j=2}^n [\underbrace{\vec{u}_i \vec{v}_i^\dagger \vec{v}_j \vec{u}_j^\dagger}_{=\delta_{ij}}]_{11} e^{\nu_i t + \nu_j(t+\Delta)}$$

If $\nu_k < 0 : \forall k > 1$ then

$$(26) \quad C(\Delta) = \sum_{i=2}^n u_{1i} u_{1i} e^{\nu_i \Delta}$$

is a sum of exponentials. The spectral density is a superposition of Lorenzians.

5.6 Statistically equivalent diffusion process (Orenstein-Uhlenbeck Process)

The jump process discussed in the previous sections is a continuous time Markov-process on a discrete domain, $K(t) \in \mathbb{N}$ with $t \in \mathbb{R}$. A *diffusion process* is a continuous time Markov-process on a continuous domain, $\eta(t) \in \mathbb{R}$ with $t \in \mathbb{R}$.

Can are in search for a a diffusion process such that

$$I = \gamma(p_1(\infty) + \sum_{k=2}^n \eta_k(t)) (E - v)$$

has the same first and second order statistics (in voltage clamp) as Eq. (22)? Let us try

$$(27) \quad \tau_k(v) \dot{\eta}_k = -\eta_k + \sigma(v) \xi(t) \text{ where } \langle \xi(0) \xi(\Delta) \rangle = \delta(\Delta)$$

To solve it, use the Fourier Transform

$$i\omega \tau \tilde{\eta}(\omega) = -\tilde{\eta}(\omega) + \sigma \chi(\omega)$$

The place holder symbol χ was introduced for the Fourier transform of the stochastic process $\xi(t)$. Rearranging yields

$$\tilde{\eta} = \frac{\sigma \chi(\omega)}{1+i\omega\tau}$$

The spectrum is

$$\tilde{\eta}(\omega) \tilde{\eta}^*(\omega) = \frac{\sigma^2 \chi(\omega) \chi^*(\omega)}{1+(\tau\omega)^2}$$

By definition $\chi(\omega) \chi^*(\omega)$ is the Fourier Transform of the covariance function $\delta(\Delta)$ and from Eq. (???) this is one. Hence,

$$\tilde{\eta}(\omega) \tilde{\eta}^*(\omega) = \frac{\sigma^2}{1+(\tau\omega)^2}$$

Applying the inverse Fourier transform results in the correlation function

$$C(t) = \frac{\sigma^2}{\tau} e^{-|t|/\tau}.$$

A super position of independent such OU process

$$\sum_{k=i}^n \eta_i(t)$$

leads to a correlation function with the same structure as in Eq. (26). We identify $\tau_i = 1/\nu_i$ and $\sigma_i = u_{1i}$.

The idea of matching the second order statistics can be formulated in a far more abstract way in terms of the Kramers-Moyal-van-Kampen expansion of the Master equation

$$\dot{p} = \int w(x' \rightarrow x)p(x', t) - w(x \rightarrow x')p(x, t)dx'$$

$$\partial p(x, t) = \sum_{n=1}^{\infty} \frac{\partial^n}{\partial x^n} K_n(x, t)p(x, t)$$

from

6 Continuation of fixpoints and orbits

Often small changes, say in an ion channel density, has only small quantitative effect on a neurons behaviour.

Often numerical solutions to nonlinear ordinary differential equations are found by (forward) time-integration. An interesting alternative is to track a found solution through parameter space, for which the solution must be *persistent* in a certain parameter. If it is *not*, then a *bifurcation* occurs and one observes a *qualitative change* of the solution. The study of system solutions under parameter perturbations is also the subject of *sensitivity analysis*.

For book on bifurcation theory consult (Izhikevich 2007) and numerical bifurcation analysis (Kielhöfer 2011).

6.1 Continuation of fixed points

Assume for

$$\dot{\vec{x}} = \vec{F}(\vec{x}, \alpha)$$

there is a steady state solution

$$(28) \quad \vec{F}(\vec{x}, \alpha) = 0$$

In biological systems like cells, parameters are rarely stable over longer periods, because there is a continuous turnover (synthesis and degradation) of all molecules. Hence, so one should be interested in *families* of solutions for varying parameters, $\vec{x}(\alpha)$.

Def. 11 (*solution banch*)

A *branch*, *famiily* or curve of solutions with regard to an index parameter α is denoted as $\vec{x}(\alpha)$.

The existence of the solution as a function of the parameter is governed by the *implicite function theorem*:

Theorem 1 (*Implicite function theorem*)

Consider a system of equations

$$\vec{F}(\vec{x}, \alpha) = 0, \text{ with } \vec{F} \in \mathbb{R}^n, \vec{x} \in \mathbb{R}^n, \alpha \in \mathbb{R} \text{ and } \nabla_{x,\alpha} \vec{F} \in \mathbb{R}^{n \times n+1}.$$

Let f and $\nabla_{x,\alpha} \vec{F}$ be smooth near x . Then if the Jacobian $\nabla_{x,\alpha} \vec{F}$ is nonsingular, \exists a unique, smooth solution family $\vec{x}(\alpha)$ such that

$$\vec{F}(\vec{x}(\alpha), \alpha) = 0.$$

This establishes the existence of lines in a bifurcation diagram.

The method of continuation is a *predictor-corrector* method. In practice, assume the fixpoint is known for one particular parameter value α_0 , then for a small change in parameter the solution is is predicted

Predictor step: Taylor's linearisation

$$(29) \quad \vec{x}(p + \delta p) \approx \vec{x}(p) + \delta p \frac{\partial \vec{x}}{\partial p}.$$

To predict the new solution, the old solution is required and the derivative of the solution w.r.t. the parameter that is changed. How to compute the latter? Take the total derivative of Eq. (28) w.r.t. the parameter

$$(\nabla_x f) \frac{\partial \vec{x}}{\partial p} + \frac{\partial \vec{f}}{\partial p} = 0.$$

with formal solution

$$\frac{\partial \vec{x}}{\partial p} = -(\nabla_x \vec{f})^{-1} \frac{\partial \vec{f}}{\partial p}.$$

If $\nabla_x \vec{f}$ is full rank one can use some efficient linear algebra library to find the vector $\frac{\partial \vec{x}}{\partial p}$ and back insert it into Eq. (29). For too large δp the predicted solution will be wrong. Yet, it is a good initial guess form which to find the correct version.

Corrector step: Newton iterations to find the root of $\vec{f}(\vec{x}, p)$

$$(30) \quad \vec{x}_{n+1} = \vec{x}_n - (\nabla_x \vec{f})^{-1} \vec{f}(\vec{x}_n, p)$$

Actually that Newton's iterations are also obtained by linearisation

$$0 = \vec{f}(\vec{x}_{n+1}, p) = \vec{f}(\vec{x}_n) + (\nabla_x \vec{f})(\vec{x}_{n+1} - \vec{x}_n),$$

which if solved for \vec{x}_{n+1} yields Eq. (30).

Convergence analysis of Newton iterations yields that with each newton iterations the number of correct decimal places doubles. Hence often a low number of iterations (3-7) suffice to achieve sufficient numerical accuracy.

Example 2 (*Continuation of the QIF model*)

$$\dot{v} = I + v^2 = F(v, I) \text{ with the solution branches } v(I) = \pm\sqrt{-I}.$$

From $\nabla_v F = 2v$ and $\frac{\partial F}{\partial I} = 1$, one gets $\frac{\partial v}{\partial I} = -\frac{1}{2v} = -\frac{1}{2\sqrt{-I}}$. What happens at $I = v = 0$?

Example: Say $f(x, p) = \sqrt{x^2 + p^2} - 1$, then the solution branches are $x(p) = \pm\sqrt{1 - p^2}$. The linear stability analysis $\partial_x f = \frac{x}{\sqrt{x^2 + p^2}}$ that

$$x > 0 \rightarrow \partial_x f > 0 \rightarrow \text{unstable}$$

$$x < 0 \rightarrow \partial_x f < 0 \rightarrow \text{stable}$$

Also $\partial_p f = \frac{p}{\sqrt{x^2 + p^2}}$ and thus $\partial_p x = \frac{p}{x} = \frac{p}{\pm\sqrt{1 - p^2}}$. What happens at $p = \pm 1$ or $x = 0$?

Or more general: What happens if we find that the condition number of $\nabla \vec{f}$ explodes?

In the example above the branch switches its stability and it bends back in a *fold* or *turning point*. In general folds can occur with and without stability change.

6.2 Local bifurcations: What happens if $\nabla \vec{f}$ is singular?

Bifurcating analysis is one big "case discrimination" task. Luckily, and due to topology the cases are, given certain constraints, finite.

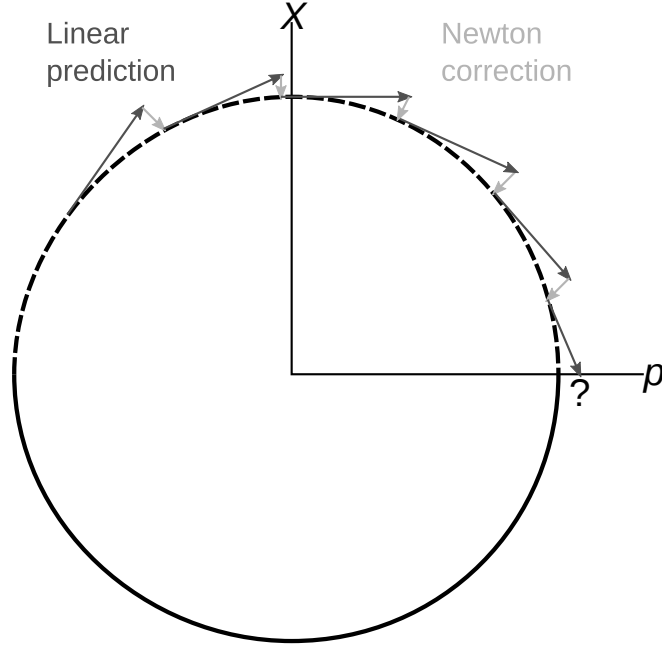
6.2.1 Folds and one-dimensional nullspaces

Recall some definitions

Def. (nullspace, kernel): The kernel or nullspace of a matrix J is

$$N(J) = \{\vec{x} \in \mathbb{R}^n \mid J\vec{x} = 0\}$$

Def. (range, image): The range of a matrix J is



Numerical continuation

$$R(\mathbf{J}) = \{\vec{y} | \exists x \in \mathbb{R}^n : \mathbf{J}\vec{x} = \vec{y}\}$$

Def: Let Q be the projection onto the range

Def: Eigensystem at the fold. Let Jacobian matrix $\mathbf{J} = \nabla \vec{f}(\vec{x}(0), p(0))$

$$\mathbf{J}\vec{r}_k = \lambda_k \vec{r}_k \text{ and } \vec{l}_k \mathbf{J} = \lambda_k \vec{l}_k.$$

So that the nullspace is spanned by \vec{l}_0 .

This section considers $\dim N(\mathbf{J}) = 1$. Hence, the implicate function theorem is not applicable. From the example above it is apparent that $\vec{x}'(p) = \infty$ at the bifurcation. The problem can be circumvented by defining a new “arclength parameter”, $p(s)$. The bifurcation branch is then a parametric curve, $(\vec{x}(s), p(s))$. Without loss of generality the bifurcation is to be at $s = 0$.

If the Jacobian matrix $\mathbf{J} = \nabla \vec{f}$ is rank-deficient the Lyapunov-Schmidt reduction can be applied. Intutiefely the problem is reduced from a high-dimensional, possibly infinite-dimensional, one to one that has as many dimension as the deffect of ∇f .

The nullspace is spanned by the eigenvector, r_0 of \mathbf{J} , corresponding to the eigenvalue 0.

Assume that f is twice differentiable w.r.t. \vec{x} , then differentiate $\vec{f}(\vec{x}(s), p(s)) = 0$ w.r.t. s and evaluate at $s = 0$

$$(31) \quad \frac{d}{ds} \vec{f}(\vec{x}(s), p(s)) = \nabla_x \vec{f} \vec{x}'(s) + \partial_p \vec{f} p'(s) = \mathbf{J} \vec{x}'(s) + \partial_p \vec{f} p'(s)$$

Let $\mathbf{H} = \nabla \nabla_x \vec{f}$ be the Hessian tensor.

$$\frac{d^2}{ds^2} \vec{f} = \mathbf{H} \vec{x}'(s) \vec{x}'(s) + \mathbf{J} \vec{x}''(s) + \partial_p^2 \vec{f} p'(s) + \partial_p \vec{f} p''(s) = 0$$

At $s = 0$ one has $p'(0) = 0$ and hence from Eq. (31) $\vec{x}'(0) = \vec{r}_0$. Projecting onto the left-eigenvector \vec{l}_0 to the eigenvalue 0. at $s = 0$ one finds

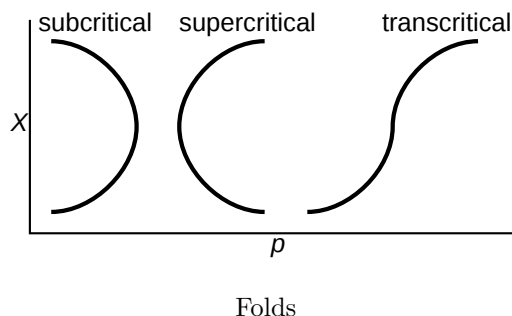
$$\vec{l}_0 \mathbf{H} \vec{r}_0 \vec{r}_0 + \vec{l}_0 \partial_p \vec{f} p''(0) = 0$$

or with $\partial_p \vec{f} \notin R(\mathbf{J})$

$$p''(0) = -\frac{\vec{l}_0 \mathbf{H} \vec{r}_0 \vec{r}_0}{\vec{l}_0 \partial_p \vec{f}}.$$

This is a test function of whether the bifurcation is

- (i) subcritical ($p''(0) < 0$)
- (ii) supercritical ($p''(0) > 0$)
- (iii) transcritical



Def: Let P be the projection onto the null space

There are several cases to be distinguished.

