Universidad de Granada

IMAG INSTITUTO DE MATEMÁTICAS Universidad de Granada

Departamento de Matemática Aplicada

Mathematical Models in Neurobiology

María J. Cáceres

CIMPA 2025

La Habana, 9-20 June 2025

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Some Mathematical Models in Neurobiology

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It is now well known that neurons are the key units of the animal nervous system

In the human brain there are around 10^{12} neurons

In $1mm^3$ of cortical tissue, there are about 10^5 neurons

Better understanding how the brain works is one of the great challenges of today

How can mathematics help achieve this goal?

- Mathematical models have been key to understanding how neurons work
- And they are a fundamental tool in current research

In this course we will present different models considering different scales of observation

The motivation is to collaborate as mathematicians to better understand the brain, but we also face a double mathematical challenge:

- to understand the mathematical properties of the models used by neuroscientists
- to develop new mathematical techniques that can be applied to other models

Teamwork

Structure of the course

- Neuron’s biology
- Microscopic models
    - Hodgkin-Huxley model
    - Morris-Lecar model
    - FitzHugh-Nagumo model
    - Integrate-and-fire model
    - Stochastic differential equations (SDE)
- Partial differential equations (PDE)
    - Nonlinear Noisy Leaky Integrate and Fire (NNLIF)
    - Age-structured partial differential equations
- Open problems

Structure of the course

We will study

- Different scales/systems to model the behaviour of neurons populations
- Long time behaviour for some PDE models
    - Global existence versus blow-up
    - Number of equilibria
    - Stability of the equilibria
        - Entropy method
        - Discrete description for system with large transmission delay: pseudo-equilibria sequence
        - New technique using Volterra-type equation

Structure of the course

Some general references:

- Books:
  - ◇ Ermentrout & Terman, Mathematical Foundations of Neuroscience, 2010
  - ◇ Coombes & Wedgwood, Neurodynamics, 2023
- PhD Thesis:
  - ◇ Alejandro Ramos-Lora, Microscopic and mesoscopic descriptions of the Nonlinear Noisy Leaky Integrate-and-Fire model: long-time behavior and numerical simulations, 2024
  - ◇ Ricarda Schneider, Analysis and numerical simulation of network of noisy leaky integrate and fire neuron models, 2018
  - ◇ Nicolás Torres, Asymptotic behavior of solutions of the elapsed time model for neural assemblies, 2021
- Review: Carrillo & Roux, Nonlinear partial differential equations in neuroscience: from modelling to mathematical theory, 2025

Neuron’s biology

- In the late 19th century, scientists debated the basic structure of the nervous system:
    - it was a continuous network of fibers
    - it was composed of individual units

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    - it was a continuous network of fibers
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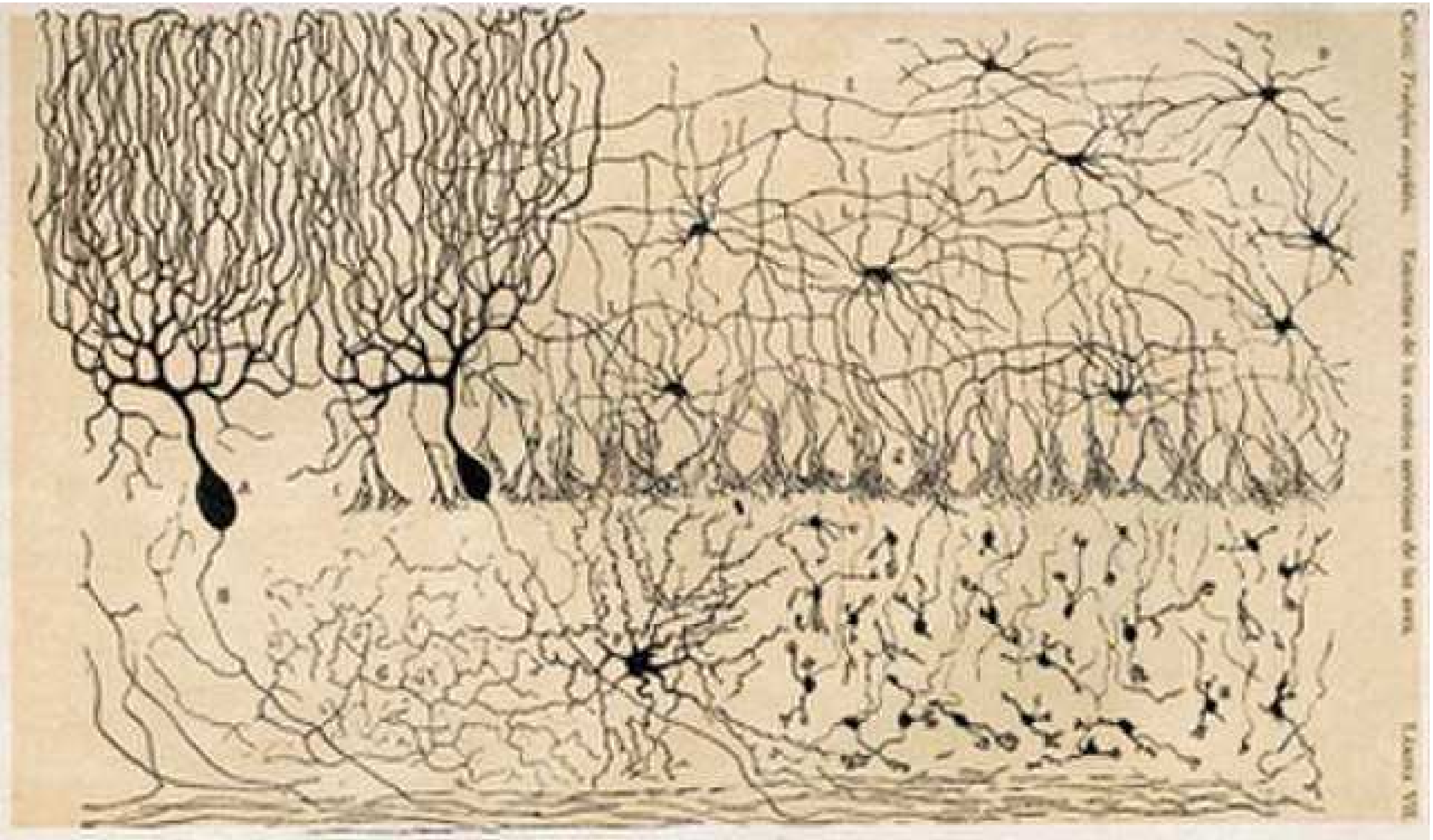
- **Camillo Golgi** developed a silver nitrate staining technique (*Golgi stain*) that made neurons visible under the microscope. And he supported the reticular theory, which held that nerve cells formed a continuous web

- **Santiago Ramón y Cajal** used Golgi's technique and arrived at a different conclusion: neurons are discrete, individual cells that communicate through tiny gaps. His work led to the formulation of the neuron doctrine, which remains a cornerstone of modern neuroscience

- Golgi and Ramón y Cajal were jointly awarded the **Nobel Prize in Physiology or Medicine in 1906**, "in recognition of their work on the structure of the nervous system"



Drawing of the cells of the chick cerebellum by Santiago Ramón y Cajal, from "Estructura de los centros nerviosos de las aves", Madrid, 1905 (Wikimedia Commons, Public Domain)

Neuron's biology

- WHAT IS A NEURON?

- WHICH IS ITS FUNCTION?

- HOW IS A NEURON?