The fold: If the rank deficiency is one-dimensional, $\dim N(\mathbf{J}) = 1$.

The Andronov-Hopf: If the rank deficiency is two-dimensional.

6.3 Stability exchange

At a simple fold one eigenvalue is zero. Study the eigen system of $\mathbf{J} = \nabla \vec{f}(\vec{x}(s), p(s))$ near $s = 0$

$$\mathbf{J}(\vec{r}_0 + \vec{w}(s)) = \lambda(s)(\vec{r}_0 + \vec{w}(s)).$$

With a bit of analysis

$$\lambda'(0) = -\vec{l}_0 \cdot \partial_p \vec{f}(\vec{x}(0), p(0)) p''(0)$$

6.3.1 Extended system

Continue the extended system (linear and nonlinear)

$$\vec{f}(\vec{x}(p), p) = 0$$

$$\nabla \vec{f}(\vec{x}, p) \vec{w} = 0$$

$$(\nabla \vec{f}(\vec{x}, p))^T \vec{z} = 0$$

6.4 Continuation of boundary value problems and periodic orbits

The same procedure than above can be applied to the continuation of periodic orbits and boundary value problems. Define the implicit function to encompass the time derivative

$$\vec{g}(\vec{x}, p) = \frac{d}{dt} \vec{x} - T \vec{f}(\vec{x}, p) = 0, \text{ with } t \in [0, 1].$$

Then proceed as above. Note that the time derivative d/dt is a linear operator which has a matrix representation just like the Jacobian. in that sense

$$\nabla_x \frac{d}{dt} \vec{x} = \frac{d}{dt} \mathbf{I}$$

Def. 12 (*saddle-node/fold bifurcation*)

The fixpoint defined by $\vec{F}(\mathbf{x}^{\text{sn}}, \alpha_{\text{sn}}) = 0$ is a fold of a saddle and a node if

- i) the Jacobian $J(\mathbf{x}^{\text{sn}}, \alpha_{\text{sn}})$ has one eigenvalue $\lambda_0(\mathbf{x}^{\text{sn}}, \alpha_{\text{sn}}) = 0$ with algebraic multiplicity one,
- ii) $\frac{\partial^2 \lambda_0}{\partial \alpha^2} |_{\mathbf{x}^{\text{sn}}, \alpha_{\text{sn}}} \neq 0$

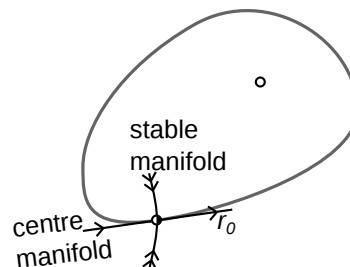
Def. 13 (*Hopf bifurcation*)

Assuming all but two eigenvalues have negative real parts, except for a conjugate pair of purely imaginary eigenvalues.

7 Normal forms, centre manifold and simple spiking models

7.1 Example: Dynamics in the centre manifold of a saddle-node

At arbitrary parameters the periodic solution adjoint to the first variational equation on the limit cycle yields the PRC. It can be calculated numerically with the continuation method. Near a bifurcation, however, if major parts of the dynamics happen in the centre manifold the PRC can be calculated analytically. As an example take the saddle-node on limit cycle bifurcation (SNLC). The spike in this case is a *homoclinic orbit* to a saddle-node, that enters and leaves via the semi-stable (centre) manifold that is associated with the eigenvalue $\lambda_0 = 0$ of the Jacobian at the saddle.



Saddle-node on a limit cycle (SNLC). The dynamics on the stable manifold is fast $\dot{x} = \lambda_1 x$, while the dynamics along the centre subspace is slow $\dot{x} = bx^2$.

$$(32) \quad \dot{\vec{x}} = \vec{F}(\vec{x}) + p \vec{G}(\vec{x})$$

$$\begin{pmatrix} c\dot{v} \\ \tau\dot{n} \end{pmatrix} = \begin{pmatrix} I - I(n, v) \\ n_\infty(v) - n \end{pmatrix}$$

Let there be a saddle-node (fold) bifurcation at some value p_0 and the saddle-node position is \vec{x}_0 . In the previous lecture we noted that if the bifurcation is not transcritical (degenerated)

$$\frac{d^2 p(s)}{ds^2} = -\frac{\vec{l}_0 \mathbf{H} \vec{r}_0 \vec{r}_0}{\vec{l}_0 \partial_p \vec{F}} \neq 0$$

The change of the solution w.r.t. the pseudo-arclength parameter was

$$\frac{d\vec{x}}{ds} = \vec{r}_0.$$

Given that the linear part of the dynamics is degenerated at the bifurcation, one might look at the leading nonlinear term.

Expanding the right-hand side around *saddle-node fixpoint*, \vec{x}_0 , yields (B. Ermentrout 1996)

$$\vec{F}(\vec{x}_0 + \delta\vec{x}) = \vec{F}(\vec{x}_0) + \mathbf{J}(\delta\vec{x}) + \mathbf{H}(\delta\vec{x})(\delta\vec{x}) + \dots$$

Establish the eigen system at the saddle-node $\mathbf{J} = \nabla \vec{f}(\vec{x}_0)$

$$\vec{l}_k \mathbf{J} = \lambda_k \vec{l}_k \quad \text{and} \quad \mathbf{J} \vec{r}_k = \lambda_k \vec{r}_k \quad \text{with} \quad \vec{l}_j \cdot \vec{r}_k = \delta_{jk}.$$

By assumption of a saddle-node the Jacobian has a simple zero with an associated eigenvector. All other eigenvalues are exponentially contracting $\lambda_k < 0, \forall k > 0$, while \vec{r}_0 is slow.

Def (centre subspace): The subspace spanned by \vec{r}_0 is called the *centre subspace* or *slow subspace*.

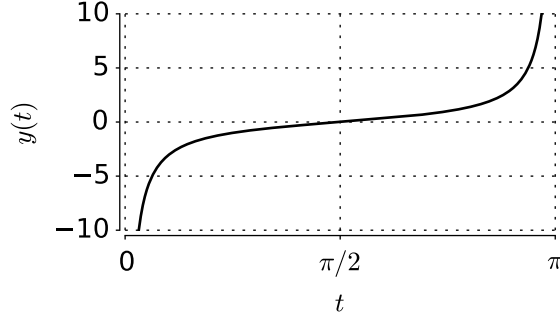
Write the dynamics around the saddle-node as $\vec{x}(t) = \vec{x}_0 + y\vec{r}_0$, and also use small changes in the bifurcation parameter $p_0 + p$. Then Eq. (32) is

$$\frac{d\vec{x}_0}{dt} + y\vec{r}_0 = \vec{F}(\vec{x}_0, p_0) + y\mathbf{J}\vec{r}_0 + y^2\mathbf{H}\vec{r}_0\vec{r}_0 + p\frac{\partial\vec{F}}{\partial p}.$$

Projecting this equation onto the left eigenvector \vec{l}_0 yields the isolated dynamics along the centre manifold:

$$(33) \quad \dot{y} = ay^2 + b \text{ with } a = \vec{l}_0\mathbf{H}\vec{r}_0\vec{r}_0 \text{ and } b = p\vec{l}_0 \cdot \frac{\partial\vec{F}}{\partial p}.$$

Note: In the literature often y is suggestively written as v assuming the quadratic dynamics is a long the voltage dimension. However, it can be shown that the centre manifold of a conductance-based neuron is never parallel to the voltage dimension.



Solution of Eq (33)

The centre manifold is only tangential to the spiking limit cycle dynamics near the saddle. Although the proportion of time spend near the saddle is large at some point the trajectories depart so it is only locally valid.

The formal solution of Eq. (33) with initial condition $y(0) = -\infty$ is

$$(34) \quad y(t) = \sqrt{\frac{b}{a}} \tan(\sqrt{ab}t - \pi/2).$$

Away from the saddle-node the slow manifold accelerates again and the variable y explodes at $\pi/2$. This blowing up is like a spike. So for the SNLC centre manifold one can think of the the spike at $y = \infty$ and reset to $y = -\infty$. The time it takes from $y = -\infty$ to $y = \infty$ is finite and given by

$$T_p = \frac{\pi}{\sqrt{ab}}.$$

Note that for $y(0) = 0$ it is

$$(35) \quad y(t) = \sqrt{\frac{a}{b}} \tan(\sqrt{ab}t)$$

and

$$T_p = \frac{\pi}{2\sqrt{ab}}.$$

The bifurcation parameter enter in a . If $q\vec{g}(\vec{x}) = [c^{-1}I, 0, 0, \dots]^T$, then the firing rate has the typical square-root scaling

$$f_0 = \frac{1}{T_p} = \pi^{-1} \sqrt{bl_{00}c^{-1}(I - I_0)}.$$

Let us check this numerically in the practical.

8 Fundamental organisation of neuronal excitability

The last chapter argued that conductance-based neuron models, are a consistent continuum limit of Markov description of finite ion channels. Hallmarks of the resulting ordinary differential equations include first-order kinetic equations for ion channel components, *i.e.* gates, and certain polynomial nonlinearities. There is a rich literature on the dynamical systems analysis of single neurons, such that it is difficult to structure it for a lecture. Typically, the starting point is the different “simple” bifurcations that can be found in neuron models. One can also start with the “simplest” of the complicated bifurcations that summarises all possible simple ones. This is asking for the simplest chimera neuron with as many of the known features as possible (Kirst 2012; Kirst et al. 2015).

Start by restating some empirical observations on the *phenomenology* of excitable nerve cells. For pulsed-based communication these equations need a *stable resting potential* and a limit cycle-like transient pulsatile solution for certain input perturbations (Pereira, Coulet, and Tirapegui 2015).

Phenomenon	Dynamics
resting potential	stable node
subthreshold oscillations	stable spiral
action potential	stable limit cycle
thresholds	saddle, unstable limit cycle

Note that the focus on the generation of single or tonic spikes, not bursts. Bursts require at least one additional time scale to the pulse generating ones and are not minimal in that sense.

Observation 2 (*nerve cells*)

- i) stable resting potential, for $I_{\text{in}} = 0$ in the convex hull of reversal potentials,
- ii) stable pulses

Remark 1 (*dimensionality of state space*)

The minimal dimensionality of the state space to get spikes (but not bursts) is $n = 2$.

Def. 14 (*Class-1 excitability*)

Class one neurons have arbitrary low frequencies (long periods). This also implies they can show very long (and in the presence of noise varied) latencies to the first spike.

Lets write the conductance-based model as follows

Def. 15 (*Conductance-based neuron model*)

$$C_m \dot{v} = I_{\text{dc}} - \bar{g}_L v - I_{\text{ion}}(v, \mathbf{a})$$

where

$$I_{\text{ion}}(v, \mathbf{a}) = \sum_k G_k(v, \mathbf{a})(v - E_k)$$

and the components of the vector of gates \mathbf{a} evolve according to

$$\tau_k(v) \dot{a}_k = a_k^{(\infty)}(v) - a_k.$$

For brevity, introduce $\mathbf{x} = [a_1, \dots, a_{n-1}, v]$ and denote $\forall 1 \leq k < n : F_k = (a_k^{(\infty)}(v) - a_k)/\tau_k(v)$ and $F_n = (I_{dc} - \bar{g}_L v - I_{ion}(v, \mathbf{a}))/C_m$, such that $d\mathbf{x}/dt = \mathbf{F}(\mathbf{x})$.

The goal is to find “the simplest” of the complicated bifurcations that allows for all known phenomena. What is meant by the simplest? Bifurcations can be ordered according to the codimension, *i.e.* how many parameters are required to tune into them. Codimension one bifurcations are points in one-dimensional parameter spaces, they are lines in two-dimensional spaces and sheets in three-dimensional spaces, and so on. Which codimension should one allow for? It does not make sense to use more parameters than are biophysically present in all the neuron models from the model class of interest. These are three for conductance-based neuron models:

Def. 16 (*fundamental parameter*)

Conductance-based neuron models may have a very diverse potpourri of ion channel with different parameters, but all share the following fundamental parameters: (C_m, I_{dc}, \bar{g}_L) . C_m is the time-scale separation between kinetics and current balance equation. I_{dc} and \bar{g}_L are the constant and linear term of the total membrane current. All other “kinetic parameters” depend on which exact channels are present in the nerve cell model and may vary substantially.

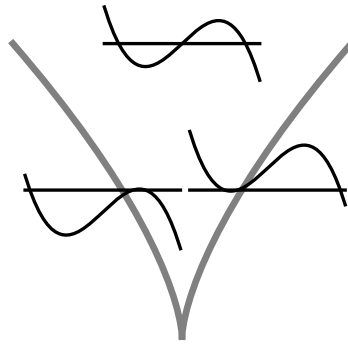
The simplest known bifurcation that can be broad into agreement with the phenomenology above is

Def. 17 (*Bogdanov-Takens cusp bifurcation*)

A zero eigenvalue of algebraic multiplicity two. And a degeneracy assumption to be able to get rid of the fold via a cusp, which reads that the quadratic normal form coefficient must be zero.

Assertion 1 (*BT point*)

A BT point implies the emergence of a homoclinic orbit to a saddle. Importantly, due to the coincidence with the planar limit cycle of the Hopf bifurcation, the homoclinic orbit is planar and not as three dimensional as a homoclinic orbit to a saddle-focus (Shilnikov). It may turn into that further away from the unfolding.



Cusp bifurcation

Assumptions 1 (*Electrophysiology*)

The following assumptions can be motivated from biophysics of excitable membranes or electrophysiological measurements:

- a) All conductances are positive, $\forall k : G_k > 0$.
- b) The kinetics of the ion channel gates is of first order, with all activation curves are bounded, monotonic, twice-differentiable functions, that become sufficiently flat at

$v = \pm\infty$. More specifically the derivative of the activation curve has to vanish at $\pm\infty$ and do so faster than linearly, *i.e.* $\lim_{v \rightarrow \pm\infty} v \frac{\partial a(v)}{\partial v} = 0$.

c) Channels are voltage-gated only.

d) Class 1 \rightarrow some slow positive feedback exists, *i.e.*, $\exists \bar{v} : \left. \frac{dI^{(\infty)}}{dv} \right|_{v=\bar{v}} > 0$

Remark 2 (*excitable system vs limit cycle*)

Before proceeding to the actual argument, what of “excitable systems”. Many neurons do not spike tonically but only if excited by a synaptic perturbation or noise. Or in more physiological terms this is tonic spiking vs Poisson like spiking (low vs high CV). In such cases they cross a “potential barrier” or some threshold manifold and return to rest after a long excursion through state space. One way of producing a system with such a long excursion is to have it have a stable limit-cycle for “other parameters”. It turns out, that the Bogdavnov-Takens point plays a crucial role here two because it guarantees there are homoclinic orbits attached to a saddle, which is one way to get such excursions.

8.1 Stable resting potential and how many fixpoint are expected

Proposition 1 (*fixpoints of CBM*)

From $\dot{v} = 0$ and $\dot{a}_k = 0$ one gets:

$$v^* = \frac{I_{dc} + \sum_k G_k(v^*, \mathbf{a}^*) E_k}{\sum_k G_k(v^*, \mathbf{a}^*)}$$

$$a_k^* = a_k^{(\infty)}(v^*).$$

Provided solutions to the implicate definition of the voltage fixpoint exists, then for $I_{dc} = 0$ they lie within the convex hull of the reversal potentials E_k .

Given that $\forall v$: the fixpoints of the gates can readily be found, the steady states of the whole system are the zeros of the *steady-state steady-state I-v curve*:

Def. 18 (*steady-state I-v curve*)

Given that all gates have time to equilibrate to their steady state values (are in *kinetic steady state*), the steady-state *I-v curve* is defined as

$$I^{(\infty)}(v) = I_{dc} - g_L v - I_{ion}(v, \mathbf{a}^*(v)).$$

It is a continuous and differentiable function just like \mathbf{F} . This allows some weak statements about the number of steady states expected in a conductance-based model.

Lemma 1 (*fixpoints of class 1 neurons*)

Depending on their I_{dc} class 1 neurons can have at least one or three steady states.

Proof 1

The partial derivative of the gating equations w.r.t v at the kinetic steady state is

$$\left. \frac{\partial F_k}{\partial v} \right|_{a_k = a_k^{(\infty)}} = \frac{\partial a^{(\infty)}}{\partial v} \frac{1}{\tau_k(v)}.$$

Hence, the total derivative of a kinetic equation w.r.t v is in that case

$$\frac{dF_k}{dv} = \frac{\partial F_k}{\partial v} + \frac{\partial F_k}{\partial a_k} = \frac{\partial a^{(\infty)}}{\partial v} \frac{1}{\tau_k(v)} - \frac{1}{\tau_k(v)} \frac{\partial a}{\partial v} = 0,$$

which shows that in kinetic steady state $\partial a / \partial v = \partial a^{(\infty)} / \partial v$. Therefore, the total derivative of the steady-state *I-v relation* is

$$\frac{1}{C_m} \frac{dI^{(\infty)}}{dv} = \frac{\partial F_0}{\partial v} + \frac{\partial F_0}{\partial a_k} \frac{\partial a_k^{(\infty)}}{\partial v}.$$

Inserting the definitions yields

$$\frac{dI^{(\infty)}}{dv} = -g_L - \sum_k G_k(v, \mathbf{a}) + \sum_k \frac{G_k(v, \mathbf{a})}{\partial v} (E_k - v) + \sum_k \frac{\partial G(v, \mathbf{a})}{\partial a_k} (E_k - v) \frac{\partial a_k^{(\infty)}}{\partial v}.$$

This can be used to inspect the asymptotic behaviour of $I^{(\infty)}$ at large positive and negative voltages:

$$\lim_{v \rightarrow \pm\infty} \frac{dI^{(\infty)}}{dv} = -g_L - \sum_k G_k(v, \mathbf{a}^*) \leq -g_L,$$

where the last two terms have vanished due to *Assumptions 1a)* and *b)*. This means the slope of the I - v curve is negative at $v = \pm\infty$, and thus $I^{(\infty)} = 0$ should cross zero at least once. For the class 1 excitable system also *Assumption 1d)* stands and consequently $\frac{dI^{(\infty)}}{dv}$ must have at least one maximum. Consequently I_{dc} can be tuned such that there is at there are at least three fixpoints. \square

Let us call the maximums $\exists \hat{v} : \frac{d^2 I^{(\infty)}}{dv^2} |_{v=\hat{v}} = 0$

8.2 Rank-one updated diagonal Jacobian

Next we are making use of *Axiom #c)* to calculate the Jacobian of a conductance-based neuron model

Observation 3 (*rank-1 updated diagonal Jacobian*)

The special structure of the Jacobian in a conductance-based neuron model, a rank-1 updated diagonal matrix,

$$\mathbf{J} = \begin{pmatrix} \frac{\partial F_1}{\partial a_1} & & 0 & \frac{\partial F_1}{\partial v} \\ & \ddots & & \vdots \\ 0 & & \frac{\partial F_{n-1}}{\partial a_{n-1}} & \frac{\partial F_{n-1}}{\partial v} \\ \frac{\partial F_n}{\partial a_1} & \dots & \frac{\partial F_n}{\partial a_{n-1}} & \frac{\partial F_n}{\partial v} \end{pmatrix},$$

Proposition 2 (*Zero-eigenvectors of a CBM*)

Consider a conductance-based neuron model (*Def. 15*) at a fold bifurcation, *i.e.*, with a simple zero eigenvalue, $\lambda_1 = 0$, at the saddle-node. Then the semi-stable (centre-)manifold is tangential to the right-eigenvector corresponding to λ_1 , which is given by

$$(36) \quad \mathbf{r}_1 = r_{1n} \begin{pmatrix} \tau_k \frac{\partial F_1}{\partial v} \\ \vdots \\ \tau_{n-1} \frac{\partial F_{n-1}}{\partial v} \\ 1 \end{pmatrix} = \frac{1}{\kappa} \begin{pmatrix} \vdots \\ \frac{d}{dv} a_k^{(\infty)}(v) |_{v=\mathbf{v}^{sn}} \\ \vdots \\ 1 \end{pmatrix},$$

where $v = \mathbf{v}^{sn}$ and $a_k = a_k^{(\infty)}(\mathbf{v}^{sn})$ was used. The normalisation constant κ is given at the end of *Proof 2*.

The associated left-eigenvector is

$$(37) \quad \mathbf{l}_1 = \begin{pmatrix} \tau_k \frac{\partial F_n}{\partial a_k} \\ \vdots \\ 1 \end{pmatrix},$$

where F_n denotes the r.h.s. of the current-balance equation and F_k for $k = 1, \dots, n-1$ the r.h.s. of the kinetic equations. Note that the right eigenvector \mathbf{r}_1 gives the direction of the semi-stable manifold.

The determinant can be rewritten as

$$(38) \quad |\mathbf{J}| = \frac{(-1)^{n-1} \frac{dI^{(\infty)}}{dv}}{\prod_k \tau_k}$$

Proof 2

allows for an explicit calculation of the left and right eigenvectors corresponding to the eigenvalue $\lambda_1 = 0$.

Choosing the zero eigenvector as $\mathbf{r}_1 = \begin{pmatrix} \mu \\ 1 \end{pmatrix}$, one obtains from $\mathbf{J}\mathbf{r}_1 = \lambda_1\mathbf{r}_1 = 0$ a set of n equations:

$$(39) \quad \frac{\partial F_n}{\partial v} + \sum_{j=1}^{n-1} \mu_j \frac{\partial F_n}{\partial a_j} = 0, \text{ and}$$

$$(40) \quad \frac{\partial F_k}{\partial v} + \mu_k \frac{\partial F_k}{\partial a_k} = 0 \text{ for } k = 1, \dots, n-1.$$

From Eqs. (40), it follows that $\mu_j = -\left(\frac{\partial F_j}{\partial a_j}\right)^{-1} \frac{\partial F_j}{\partial v}$. This solution also solves Eq. (39), because the required zero eigenvalue implies that $\det \mathbf{J} = 0$. Note that according to Leibniz's formula the determinant of a matrix

$$\mathbf{J} = \begin{pmatrix} \mathbf{A} & \mathbf{B} \\ \mathbf{C} & \mathbf{D} \end{pmatrix}$$

is $|\mathbf{A}| |\mathbf{D} - \mathbf{C}\mathbf{A}^{-1}\mathbf{B}|$

$$(41) \quad \det \mathbf{J} = \left| \frac{\partial F_0}{\partial v} - \sum_{j=1}^{n-1} \left(\frac{\partial F_j}{\partial a_j}\right)^{-1} \frac{\partial F_j}{\partial v} \frac{\partial F_0}{\partial a_j} \right| \prod_{k=1}^{n-1} \frac{\partial F_k}{\partial a_k} = 0.$$

Since $\frac{\partial F_k}{\partial a_k} = -\frac{1}{\tau_k(v^{sn})} < 0$, the first factor of the determinant must be zero. Hence, μ_j also solves Eq. (39).

An analogue derivation for the left eigenvector, $\mathbf{l}_0 = \begin{pmatrix} 1 \\ \xi \end{pmatrix}$, results in the following set of equations,

$$(42) \quad \frac{\partial F_0}{\partial v} + \sum_{j=1}^{n-1} \xi_j \frac{\partial F_j}{\partial v} = 0, \text{ and}$$

$$(43) \quad \frac{\partial F_0}{\partial a_k} + \xi_k \frac{\partial F_k}{\partial a_k} = 0 \text{ for } k = 1, \dots, n-1,$$

which yields $\xi_j = -\left(\frac{\partial F_j}{\partial a_j}\right)^{-1} \frac{\partial F_0}{\partial a_j}$. The normalisation constant to ensure $\mathbf{l}_0 \cdot \mathbf{r}_0 = 1$ is

$\kappa = 1 + \sum_{j=1}^{n-1} \tau_j^2 \frac{\partial F_0}{\partial a_j} \frac{\partial F_j}{\partial v} \Big|_{v=v^{sn}, a_k=a_k^{(\infty)}(v^{sn})}$. Note that y is in units of volt here. Other conventions are possible.

A long calculation shows that

$$\alpha_2 = \mathbf{l}_1 \mathbf{H} \mathbf{r}_1 \mathbf{r}_1 = \frac{d^2 I^{(\infty)}}{dv^2}.$$

To the condition for the BTC bifurcation require the eigenvalue to be not simple, but of algebraic multiplicity two. This means there is a Jordan chain of rank two, such that for the left and right eigenvectors, \mathbf{l}_1 and \mathbf{r}_1 , corresponding to $\lambda_1 = 0$ there are also a pair of *generalised eigenvectors* (KUZNETSOV 2011), which are not denoted as \mathbf{l}_2 and \mathbf{r}_2 .

$$(\mathbf{J} - \lambda_1 \mathbf{I})\mathbf{r}_2 = \mathbf{r}_1 \text{ and } \mathbf{l}_2(\mathbf{J} - \lambda_1 \mathbf{I}) = \mathbf{l}_1 \text{ with } \mathbf{l}_1 \cdot \mathbf{r}_1 = \mathbf{l}_2 \cdot \mathbf{r}_2 = 0 \text{ and } \mathbf{l}_1 \cdot \mathbf{r}_2 = \mathbf{l}_2 \cdot \mathbf{r}_1 = 1.$$

Note that the orthonormalisation is somewhat unintuitive, but useful. The BT case is $\lambda_1 = 0$, such that $\mathbf{J}\mathbf{r}_2 = \mathbf{r}_1$ and $\mathbf{l}_2\mathbf{J} = \mathbf{l}_1$. Numerically, this equivalent to solving an extended eigenvalue problem

$$\begin{pmatrix} \mathbf{J} & \mathbf{0} \\ -\mathbf{I} & \mathbf{J} \end{pmatrix} \begin{pmatrix} \mathbf{r}_1 \\ \mathbf{r}_2 \end{pmatrix} = \mathbf{0}$$

Proposition 2 (*Generalised zero-eigenvectors of a CBM*)

Given the eigenvectors \mathbf{r}_1 and \mathbf{l}_1 and the definition $\mathbf{J}\mathbf{r}_2 = \mathbf{r}_1$ one finds

$$\mathbf{r}_2 = \begin{pmatrix} \tau_1(r_{2n} - r_{1n}\tau_1) \frac{\partial F_1}{\partial v} \\ \vdots \\ \tau_{n-1}(r_{2n} - r_{1n}\tau_{n-1}) \frac{\partial F_{n-1}}{\partial v} \\ r_{2n} \end{pmatrix}$$

Proof 2

As the normal eigenvectors have already been calculated above up to normalisation, the equations for the coefficients of the generalised eigenvectors are

$$\begin{aligned} \sum_{k=1}^{n-1} r_{2k} \frac{\partial F_n}{\partial a_k} + r_{2n} \frac{\partial F_n}{\partial v} &= r_{1n} \\ -\frac{r_{2j}}{\tau_j} + r_{2n} \frac{\partial F_j}{\partial v} &= r_{1n} \tau_j \frac{\partial F_j}{\partial v}, \quad \forall j = 1, \dots, n-1 \\ \implies r_{2j} &= \tau_j (r_{2n} - r_{1n} \tau_j) \frac{\partial F_j}{\partial v} \\ \sum_{k=1}^{n-1} l_{2k} \frac{\partial F_k}{\partial v} + l_{2n} \frac{\partial F_n}{\partial v} &= l_{1n} \\ -\frac{l_{2j}}{\tau_j} + l_{2n} \frac{\partial F_n}{\partial a_j} &= l_{1n} \tau_j \frac{\partial F_n}{\partial a_j}, \quad \forall j = 1, \dots, n-1 \\ \implies l_{2j} &= \tau_j (l_{2n} - l_{1n} \tau_j) \frac{\partial F_n}{\partial a_j} \end{aligned}$$

From $\mathbf{l}_1 \cdot \mathbf{r}_1 = 0$ one obtains

$$(44) \quad 0 = 1 + \sum_{j=1}^{n-1} \tau_j^2 \frac{\partial F_n}{\partial a_j} \frac{\partial F_j}{\partial v} \Big|_{v=\mathbf{v}^{\text{sn}}, a_k=a_k^{(\infty)}(\mathbf{v}^{\text{sn}})}$$

From $\mathbf{l}_1 \cdot \mathbf{r}_2 = 1$ we obtain l_{11}

Once the generalised eigensystem spanning the nullspace are determined the normal form of BT bifurcation can be written as

After some longer calculation one obtains a condition for obtaining the generalised eigenvectors:

Conditions 1 (*BTC*)

and the previous conditions

$$(45) \quad \frac{dI^{(\infty)}}{dv} = 0$$

$$(46) \quad \frac{dI^{(\infty)}}{dv^2} = 0$$

Proof 1

The requirement of a zero determinant as defined in Eq. (38) leads to Eq. (45). Eq. (46) follows from the degeneracy requirement of the CUSP. It was shown as a consequence of *Lemma 1* that such a point actually exists if one starts with a class 1 neuron.

From these conditions the following statement can be derived.

Lemma 2 (*unique param*)

From the above one can conclude that from the conditions of the BTC point a unique set of parameter (I_{dc}, g_l, C_m) can be determined.

Proof 2

Eq. (44) can be solved for

$$C_m = -\sum_k \frac{\partial I_{\text{ion}}}{\partial a_k} \tau_k \frac{\partial a_k^{(\infty)}}{\partial v}$$

Eq. (45) depends only on g_l and C_m . It can be solved for

$$g_l = -\frac{1}{C_m} \frac{dI_{\text{ion}}}{dv}$$

The input current can be obtained from the fixpoint condition of the current-balance equation

$$I_{\text{dc}} = g_l v^* + I_{\text{ion}}(v^*, \mathbf{a}(v^*)),$$

only if the steady state is available. Luckily condition Eq. (46) is *independent* of the *fundamental parameters* and can be solved to find v^* .

Given the biophysical nature of the parameter both the conductance and the capacitance require positive values to be realistic.

Lemma 3 (*Permissible*)

For a CBM as defined above the BTC point is biophysically permissible if $\sum_k \frac{\partial I_{\text{ion}}}{\partial a} \tau_k \frac{\partial a_k^{(\infty)}}{\partial v} < 0$

Proof 3

From $\frac{dI^{(\infty)}}{dv} = 0 \implies \frac{dI_{\text{ion}}}{dv} = -g_l$. Hence if $g_l > 0$ to begin with then

$$\text{sign}(g_l) = \text{sign}(C_m)$$

All SNIC neurons can be tuned into Hopf neurons (not necessarily *visa versa*)

Proposition 3 (*Normal form of the BTC bifurcation*)

The normal form of the degenerated BTC bifurcation is

$$\dot{y} = w$$

$$\dot{w} = \alpha_2 y^2 + \alpha_1 w y + \beta_2 y + \beta_1$$

$$\text{with } \alpha_2 = \mathbf{l}_1 \mathbf{H} \mathbf{r}_1 \mathbf{r}_1 = \frac{d^2 I^{(\infty)}}{dv^2} = 0.$$

Proof 3

Expand the solution in small variations along the directions spanning the centre manifold: $\mathbf{x}(t) = \mathbf{x}_0 + y(t)\mathbf{r}_1 + w(t)\mathbf{r}_2$. Then, project the flowfield onto the corresponding left eigenvectors and keep only leading order terms of the nonlinearity. The perturbation evolves according to

$$y\dot{\mathbf{r}}_1 + w\dot{\mathbf{r}}_2 = y\mathbf{J}\mathbf{r}_1 + w\mathbf{J}\mathbf{r}_2 + yw\mathbf{H}\mathbf{r}_1\mathbf{r}_2 + \frac{1}{2}(y^2\mathbf{H}\mathbf{r}_1\mathbf{r}_1 + w^2\mathbf{H}\mathbf{r}_2\mathbf{r}_2).$$

Remember $\mathbf{l}_1 \cdot \mathbf{r}_1 = \mathbf{l}_2 \cdot \mathbf{r}_2 = 0$ and $\mathbf{l}_1 \cdot \mathbf{r}_2 = \mathbf{l}_2 \cdot \mathbf{r}_1 = 1$ and $\mathbf{J}\mathbf{r}_2 = \mathbf{r}_1$, $\mathbf{l}_2\mathbf{J} = \mathbf{l}_1$.

Projecting onto \mathbf{l}_2

$$\dot{y} = y \underbrace{\mathbf{l}_2 \mathbf{J} \mathbf{r}_1}_{=0} + w \underbrace{\mathbf{l}_2 \mathbf{J} \mathbf{r}_2}_{=1}$$

Projecting onto \mathbf{l}_1

$$\dot{w} = \frac{1}{2}y^2 \mathbf{l}_1 \mathbf{H} \mathbf{r}_1 \mathbf{r}_1 + yw \mathbf{l}_1 \mathbf{H} \mathbf{r}_1 \mathbf{r}_2 + \frac{1}{2}w^2 \mathbf{H} \mathbf{r}_2 \mathbf{r}_2$$

9 Ultimate causation: nervous system function

Coming back to the type of questions biological theory attempts to answer, see §2.1, chapters like §5 describe the mechanistic building block present in nerve tissue, their function and where they came from is bracketed off. This is the discussion of proximate causes and the static form. What about function?

Note that function is not to be understood in a *teleological* sense, that it has a purpose given to it by something. All attempts by early German “theoretical biologist” (KE von Baer, JJ Uexkülls, J Reinke or J Schaxel) to use the nonscientific (non empirical) ideas of Hegel, Kant or Goethe as a theoretical bases for biology have proven useless today. Their theories (vitalism, semiotic, teleology) were either incorrect or had no utility, predictive power, empirical basis or falsifiability. They were romantic fancies of an introspective and ultimately authoritarian, self-serving view of the living.

But “why is it like this?”-questions are nagging us. Ultimately, evolutionary considerations, *e.g.* the contribution of nervous systems to fitness, may come into play. Fitness, however, is an abstract concept difficult to relate to some specific mechanism of a complex nervous system. In part this due to the general problem of fitness being defined as an expectation value of future offspring.

Surely, one first needs to understand more about the function of nerve tissues, what it does. But where to start?

Nerve tissues can roughly be categorised into

1. afferent pathways doing sensory processing,
2. central decision making computations, and
3. efferent motor pattern generators

There is no rule that nervous systems have to obey this modular design. These are to some extent arbitrary labels given by scientists to find their way around.

Let’s briefly go through the three classes and discuss which kind of signals are expected (not an exclusive list).

9.1 Signals and senses

A classical, ecological theory of sensory organs aims to predict the structural organisation of the peripheral sensory architecture (???, ???), and the coding scheme used to represent information early in the pathway (???), based on the properties of the *adequate stimuli* occurring in the *natural habitat*. An alternative approach is inspired by the engineering task of system identification, in which blackbox (technical) systems are probed to obtain a response which helps uncovering the exact transformation executed by them. In contrast to behavioural experiments that utilise abstractions of the actual stimuli perceived by the animal (???) (Cpt. 3), systems identification often relies on unnatural stimuli that, however, possess beneficial statistical properties to facilitate the reverse-engineering scheme. Information theory can be applied within both paradigms as long as there is sufficient data. Examples of such artificial stimuli are a short transient pulse, mathematically idealised by Dirac’s δ -function (Green’s function method) or „white” unstructured noise (Wiener’s kernel method). Both signals have a flat, uniform spectrum that contains all frequencies in an unbiased manner and thus the system’s response will not lack structures simply because of missing input complexity. In reality, a uniform spectrum of a physical stimulus can not extend its frequency range to infinity as this would require infinite power. Instead, there will be a reasonable upper bound to the frequency content, $f_c = \sup\{f : P(f) > 0\}$. In addition, artificial stimuli are at

times chosen from a Gaussian process, for reasons including the invocation of a central limit theorem, arguments based on maximum entropy, or easement of analytical treatments.

9.1.1 Natural signals and their neuronal representation

One of the first observations that environmental conditions are indeed mapped into nerve pulse activity was an experiment on the toad's optic nerve (Edgar Adrian 1928).

The external signals from the natural world relevant to animals can often be categorised into the three broad classes: (i) signals relevant to basic body kinematics and movement; (ii) signals for predator or prey detection; and (iii) communication signals from other (often conspecific) animals. Here are some examples from each category.

Example 1 (*Botoxic blowflies and careful crickets*)

Large monopolar cells, a first order interneuron of the insect compound eye, encodes light intensities differences (contrast) $I \in [0, I_{\max}]$ into the neurons raded potential response $r \in [0, r_{\max})$. This was investigated in *Calliphora stygia* (Laughlin 1981). The cricket *Acheta domestica* represents the wind direction in 4 interneurons of the cercal system, each encoding a different subinterval of the angular variable $\theta \in [0, 2\pi)$ into its firing rate (Theunissen and Miller 1991).

In the above examples the input is a real valued interval $\subset \mathbb{R}$, while the encoding neuronal activity is real or a discrete number, $\subset \mathbb{R}$ or \mathbb{N} . For example, the cercal system maps $[0, 2\pi) \mapsto [0, f_{\max})^4$. These are seemingly simple mappings, what could possibly go wrong?

A couple of questions arise:

- (47) How exactly is this read-out by upstream parts of the nervous system? Will there be errors?
- (48) A related question is: How acute is the sense? What difference in wind direction can still be resolved?
- (49) How long does the animal have to observe a constant wind direction to be able to encode it? How constant or stationary is the signal in the environment?
- (50) What is the relation between the *function* and the *dynamics* discussed in previous chapters?

If there is no noise and the coding variable is a real number infinite precision could be possible. If the output is a firing rate, then upstream neurons have to *estimate* this based on finite amount of observed spikes¹. At the same time it needs to be understood how these spike numbers are mechanistically generated from the *neuronal dynamics*.

Def 19 (*spike count*)

$$N(t) = \lfloor \phi(t) \rfloor.$$

Note that here the statistical quantity was already connected to a dynamic phase variable $\phi(t)$ for which the governing evolution equations are known in some regimes. Hence, one has related *neuronal dynamics and coding* (???)

Some signals may not be constant in time, but at least wide-sense stationary, meaning they have temporal correlations, but these are shift invariant.

Praying paddfish The primary afferents in the american paddfish *Polyodon spathula*'s electrosensory organ show a tonic response to fluctuating stimuli. In their muddy habitat the electrosensory system is used to detect their planctonic prey, like members of the crustacean genus *Daphnia*. The frequency spectrum of the bioelectric profile emitted by single moving *Daphnia* shows that most

¹Estimators should be at least consistent, hopefully unbiased, maybe efficient.

power resides in a baseband below 8-Hz [?, Fig. 4a]. For whole swarms the power is distributed over a larger interval, but still drops at high frequencies. In addition to naturalistic stimuli, the electrosensory system has been investigated with white noise analysis in order to determine the transfer function of the sensory afferents [?]. This has confirmed that information transmission is focused on a passband between 0.5–20-Hz with a steep roll-off. The stimulus response coherence of afferents shows a bassband between 0.5–20-Hz with a steeper roll-off than expected from a simple RC-circuit. In part the steep roll-off is due to noise masking from epithelial oscillators at around 23-Hz. Yet, the notch at 23-Hz is, though less strong, also apparent in the filter gain, cf Fig. 3(b) in Ref. [?].

Hiving hoverflies The *Dipteran* haltere organ [?] is a biological gyroscope that enables hoverflies to excel in aeronautics. The organ evolved from the second pair of wings. According to behavioural studies halteres measure Coriolis forces during flight. The white noise analysis of crane fly halteres under direct mechanical stimulation in Ref. [?, Fig. 3] shows that the system is sensitive to stimuli movements on time scales around 10-ms, while very fast stimulus changes are ignored.

Greeting grasshoppers Many gomphocerin grasshoppers like *Chorthippus biguttulus* use acoustic signalling to arrange mating behaviour. The detected signals are amplitude modulations of broad band carrier waves. The important information about the song structure resides in frequency band below 100-Hz, see Refs. [?, Fig. 1b,c] and [?, Fig. 1b].

If the signals in the environment are time dependent functions $x(t)$ from some function space, then the neuronal signals representing them could also be functions of time, $y(t)$.

Again some questions:

(51) But how many degrees of freedom should the function have to represent the signal?

At the dispose are the pulse trains emitted by a neuron. An event time series

Def. 20 (*Spike train and empirical measure*)

The event time series of action potential $\{t_k^{\text{sp}}\}_{k=1}^{\infty}$ can be defined in terms of the dynamics, as the k^{th} spike obeying

$$\phi(t_k^{\text{sp}}) = k.$$

Further, a spike-train can be written as the empirical measure

$$(52) \quad y(t) = \sum_{k=1}^{\infty} \delta(t - t_k^{\text{sp}}) = \sum_{k=1}^{\infty} \delta(\phi(t) - k).$$

Def. 21 (*I/O-equivalent phase oscillator*)

An I/O-equivalent phase oscillator produces with its threshold crossing process the same spike times $\{t_k^{\text{sp}}\}_k$ as a particular conductance-based model (Lazar 2010).

Def. 22 (*Instantaneous firing rate*)

This idealised quantity does not exist in finite neuronal systems. It is the ensemble average

$$r(t) = \langle y(t) \rangle_{y|x} = J(\phi, t)|_{\phi|_1=0},$$

and can be interpreted as a infinitely large population of the statistically i.i.d. neurons experiencing the same stimulus or one neuron being stimulated time and again. The probability flux is defined as

$$J(\phi, t) = a(\phi, t)p(\phi, t) - \frac{1}{2}\sigma(\phi)\frac{\partial}{\partial\phi}\sigma(\phi)p(\phi, t). \text{ The “advection”, } a, \text{ is due to active transport.}$$

A simplifying observations is that there often (but not always) is a separation of time scales between stimulus induced perturbations and those fluctuations that originate from internal biophysical noise in receptor neurons, see §5. The three examples clearly fall into this category where the stimulation cutoff renders the stimuli orders of magnitude slower than the intrinsic noise. Therefore, the fast (white) noise, $\xi(t)$, in the phase equation can be averaged

$$\dot{\phi} = f + Z(\phi)x(t) + \bar{\sigma}\xi(t) \text{ with } \bar{\sigma}^2 = \int_0^1 \sigma^2(\phi) d\phi.$$

Continuity equation

$$\frac{\partial p}{\partial t} = -\frac{\partial J}{\partial \phi}$$

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9.1.2 Bandlimited signal

A time-continuous signal does not necessarily imply an infinite degree of freedom. Deterministic signals like sinusoidal is specified by only two degrees of freedom. In contrast to white noise, a band limited signal, with no power above f_c , has only a limited number of $2f_c$ degrees of freedom per second (???). In accordance with Whittaker-Shannon sampling it can be represented as a countable set of random numbers (finite degrees of freedom per unit time). Mutual information estimations can then be based on these instead of the continuous signal without losing information. The physical signals that announce themselves on sensory organs can have their power distributed over many octaves. However, signals emitted by other animals, either voluntarily like the communication songs of grasshoppers or involuntary as moth falling prey to a bat, are often constrained to a frequency range that is related to the body size of the sound producing animal (see the next paragraph for three examples of relevant natural stimuli). In such occasions one can identify an upper frequency, f_c , above which no relevant information is expected. Additionally, all primary transduction processes have a time constant restricting the signal frequencies they can follow. This is sufficient reason to consider the stimulus $x(t)$ to fall into the class of bandlimited signals (also called baseband signals).

More precisely according to the sampling theorem a band limit signal with cutoff frequency f_c requires at least a sampling rate of $2f_c$. With the help of the Whittaker-Shannon interpolation formula the signal can be written as (???)

$$(53) \quad x(t) = \sum_{n=-\infty}^{\infty} x_n \operatorname{sinc}(2tf_c - n)$$

For an observation interval $[0, T)$ one needs a minimum of $N_T = \lceil 2Tf_c \rceil$ samples to specify the continuous bandlimited process completely.

The coefficients x_n can be continuous Gaussian random variables such that one has a bandlimited Gaussian random process. In order to compare information theoretic bounds on the information transmitted through continuous channels (physical systems) to histogram based methods for the estimation of mutual information the Whittaker-Shannon sampling can be augmented by discretisation of the (Gaussian) random variables x_n . The simplest strategy is to start with a discrete set of binomially distributed random variables, $x_n \sim \operatorname{Binom}(k, p)$ with $p = \frac{1}{2}$, and use the fact that for large k the statistics will be approximately Gaussian. With this there is a correspondence between a time-continuous process on an interval $[0, T)$ and a discrete binomial vector, so that the histogram frequency $p([x_1^1, \dots, x_1^k, \dots, x_n^1, \dots, x_n^k])$ can be estimated. For example the blue time continuous process in Fig. 9.1 between 50 and 100ms with $f_c = 100\text{Hz}$ is described by the 11 samples marked as green circles. The continuous process is statistically similar to a Gaussian process.

A bandlimited and binomially distributed ($k = 14, p_b = \frac{1}{2}$) signal as an approximation to a Gaussian process ($\mu = kp_{bn}, \sigma^2 = kp_{bn}(1 - p_{bn})$). The cutoff frequency was 100-Hz, implying that the entire stimulus over 250-ms is exactly defined by 50 regularly spaced samples, as according to the Nyquist theorem one needs at least two samples per period to define an oscillation. To check if the binomial amplitude distribution is an adequate approximation to a Gaussian, the Shapiro-Wilk test for normality is used. The Samples are accepted as Gaussian with an α -level of 0.4 (very small α -level would mean rejection of normality).

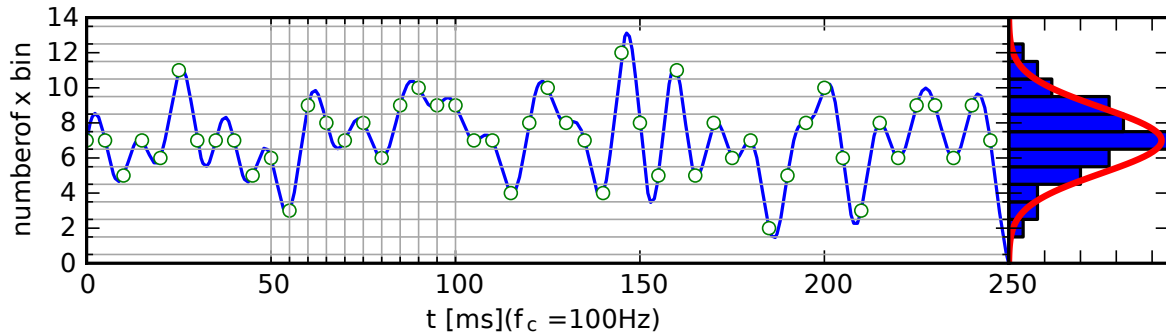


Figure 9.1: A bandlimited and binomially distributed ($k = 14$, $p_b = \frac{1}{2}$) signal as an approximation to a Gaussian process ($\mu = kp_{bn}$, $\sigma^2 = kp_{bn}(1 - p_{bn})$). The cutoff frequency was 100~Hz, implying that the entire stimulus over 250~ms is exactly defined by 50 regularly spaced samples, as according to the Nyquist theorem one needs at least two samples per period to define an oscillation. To check if the binomial amplitude distribution is an adequate approximation to a Gaussian, the Shapiro-Wilk test for normality is used. The Samples are accepted as Gaussian with an α -level of 0.4 (very small α -level would mean rejection of normality).

9.2 Decision making, multimodality, and universal codes

9.3 Motor system

9.4 Stimulus representation in single neurons

In previous lectures the biophysical details of the action potential voltage dynamics in membrane patches were discussed, highlighting its key features: (i) the nonlinear feedback, provided by voltage gated channels; and (ii) the inherent stochasticity. These two combined make for a complex system that shirks being amenable to a complete analytical treatment. How can one answer the question „Which frequencies in a stimulus is it sensitive to?“.

A particular useful strategy has been to derive approximate filters² from model equations that are easier to analyse (???). These models must omit many biophysical details to remain analytically tractable.

The calculation of response filters for neuronal models is a long standing exercise in theoretical biology (???).

9.4.1 Spike-triggered ensemble

A classic approach to investigate which stimulus characteristics are represented in the activity of sensory neurons is to estimate their receptive field or spike-triggered average [?]. The analysis characterises the components of a complex stimulus that are relevant to elicit a spike response or increased firing rate. Hence, the concept is related to that of a visual receptive field and could ultimately cause behavioural reactions. It is, therefore, related to the antedating concept of sign stimuli in ethology (???; ???). The method has been applied to recordings from the visual (???) and auditory (???) system.

One can also turn the paradigm around by applying a simple stimulus such as a delta pulse and characterising the nature of the response, which is then called transfer functions or point spread function in the visual system. The term transfer function stems from signal processing and stresses the fact

²The biological literature often uses dynamical systems jargon to describe mechanistic explanation and resorts to engineering vocabulary in order to describe the function of nerve cells.

that the neuron is viewed as a linear filter. It is surprising how complete a description of an inherently nonlinear neuron, a linear response filter can give, despite the fact that neurons contain so many nonlinear elements. In a sense it parallels the success of linear response theory in complex physical problems (??). Of course, there is no one linear filter that describes the whole range of dynamical features of the neuron. But different aspects may be characterised by different filter. In particular, we will linearise around the suprathreshold periodic solution to derive a firing rate filter in ?. Linearising the voltage response around the resting potential yields quite a different filter that describes the subthreshold response. So essentially it depends on which output variable one analyses.

There are two different filter

1. the encoding filter maps input to output;
2. the decoding filter reconstructs the input from the output.

This is related to the question “what causes a neuron to spike” or how does observing the neuronal spike response affect the conditional statistics of the stimulus $p(x|y)$? After observing the spike train some external stimuli should have been more likely their cause than others. An immediate idea is to look at the first moments of the conditional ensemble. For example, the mean stimulus before a spike in one trial is

$$\text{STA}(\tau) = \frac{1}{N_{\text{sp}}} \sum_{k=1}^{N_{\text{sp}}} x(t_k - \tau) = \frac{1}{N_{\text{sp}}} \int_{-\infty}^{\infty} dt y(t)x(t - \tau),$$

where we used the platonic spike train from *Def. 20*.

To improve the signal to noise ratio, an experimenter might repeat the same stimulus, so that a trial average might smooth out the effect of intrinsic noise. Then, if the number of spikes, N_{sp} , per trial is large and almost constant (modest Fano factor) it may be approximated by

$$\left\langle \frac{1}{N_{\text{sp}}} \int dt y(t)x(t - \tau) \right\rangle_{y|x} \approx \frac{1}{\langle N_{\text{sp}} \rangle} \int dt r(t)x(t - \tau) = \frac{1}{r_0} R_{rx}(-\tau),$$

where r_0 is the mean firing rate. This gives rise to the term *reverse-correlation* method, see Ref.~[?, Cpt. 1.3] and Ref.~[?].

Given that the rate causally depends on previous stimulus it can be expanded as a Volterra series in orders of the stimulus magnitude

$$r(t) = r_0 + \int_0^{\infty} h(t-s)x(s)ds + \dots$$

This implies that also $p(\phi, t) = p_0(\phi) + p_1(\phi, t) + \dots$ and $J(\phi, t) = J_0 + J_1(\phi, t) + \dots$, as well as the Fokker-Planck operator

$$\dot{p} = (L_0 + L_1)p, \text{ where } L_0(\phi) = \left(\frac{\sigma^2}{2} \frac{\partial^2}{\partial \phi^2} - f \frac{\partial}{\partial \phi} \right), \text{ and } L_1(\phi, t) = -x(t) \frac{\partial}{\partial \phi}.$$

The right eigen system of the Fokker-Planck operator, $L_0 q_k(\phi) = \mu_k q_k(\phi)$ has the fourier basis as solution $q_k(\phi) = e^{i2\pi k \phi}$ with eigenvalues $\mu_k = -\frac{1}{2}(2\pi k \sigma)^2 - ik2\pi f$.

$\forall k \neq 0$ the eigenvalues have negative real part and the contribution of the corresponding eigenfunction vanishes for $t \rightarrow \infty$, only the eigen mode $k = 0$, *i.e.*, $q_0 = 1$ survives.

Hence, the zeroth order equation ($x = 0$), $\dot{p}_0 = L_0 p_0$ has a stationary solution $p_0 = q_0 = 1$. Consequently the zeroth order flux is constant, too. Hence, $J(1, t) = f$.

The first order equation is

$$\dot{p}_1 = L_0 p_1 + L_1 p_0 = \frac{\sigma^2}{2} \frac{\partial^2}{\partial \phi^2} p_1 - f \frac{\partial}{\partial \phi} p_1 - Z'(\phi)x(t).$$

The simplest time dependent solution can be obtained by Laplace transforming and Fourier series expanding this equation, $p(\phi, t) \rightarrow P(\phi, s)$.

$$\frac{\sigma^2}{2} \frac{\partial^2}{\partial \phi^2} P - f \frac{\partial}{\partial \phi} P - sP = Z'(\phi)X(s)$$

With $Z(\phi) = \sum_{k=-\infty}^{\infty} c_k e^{i2\pi k \phi}$ and in the orthogonal Fourier basis

$$P_1(k, t) = -\frac{i2\pi k c_k X(s)}{s + i2\pi k f + \frac{1}{2}(k\sigma)^2}$$

or

$$P(\phi, s) = - \sum_{k=-\infty}^{\infty} \frac{i2\pi k c_k X(s) e^{i2\pi k \phi}}{s - \mu_k}$$

From the definition of the flux $J(\phi, t) = (f + Z(\phi)x(t))p - \frac{\sigma^2}{2} \frac{\partial}{\partial \phi} p$, the first order equation for the flux is

$$J_1(k, s) = \left(f - \frac{\sigma^2}{2} \frac{\partial}{\partial \phi} \right) P_1(k, s) + c_k X(s)$$

$$J_1(k, s) = \left(\frac{-\mu_k}{s - \mu_k} + 1 \right) c_k X(s) = \left(\frac{s}{s - \mu_k} \right) c_k X(s)$$

$$R_1 = J(\phi = 0, s) = H(s)X(s)$$

$$\text{with } H(s) = \sum_{k=-\infty}^{\infty} \frac{c_k s}{s - \mu_k}$$

$$\text{for } t > 0 \quad h(t) = \sum_k c_k (\mu_k e^{\mu_k t} + \delta(t))$$

9.5 Properties of the firing rate's linear response filter

The low frequency limit of the transfer function H is

$$\lim_{f \rightarrow 0} H(i2\pi f) = c_0 = \int_0^1 Z(\phi) d\phi = \langle Z(\phi) \rangle.$$

Consequently, PRCs with a mean can transfer arbitrarily low frequencies.

$$\frac{\partial f_0}{\partial I} = -\frac{1}{P_0^2} \frac{\partial P_0}{\partial I} = \frac{1}{P_0} \langle Z(\phi) \rangle.$$

The latter identity was already established in Eq. (17).

Proposition 1 (*DC limit of transfer function*)

In the mean driven regime, the susceptibility of the instantaneous firing rate to very low frequencies is related to the mean component of the PRC and the derivative of the f_0 - I curve

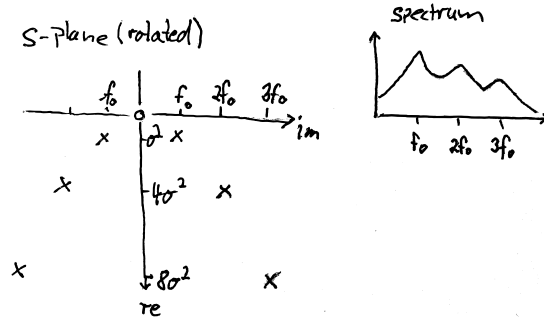
$$\lim_{f \rightarrow 0} H(i2\pi f) = \langle Z(\phi) \rangle = \frac{1}{f_0} \frac{\partial f_0}{\partial I} = \frac{\partial \ln f_0}{\partial I}.$$

Remark 3

As all known neuron models have $\partial f_0 / \partial I > 0$ above their rheobase, PRC are guaranteed to have a – at least small – mean component and the transfer function is susceptible to low frequencies. There are however quantitative differences between the different onset bifurcations.

Using $c_k = a_k + ib_k$ one obtains $Z(\phi) = a_0 + \sum_k a_k \cos(2\pi k \phi) + b_k \sin(2\pi k \phi)$. With this

$$\lim_{f \rightarrow \infty} H(i2\pi f) = \sum_k a_k = Z(0)$$



Left: Poles-zeros plot of the transfer function. Right: transfer spectrum.

10 Information theory for the living

Back to function. But where to start?

During the discussion of action potential stability “pulse-based communication” using spike events was mentioned as a motivation in §3. In very general terms, nervous system communication information for the senses to some place where decisions are made and further to places where motor commands are produced and executed, a reflex would be the simplest form (Braitenbergian view [4]). In the literature one finds a theory of communication called *information theory* (Shannon 1948).

10.1 Disclaimer

The author of this script is uncertain about the utility of information theory in biology at large (this is always a good reason to give a lecture on it), it looks exciting but has some shortcomings: This theory was originally never intended to be used to describe living systems in which information bears *meaning* and consequences, *i.e.*, the content of a message actually matters for your survival. Information theory deals with optimal compression, lossless transmission of signals irrespective of whether it is relevant or a youtube video. Nonetheless a look at a quantitative science of communication may be insightful.

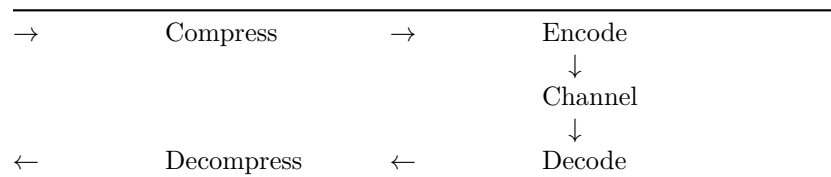
Information theory has long been in the discussion as an ecological theory upon which to judge the performance of sensory processing (Atick 1992). This led Joseph Atick, Horace Barlow and others to postulate to use this theory to study how nervous systems adapt to the environment. The goal is to make quantitative predictions about what the connectivity in the nervous system and the structure of receptive fields should look like, for instance. In this sense, information theory was hoped to become the basis for an ecological theory of adaptation to environmental statistics (Atick 1992, Barlow (1961)).

It may not seem obvious how the mechanistic theories of dynamical system and the functional theory of information should be brought together, but that is of course the goal. One would like to decide which dynamical features have what kind of function, this will be addressed after the introduction to information theory (G. B. Ermentrout, Galán, and Urban 2007; Schleimer and Stemmler 2009).

10.2 The communication process

The science of communication is concerned with at least two subtopics: (i) the efficient representation of data (compression); and (ii) the safe transmission of data through unreliable channels (coding).

A source (the message) typically runs through the following processing sequence:



One of the formal assertions of information theory is that these two problems can be addressed separately (without loss of generality or efficiency): Meaning first one compresses by removing redundancies. Then

one again adds failsafe redundancy to combat the unreliability.

However convenient for engineering, this does not mean that biological systems have to make use of this fact (source coding and channel coding could be very intertwined).

Also note that many of the mathematical results in information theory are bounds, inequalities not achievable in real systems.

(An ergodic system has an invariant phase volume, which is a necessary condition for an organism to exist, in the sense that it would otherwise transgress phase boundaries and cease to exist)

10.3 Channel coding

One may start by wrongly assuming that the function of nerves is to communicate information, irrespective of its semantic meaning. In reality, it is more likely that the function is to *filter information*, i.e., reliably communicate the import parts and filter out the irrelevant information (or noise). But to introduce the classical quantities, dispense with the semantics.

If the function of nervous system (in part) is to communicate information, then the repertoire and speed of biological computations are limited by thermodynamic or metabolic constraints (??-). The second will be deferred to later chapters, but as an outlook. There is no free lunch. It follows from basic thermodynamics that to obtain information work needs to be performed.

Here we consider a „memoryless” channel:

$$\text{message } W \xrightarrow{\text{encode}} X \ni x \xrightarrow{\text{noisy channel } p(y|x)} y \in Y \xrightarrow{\text{decode}} \text{est. Message } \hat{W}$$

The rate R with which information can be transmitted over a channel without loss is measured $\frac{\text{Bits}}{\text{transmission}}$ for a discrete time channel or $\frac{\text{Bits}}{\text{second}}$ for a continuous time channel. Operationally, we wish all bits that are transmitted to be recovered with negligible probability of error.

A measure of information could be:

The average reduction in the number of binary-questions needed to identify $x \in X$ before and after observing $y \in Y$.

This would just be the difference in entropies:

$$\mathcal{I}(X; Y) = H(X) - H(X|Y) = - \sum_{x \in X} p(x) \log_2 p(x) + \sum_{\substack{x \in X \\ y \in Y}} p(x, y) \log_2 p(x|y).$$

This goes by the name of *mutual information* or *transinformation*. Remember marginalisation

$$p(x) = \sum_{y \in Y} p(x, y).$$

So the mutual information is

$$\mathcal{I} = - \sum_{\substack{x \in X \\ y \in Y}} p(x, y) \log_2 p(x) + \sum_{\substack{x \in X \\ y \in Y}} p(x, y) \log_2 \left(\frac{p(x|y)p(y)}{p(y)} \right)$$

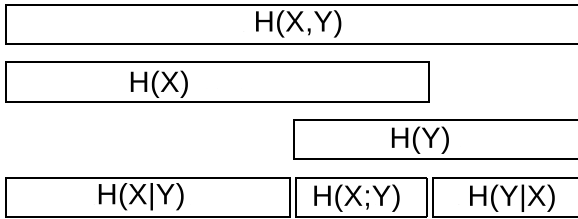
or

$$\mathcal{I}(X; Y) = \sum_{\substack{x \in X \\ y \in Y}} p(x, y) \log \frac{p(x, y)}{p(x)p(y)}$$

From the complete symmetry of this quantity we can also write it as

$$\mathcal{I}(X; Y) = H(Y) - H(Y|X).$$

The following Figure illustrates how the mutual information is related to respective (conditional) entropies of the input and output ensemble.



We have heard that $\mathcal{I}(X;Y)$ quantifies the statistical dependence of X and Y , but how is that related to error-free communication? What makes the error is the channel. $\mathcal{I}(X;Y)$, however, also depends on the input ensemble $p(x)$. To focus on the properties of the channel one can simply take an „optimal” input ensemble and define the *channel capacity*

$$C = \max_{p(x)} \mathcal{I}(X;Y).$$

It will be left to the sender to actually find the optimal input statistics. Note that $\mathcal{I}(X;Y)$ is a concave function (\cap) of $p(x)$ over a convex set of probabilities $\{p(x_i)\}$ (this is relevant for procedures like the Arimoto-Blahut algorithm for estimating C) and hence a local maximum is a global maximum.

```
p = []
while
  p(
```

Shannon’s channel coding theorem established that this capacity indeed measures the maximum amount of error-free information that can be transmitted.

10.4 Maximum entropy, discrete finite alphabet

A trivial upper bound on the channel capacity is

$$C \leq \min\{\log |X|, \log |Y|\}.$$

This is due to the maximum entropy property of the uniform distribution in the discrete case:

Example (Maximum entropy, discrete case): For the derivative of the entropy from Eq. (???) one gets: $\frac{\partial}{\partial p_i} H = -\log_2 p_i - 1$, which leads to $p_i \propto e^{-1} \quad \forall i$. After normalisation one has $p_i = 1/N$, so the *uniform distribution* maximises the entropy in the discrete case.

10.5 Information transmission (continuous case)

Some of the signals in nature (and those applied in the laboratory) have continuous alphabets, *e.g.*, light intensity values. Does it make sense to extend the definition of the entropy as

$$(54) \quad H(x) = - \int dx p(x) \ln p(x)?$$

Maybe. Let us see how far one gets with this definition. It is called *differential entropy* by the way. Through quantisation this can be related back to the entropy of discrete alphabets.

If the $p(x)$ is smooth then one associates the probability of being in $i\Delta \leq x \leq (i+1)\Delta$ with

$$p_i = p(x_i)\Delta = \int_{i\Delta}^{(i+1)\Delta} dx p(x)$$

The entropy of the quantised version is

$$H_\Delta = - \sum_{i=-\infty}^{\infty} p_i \ln p_i = - \sum_{i=-\infty}^{\infty} \Delta p(x_i) \ln(p(x_i)\Delta)$$

$$= - \sum_{i=-\infty}^{\infty} \Delta p(x_i) \ln p(x_i) - \ln \Delta$$

This is problematic as the second term goes to infinity for small quantisations. Formally, if $p(x)$ is Riemann integrable, then

$$\lim_{\Delta \rightarrow 0} = H_{\Delta} + \ln \Delta = - \int dx p(x) \ln p(x)$$

Since the infinitesimal limit is taken we can also take n to be the number of quantal intervals so that in the limit

$$\lim_{\substack{\Delta \rightarrow 0 \\ n \rightarrow \infty}} \ln \Delta \approx n.$$

So that an n -bit quantisation of a continuous random variable x has entropy

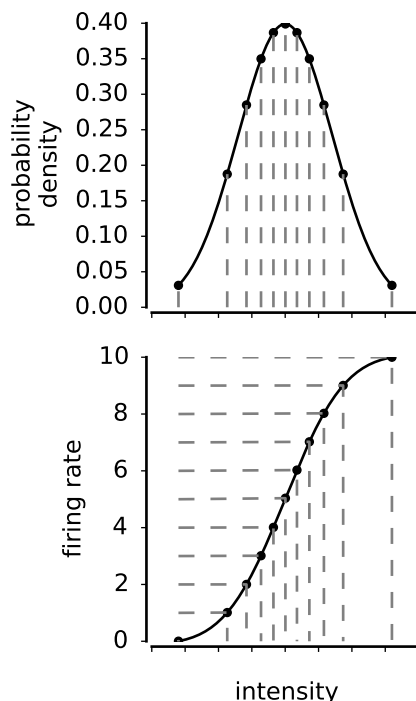
$$H(x) + n.$$

With the mutual information being the difference of entropies the quantisation term vanishes.

10.6 Optimal coding

A first example can be taken from rate coding¹. In terms of our spike trains from Eq. (52), the *instantaneous firing rate* can be defined as

Example (Optimal coding in flies (Laughlin 1981)): In short, Simon measured the distribution of light intensities that would impinge on the fly's compound eye in a natural environment: It was more or less *normally distributed*. He asked *What is the optimal contrast-response function?* He postulated that an efficient allocation of resources (of the possible responses) would be, to spread more likely inputs over a broader range of firing rates. Why? It makes them easier to differentiate by upstream neurons. Via experiments he found that the fly's compound eye approximates the cumulative probability distribution of contrast levels in natural scenes.



¹Here, the alphabet is a firing rate $f_0 \in \mathbb{R}$. It might be more reasonable to think about spike counts in a given time window, which is still a countable set.

Def. 23 (*Gaussian nonlinear channel*)

The channel is defined by the following mapping:

$$y = f(x) + z$$

where $z \sim \mathcal{N}(0, \sigma^2)$ is zero mean normally distributed .

Which encoding function (*e.g.*, the contrast-response function from above) maximises the mutual information across the channel given that we know the input statistics?

Assumptions:

- 1) f is a continuous monotonous function with a somewhat restricted band width $f(x_{\max}) - f(x_{\min}) = a$.
- 2) For convenience the noise is really small, *i.e.*, $\sigma \rightarrow 0$ $p_z(z) = \delta(z)$.

The mutual information is

$$I = \int p(y|x)p(x) \ln \frac{p(y|x)}{p(y)} dx dy$$

$$= H(y) - H(y|x)$$

$$H[y|x] = H(z) = \frac{1}{2} \ln(2\pi e \sigma^2) = \frac{1}{2} (1 + \ln(2\pi \sigma^2))$$

The *noise entropy* does not depend on x nor on $f(x)$ in this particular channel.

To calculate the entropy of the output random variable y not that it is added from two numbers, $y = f + z$. This means

$$p_y(y) = \int p_z(y - w)p_f(w)dw = p_f(y).$$

The last identity used Assumption 1). From the transformation rules of random variables one has $p(f) \frac{df}{dx} = p(x)$ or $p(f) = \frac{p(x)}{f'(x)}$.

Hence,

$$H(y) = - \int dy p(y) \ln p(y) = - \int dy \frac{p(x)}{f'(x)} \ln \frac{p(x)}{f'(x)} = - \int dx p(x) \ln p(x) + \int dx p(x) \ln f'(x)$$

From assumption 2) we have

$$J[f'(x)] = \int_{x_{\min}}^{x_{\max}} f'(x) dx = f(x_{\max}) - f(x_{\min})$$

$$C[f'(x)] = H[f'(x)] - \lambda(J[f'(x)] - a)$$

$$\frac{\delta C[f'(x)]}{\delta f'(x)} = \frac{p(x)}{f'(x)} - \lambda = 0$$

Maximum Mutual information given $p(x)$ is

$$f'(x) = \lambda p(x) \text{ or } f(x) = \lambda P(x) = \lambda \Phi(x).$$

This means that under the assumptions above, the contrast-response function should be proportional to the cumulative density function of the input.

10.7 Maximum entropy, continuous alphabet

Let us pause and ask: *What is the maximum entropy distribution for a continuous alphabet?*

Example (Maxent, continuous with variance constraint): Take a random variable $x \in \mathbb{R}$. It can not be the uniform distribution as in the discrete case. In fact we need additional constraints. For example one may ask for the maximum entropy distribution, $p(x)$, given a fixed mean, μ , and variance σ . Using *Lagrange's multipliers* to formulate the *constraint optimisation* problem

$$C = H + \lambda_0 \int dx p(x) + \lambda_1 \left(\int dx p(x)x - \mu \right) + \lambda_2 \left(\int dx p(x)(x - \mu)^2 - \sigma^2 \right)$$

One searches for $p(x)$ that fulfils $\delta C/\delta p(x) = 0$ and $\partial C/\partial \lambda_i = 0$, where $\delta/\delta p(x)$ is the variational derivative. One finds

$$p(x) = \exp(\lambda_0 - 1 + \lambda_1 x + \lambda_2(x - \mu)^2).$$

With the normalisation from $\partial C/\partial \lambda_i = 0$ we get the normal distribution ($e^{\lambda_0 - 1} = 1/\sqrt{2\pi\sigma^2}$, $\lambda_1 = 0$ and $\lambda_2 = 1/\sigma^2$).

10.8 Bounds on the estimation error

What did we learn? Well

$$(55) \quad H(x) \leq H_{\text{Gauss}}(x).$$

If we consider the whole spike train $y(t) = \sum_k \delta(t - t_k^{\text{sp}})$ (see Eq. (52)) as the output, not just its mean input intensity and mean firing rate, we have a continuous time dependent stochastic processes to deal with. Note that the definition of the spike train, if integrated, is related to the *empirical distribution function*.

If we average infinitely many trials we get the instantaneous firing rate $r(t) = \langle y(t) \rangle_{y|x}$. We will give a mathematical definition of $r(t)$ later. Our communication channel looks like that

input signal	→	neural pathway	→	response $y(t) \in \mathbb{R}$
$x(t) \in \mathbb{R}$				

The entropy rate of an ergodic process can be defined as the the entropy of the process at a given time conditioned on its past realisations in the limit of large time

$$(56) \quad H[x] = \lim_{t \rightarrow \infty} H[x_t | x_\tau : \tau < t].$$

The mutual information rate measures the amount of information a neural pathway transmits about an input signal $x(t)$ is the mutual information rate,

$$(57) \quad I[x, y] = H[y] - \underbrace{H[y|x]}_{\text{encoding}} = H[x] - \underbrace{H[x|y]}_{\text{decoding}},$$

between the stochastic process, $x(t)$, and the stochastic response process, $y(t)$. The entropy rate H measures the number of discriminable input or output states, either by themselves, or conditioned on other variables.

The mutual information rates, which is the difference between unconditional and conditional entropy rates, characterises the number of input states that can be distinguished upon observing the output. The response entropy rates $H[y]$, for instance, quantifies the number of typical responses per unit time, while $H[x|y]$ is a measure of the decoding noise in the model. If this noise is zero, then the mutual information rate is simply $H[x]$, provided that this is finite.

The conditional entropy rates $H[y|x]$ and $H[x|y]$, characterising the noise in the encoding and decoding model respectively, are each greater than zero. In information theory, these quantities are also called *equivocation*. Hence, both the stimulus and response entropy rates, $H[x]$ and $H[y]$, are upper bounds for the transmitted information.

Example (Info rate continuous discrete-time Gaussian process): The OU-process from Eq. (27) is an example of a Gaussian process. Take a discretised version, $\vec{x} = [x(t_1), x(t_2), \dots]$, of it such that

$$p(\vec{x}) = |2\pi\mathbf{K}|^{-1/2} \exp\left(-\frac{1}{2}(\vec{x} - \vec{\mu})^\dagger \mathbf{K}^{-1}(\vec{x} - \vec{\mu})\right)$$

$$H_n = \frac{1}{2} \ln 2\pi|\mathbf{K}| + \frac{n}{2}$$

This is similar to the quantisation problem. It might be reasonable to drop the n term (sometimes this is done, sometimes not). For the one dimensional case we have

$$H = \frac{1}{2}(1 + \ln 2\pi\sigma^2)$$

or, if we drop the $n = 1$

$$(58) \quad \sigma^2 = \frac{1}{2\pi} e^{2H_{\text{Gauss}}(x)}$$

Any practical consequences?

Def. (Estimation error): For a random variable x the estimation error of an estimator \hat{x} is

$$\langle (x - \hat{x})^2 \rangle$$

The best estimator is the mean, so the statisticians say. Therefore a lower bound to the estimation error is given by

$$(59) \quad \langle (x - \hat{x})^2 \rangle \geq \langle (x - \langle x \rangle)^2 \rangle = \sigma^2 = \frac{1}{2\pi} e^{2H_{\text{Gauss}}(x)} \geq \frac{1}{2\pi} e^{2H(x)}.$$

The last inequality followed from Eq. (55).

Example (Info rate continuous continuous-time Gaussian process): Up to an additive constant the entropy of a multivariate Gaussian was²³

$$H = \frac{1}{2} \ln |\mathbf{K}| = \frac{1}{2} \text{tr} \ln \mathbf{K} = \frac{1}{2} \text{tr} \ln \mathbf{\Lambda} = \frac{1}{2} \sum_k \ln \lambda_k.$$

First let us observe the process for ever $\vec{x} = [x(-\infty), \dots, x(\infty)]$, a bi-infinite series with countable elements. The elements of the covariance matrix $\mathbf{K}_{ij} = c(i * dt - j * dt)$. The orthogonal eigen-function for the continuous covariance operator on $t \in \mathbb{R}$ are the Fourier bases. It can be shown that in the continuum limit

$$H = \int df \ln \lambda(f)$$

The result is due to Kolmogorov see also (???, Golshani and Pasha (2010)).

10.9 Linear stimulus reconstruction and a lower bound on the information rate (decoding view)

Without a complete probabilistic description of the model the mutual information can not be calculated. And even with a model the involved integrals may not be tractable. At least two strategies to estimate it exist, though: Either, create a statistical ensemble of inputs and outputs by stimulation, followed by (histogram based) estimation techniques for the mutual information; or, find bounds on the information that can be evaluated more easily. In general, the estimation of mutual information from empirical data is difficult, as the sample size should be much larger than the size of the alphabet. Indeed, each element of the alphabet should be sampled multiple times so that the underlying statistical distribution can, in principle, be accurately estimated. But this prerequisite is often violated, so some techniques of estimating the information from data directly rely on extrapolation (???). The problem becomes particularly hairy when the alphabet is continuous or a temporal processes had to be discretised, resulting in large alphabets.

Another approach, which will allow us to perform a theoretical analysis of phase dynamics, relies on a comparison of the neuronal “channel” to the continuous Gaussian channel (???, Cpt.~13) is analytically solvable (Cover and Thomas 2012). The approach can be used to estimate the information transmission of neuronal models (???). Also experimental system have been analysed in this way, e.g.:

1. the spider’s stretch receptor (???)

²Remember the determinant is $|\mathbf{K}| = \prod_{i=1}^n \lambda_i$. So $\ln |\mathbf{K}| = \sum_{i=1}^n \ln \lambda_i$. In terms of the matrix-logarithm and the trace the determinant can be expressed as $|\mathbf{K}| = \exp \text{tr} \ln \mathbf{K}$.

³Because the trace is invariant under similarity transforms $\text{tr} \mathbf{K} = \sum_{i=1}^n \lambda_i$.

2. the electric sense of weakly electric fish (???) and paddle fish (???);
3. the posterior canal afferents in the turtle (???)

It was proven that in that this method leads to a guaranteed lower bound of the actual information transmitted (???)

If one has experimental control of the stimulus ensemble it can be chosen to be a Gaussian process with a flat spectrum up to a cutoff as to not introduce biases for certain frequency bands. The mutual information between stimulus $x(t)$ and response $y(t)$ can be bound from below as

$$(60) \quad I[x, y] = H[x] - H[x|y] \geq H[x] - H_{\text{gauss}}[x|y],$$

Here, $H_{\text{gauss}}[x|y]$ is the equivocation of a process with the same mean and covariance structure as the original decoding noise, but with Gaussian statistics. The conditional entropy of the stimulus given the response is also called reconstruction noise entropy. It reflects the uncertainty remaining about the stimulus when particular responses have been observed.

It turns out that the inequality in Eq. (59) also holds if the estimator is conditioned. Say from the output of the neuron we estimate its input

$$\hat{x}(t) = \hat{x}_t[y].$$

So if the process has a stationary variance

$$\langle (x(t) - \hat{x}(t))^2 \rangle_{x|y} \geq \inf_{\hat{x}} \langle (x(t) - \hat{x}(t))^2 \rangle_{x|y} = \langle (x(t) - \langle x(t) \rangle_{x|y})^2 \rangle_{x|y} = e^{2H_{\text{gauss}}[x|y]}.$$

The second line uses the fact that in this case the optimal estimator is given by the conditional mean. We have the following bound on the equivocation

$$(61) \quad H[x|y] \leq H_{\text{gauss}}[x|y] \leq \frac{1}{2} \ln \langle (x(t) - \hat{x}(t))^2 \rangle \leq \ln \langle n^2(t) \rangle,$$

The deviation between stimulus and its estimate, $n(t) = x(t) - \hat{x}(t)$, is treated as the noise process.

In order to obtain a tight bound the estimator $\hat{x}(t)$ should be as close to optimal as possible. For the case of additional information given by the response of the neural system $y(t)$ to the process $x(t)$, the estimator should make use of it, $\hat{x}_t[y]$. For simplicity one can assume it is carried out by a filtering operation, $\hat{x}(t) = (f * y)(t)$ specified later (Gabbiani and Koch 1998). Like the whole system the noise process is stationary, and its power spectral density, $P_{nn}(\omega)$, is

$$H_{\text{gauss}}[x|y] \leq \frac{1}{2} \ln \langle n^2(t) \rangle = \frac{1}{2} \int_{-\infty}^{\infty} \frac{d\omega}{2\pi} \ln P_{nn}(\omega).$$

Together

$$(62) \quad I[x, y] \geq \frac{1}{2} \int_{-\infty}^{\infty} \frac{d\omega}{2\pi} \ln \left(\frac{P_{xx}(\omega)}{P_{nn}(\omega)} \right)$$

So as to render the inequality in Eq. (61) as tight a bound as possible one should use the optimal reconstruction filter from y to \hat{x} . In other words, it is necessary to *extract as much information about x from the spike train y as possible*.

The next step should be to find an expression for the noise spectrum, $P_{nn}(\omega)$, based on the idea of ideal reconstruction of the stimulus. As opposed to the forward filter, the reconstruction filter depends on the stimulus statistics (even without effects such as adaptation). We seek the filter h that minimises the variance of the mean square error

$$(63) \quad \langle n^2(t) \rangle = \langle (x(t) - \hat{x}(t))^2 \rangle, \text{ with } \hat{x}(t) = \int d\tau h(\tau)y(t - \tau).$$

Taking the variational derivative [?] of the error w.r.t.

the filter (coefficients) $h(\tau)$ and equating this to zero one obtains the orthogonality condition for the optimal Wiener filter (???)

$$(64) \quad \langle n(t)y(t - \tau) \rangle = 0, \forall \tau.$$

Inserting the definition of the error, $n(t) = x(t) - \hat{x}(t)$, into Eq. (64) yields

$$\langle x(t)y(t - \tau) \rangle - \int d\tau_1 h(\tau_1) \langle r(t - \tau_1)r(t - \tau) \rangle = R_{xy}(\tau) - (h * R_{yy})(\tau) = 0$$

In order to obtain h we need to deconvolve the equation, which amounts to a division in the Fourier domain

$$(65) \quad P_{xy}(\omega) = H(\omega)P_{yy}(\omega) \implies H^{\text{opt}}(\omega) = \frac{P_{xy}(\omega)}{P_{yy}(\omega)}.$$

To compute the mutual information rate, we now calculate the full auto-correlation of the noise when the filter is given by Eq. (65). For an arbitrary filter $h(t)$, we have

$$R_{nn}(\tau) = \langle n(t)n(t+\tau) \rangle = \langle n(t)x(t+\tau) \rangle - \int d\tau_1 h(\tau_1) \langle n(t)y(t+\tau-\tau_1) \rangle.$$

When the orthogonality condition of Eq. (64) holds, the right-most term vanishes. Proceeding by expanding the first term algebraically leads to an expression for the noise correlations

$$R_{nn}(\tau) = \langle n(t)x(t+\tau) \rangle = R_{xx}(\tau) - \int d\tau_1 h(\tau_1)R_{xy}(\tau-\tau_1).$$

This expression can be Fourier transformed in order to obtain the required noise spectrum

$$P_{nn}(\omega) = P_{xx}(\omega) - H(\omega)P_{xy}(\omega) = P_{xx}(\omega) - \frac{|P_{xy}(\omega)|^2}{P_{yy}(\omega)},$$

where the definition of the optimal filter, Eq. (65), was utilised. This result can then be inserted into Eq. (62) to obtain the following well known bound on the information rate (???, lindner2005j:mi, holden1976b, stein1972j:coherenceInfo)

$$(66) \quad \mathcal{M}[x, y] \geq -\frac{1}{2} \int_{-\omega_c}^{\omega_c} \frac{d\omega}{2\pi} \ln \left(1 - \frac{|P_{xy}(\omega)|^2}{P_{xx}(\omega)P_{yy}(\omega)} \right).$$

This information bound involves only spectra and cross-spectra of the communication channel's input and output processes which are experimentally measurable in macroscopic recordings [?, ?, ?, ?]. The channel, in this case the neuron, can remain a black box. But since we can bridge the divide between microscopic, biophysical models and their filtering properties, we will, in the following section, derive the mutual information rates.

Def. (spectral coherence): The expression in Eq. (66) is termed the squared signal response coherence

$$(67) \quad c^2(\omega) = \frac{|P_{xy}(\omega)|^2}{P_{xx}(\omega)P_{yy}(\omega)}.$$

It quantifies the linearity of the relation between x and y in a way that it equals 1 if there is no noise and a linear filter transforms input to output. Both nonlinearities and noise reduce the coherence. The coherence can be estimated from data using the FFT algorithm and spectrum estimation. It is implemented in the free software packages `scipy` and `matplotlib`.

What renders the coherence a useful quantity? While the cross-spectrum informs us when stimulus and output have correlated power in a spectral band, the normalisation with the output auto-spectrum can be crucial. Say we find a particular high power in $P_{xy}(\omega)$, this may not be related to the stimulus but could just be the intrinsic frequency of the neuron itself.

The coherence is a quantity without mention of the explicit decoding filter, in fact it is symmetric in input and output just as the mutual information. This is beneficial because one can now take the encoding view in the next chapter.

11 Linear response filter

The stimulus spectral density is given by the environment or controlled by the experimental setup, while cross- and output spectra need to be measured or calculated from the model in question. In this lecture cross-spectral and spike train spectral densities are derived from phase oscillator, see Eq. (??), that are in turn derived from biophysical models. This means we do not treat the channel as a blackbox but assume a particular model.

The first quantity we need to calculate Eq. (67) is the cross-spectrum. On the one hand it is the Fourier of the cross-correlation, on the other it can be written as averages of the Fourier transforms (FT and average are linear operation).

$$(68) P_{yx}(\omega) = \langle \langle \tilde{y}(\omega) \tilde{x}^*(\omega) \rangle_{y|x} \rangle_x = \langle \langle \tilde{y}(\omega) \rangle_{y|x} \tilde{x}^*(\omega) \rangle_x.$$

What has happened here? The cross-spectrum can be obtained by averaging the Fourier transformed quantities over trials and the stimulus ensemble. The average can be split into the conditional average over trials $\langle \cdot \rangle_{y|x}$, given a fixed, *frozen* stimulus and the average over the stimulus ensemble, $\langle \cdot \rangle_x$. The former is essentially an average over the encoding noise (Chacron, Lindner, and Longtin 2004, Lindner, Chacron, and Longtin (2005)).

Observe that $\langle \tilde{y}(\omega) \rangle_{y|x}$ is Fourier transform of the trial averaged firing rate conditional on a frozen stimulus

$$r(t) = \langle y(t) \rangle_{y|x}.$$

Thus, it is sufficient to derive a filter that maps input $x(t)$ to a firing rate, not an individual spike train.

Def. (forward, encoding filter): Let $g(t)$ be the filter kernel that maps stimulus into instantaneous firing rate

$$(69) r(t) = (g * x)(t) = \int_{-\infty}^t dr g(r) x(t - r)$$

The filter is causal, since it is implemented by a differential equation and the Laplace transform yields

$$(70) R(s) = G(s)X(s),$$

where $G(s)$ denotes the transfer function of the *encoding filter*.

With this definition the cross-spectrum is written as

$$(71) P_{yx}(\omega) = \langle \langle \tilde{y}(\omega) \rangle_{y|x} \tilde{x}^*(\omega) \rangle_x = G(i\omega)P_{xx}(\omega).$$

This shows us that although we are computing the cross-spectrum of stimulus and spike train the response filter $G(i\omega)$ for the instantaneous firing rate suffices. This simple relation reminds us of the fact that the cross-spectrum is not really a second order quantity, but can be exactly determined by linear response theory. The spike train spectrum $P_{yy}(\omega)$, on the other hand, is truly a second order quantity, viz, the Fourier transform of the auto covariance, and can not be related to the linear response filter without further approximations.

11.1 Instantaneous firing rate in the continuum limit

The instantaneous firing rate can be estimated via binning and trial averaging

$4\Delta r(k\Delta)$:	0	3	1	0	0	0	0	3	1	0	0	0	1	2	1	0
Trials:	0	1	0	0	0	0	0	1	0	0	0	0	0	1	0	0
	0	0	1	0	0	0	0	1	0	0	0	0	0	0	1	0
	0	1	0	0	0	0	0	0	1	0	0	0	0	1	0	0
	0	1	0	0	0	0	0	1	0	0	0	0	1	0	0	0

Two equivalent descriptions¹ of Markov dynamics exist

(i) the *path* view,

$$(72) \quad \dot{x} = u(x, t) = f(x) + g(x)\xi(t);$$

(ii) the *ensemble* view

$$\dot{p}(x, t) = ?.$$

For (i) one can simulate many paths of a stochastic differential equation, with different initial conditions and noise realisations. Histograms can provide the ensemble statistics. But it is also possible to find an evolution equation for the whole ensemble.

The relation between the two can be formally established by the

Def. (empirical measure): Given a stochastic path realisation, $x(t)$, from Eq. (72) the empirical measure is

$$(73) \quad \varrho(y, t) = \delta(x(t) - y).$$

With all the lovely properties of a δ -function.

The probability density

$$(74) \quad p(y, t) = \langle \varrho(y, t) \rangle,$$

where the average is over all paths, $x(t)$, and therefore over all realisations of the noise process $\xi(t)$.

The chain rule yields

$$\frac{\partial}{\partial t} \varrho(y, t) = \dot{x}(t) \frac{\partial}{\partial x} \varrho(y, t) = - \frac{\partial}{\partial y} \varrho(y, t) u(x(t), t)$$

Solving such a PDE involves time integration or other integral transformations (Fourier and Laplace's). Since

$$\int dy \delta(x(t) - y) f(y) = f(x(t)) = \int dy \delta(x(t) - y) f(x(t))$$

Therefore

$$(75) \quad \frac{\partial}{\partial t} \varrho(y, t) = - \frac{\partial}{\partial y} \varrho(y, t) u(y, t) = - \frac{\partial}{\partial y} f(y) \varrho(y, t) - \frac{\partial}{\partial y} g(y) \xi(t) \varrho(y, t)$$

Averaging on both sides results in

$$\frac{\partial}{\partial t} p(y, t) = - \frac{\partial}{\partial y} f(y) p(y, t) - \frac{\partial}{\partial y} g(y) \langle \xi(t) \varrho(y, t) \rangle.$$

The correlation between a stochastic process $\xi(t)$ and a nonlinear functional of it is given by the Novikov-Furutsu-Donsker formula

$$(76) \quad \langle \xi(t) \varrho(y, t) \rangle = - \frac{1}{2} \langle \frac{\delta \varrho}{\delta \xi(t)} \rangle = - \frac{1}{2} \frac{\partial}{\partial y} g(y) p(y, t)$$

All to gether we have the

Def. (Fokker-Planck equation): The FPE corresponding to Eq. (72) is

$$(77) \quad \frac{\partial}{\partial t} p(y, t) = \frac{1}{2} \frac{\partial}{\partial y} g(y) \frac{\partial}{\partial y} g(y) p(y, t) - \frac{\partial}{\partial y} f(y) p(y, t).$$

This is a diffusion equation. It can be written in the form

¹Similar to the particle and wave duality in quantum mechanics.

$$(78) \quad \frac{\partial}{\partial t} p(y, t) = -\frac{\partial}{\partial y} J(y, t).$$

$$J(y, t) = f(y)p(y, t) - \frac{1}{2}g(y)\frac{\partial}{\partial y}g(y)p(y, t)$$

One needs boundary conditions and initial conditions to solve this PDE.

11.2 Phase flux = firing rate

For convenience rewrite the I/O-equivalent phase oscillator from Eq. ((??)) as

$$(79) \quad \dot{\phi} = f_0 + z(\phi)x(t) + \sigma \xi(t).$$

Here, as opposed to Eq. ((??)) $\vec{Z}(\phi) \cdot \vec{\eta}(\phi, t)$ was split into the part that results from the presented stimulus, now denoted $x(t)$, and the part that originated from, *e.g.* intrinsic noise. From Eq. (27) the perturbation vector has

$$\vec{\eta} = \begin{pmatrix} x(t) \\ \sigma_1(v(\phi))\xi_1(t) \\ \vdots \end{pmatrix}.$$

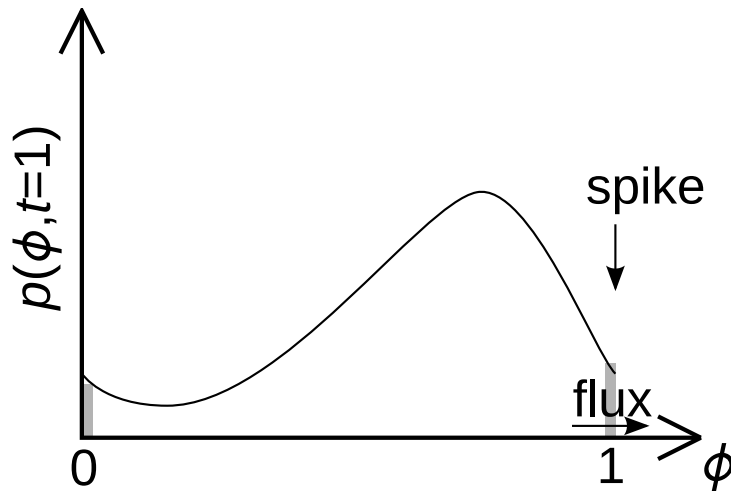
As long as the intrinsic noise is fast enough compared to the stimulus an averaging can be applied² to obtain an effective diffusion

$$\sigma^2 = \int_0^1 d\phi \sum_i \sigma_i^2(v_{LC}(\phi)),$$

which enters Eq. (79). The benefit is that the corresponding The Fokker-Planck equation

$$(80) \quad \frac{\partial}{\partial t} p(\phi, t) = \frac{\sigma^2}{2} \frac{\partial^2}{\partial \phi^2} p(\phi, t) - \frac{\partial}{\partial \phi} (f_0 + Z(\phi)x(t))p(\phi, t) = -\frac{\partial}{\partial \phi} J(\phi, t)$$

is tractable in a perturbation expansion. But first, remember what is the goal: Identification of the forward filter $g(t)$ in $r(t) = \int_{-\infty}^t dr g(r)x(t-r)$.



Phase density

$$r(t) = J(1, t) = (f_0 + Z(\phi)x(t))p(\phi, t) - \frac{\sigma^2}{2} \frac{\partial}{\partial \phi} p(\phi, t) \Big|_{\phi=1}$$

The equation is solved with the following perturbation ansatz

$$(81) \quad p(\phi, t) = p_0(\phi) + \sum_i p_i(\phi, t),$$

²This can be done formally using Chapman-Enskog or adiabatic elimination procedures. The derivation may be included in to future.

with the normalisation requirement

$$(82) \int d\phi p_0(\phi) = 1 \text{ and } \forall i \in \mathbb{N}, t \in \mathbb{R} : \int d\phi p_i(\phi, t) = 0.$$

The $p_i(\phi, t)$ are assumed small correctin terms, given that the stimulus $x(t)$ is also small.

at the same time one gets

$$J(\phi, t) = J_0(\phi) + \sum_i J_i(\phi, t)$$

In perturbation theory one solves iteratively the equations of the same order

$O(0)$: For the lowest order the stimulus $x(t) = 0$ the FPE is

$$\dot{p}_0 = \frac{\sigma^2}{2} \frac{\partial^2}{\partial \phi^2} p_0 - f_0 \frac{\partial}{\partial \phi} p_0.$$

This equation is homogeneous so we find a time independent steady state solution

$$p_0(\phi) = 1.$$

One may test this by back insertion. Here both the boundary conditions and Eq. (82) are inforced. The solution can be inserted into the definition of the flux to obtain the zeroth order flux

$$J_0 = f_0 p_0 = f_0$$

The next order involves the time-dependent stimulus

$O(x)$: Note that multplying two terms of order $O(x)$ yields a term of order $O(x^2)$ and is discarded. One is left with

$$\dot{p}_1 = \frac{\sigma^2}{2} \frac{\partial^2}{\partial \phi^2} p_1 - f_0 \frac{\partial}{\partial \phi} p_1 - p_0 x(t) \frac{\partial}{\partial \phi} Z(\phi)$$

To turn the PDE into an algebraic equation one can apply both the Fourier series expansion and the Laplace transform. For this the Laplace transform of the stimulus is denoted as $X(s)$ and the periodic function $Z(\phi) = \sum_{k=-\infty}^{\infty} c_k e^{i2\pi k \phi}$

$$sP_1(k, s) = -\frac{(2\pi k \sigma)^2}{2} P_1(k, s) - f_0 i2\pi k P_1(k, s) - X(s) i2\pi k c_k$$

Solving for $P_1(\phi, s)$

$$P_1(\phi, s) = \sum_{k=-\infty}^{\infty} P_1(k, s) e^{i2\pi k \phi} = \sum_{k=-\infty}^{\infty} \frac{i2\pi k c_k X(s) e^{i2\pi k \phi}}{s + (2\pi k \sigma)^2/2 + i2\pi k f_0}$$

For brevity define the pole $\nu_k = -(2\pi k \sigma)^2/2 - i2\pi k f_0$

The first order flux is

$$J_1(k, s) = f_0 P_1(k, s) + c_k X(s) - \frac{i2\pi k \sigma^2}{2} P_1(k, s)$$

$$= f_0 P_1(k, s) + \frac{s - \nu_k}{i2\pi k} P_1(k, s) - \frac{i2\pi k \sigma^2}{2} P_1(k, s)$$

and

$$i2\pi k J_1(k, s) = i2\pi k f_0 P_1(k, s) + \frac{(2\pi k \sigma)^2}{2} P_1(k, s) + (s - \nu_k) P_1(k, s) = s P_1(k, s)$$

$$J_1(1, s) = \sum_{k=-\infty}^{\infty} \frac{s c_k}{s - \nu_k} X(s)$$

Happily and consistently one finds

$$G(s) = \sum_{k=-\infty}^{\infty} \frac{s c_k}{s - \nu_k}$$

The power spectrum correponds to the imaginary axis, $G(i\omega)$. The low frequency limit is

$$\lim_{\omega \rightarrow 0} G(i\omega) = c_0 = \langle Z(\phi) \rangle.$$

With $c_k = a_k + ib_k$, the high frequency limit is

$$\lim_{\omega \rightarrow \infty} G(i\omega) = \sum_{k=-\infty}^{\infty} a_k = Z(0).$$

12 No free lunch: energy and information processing

13 Networks

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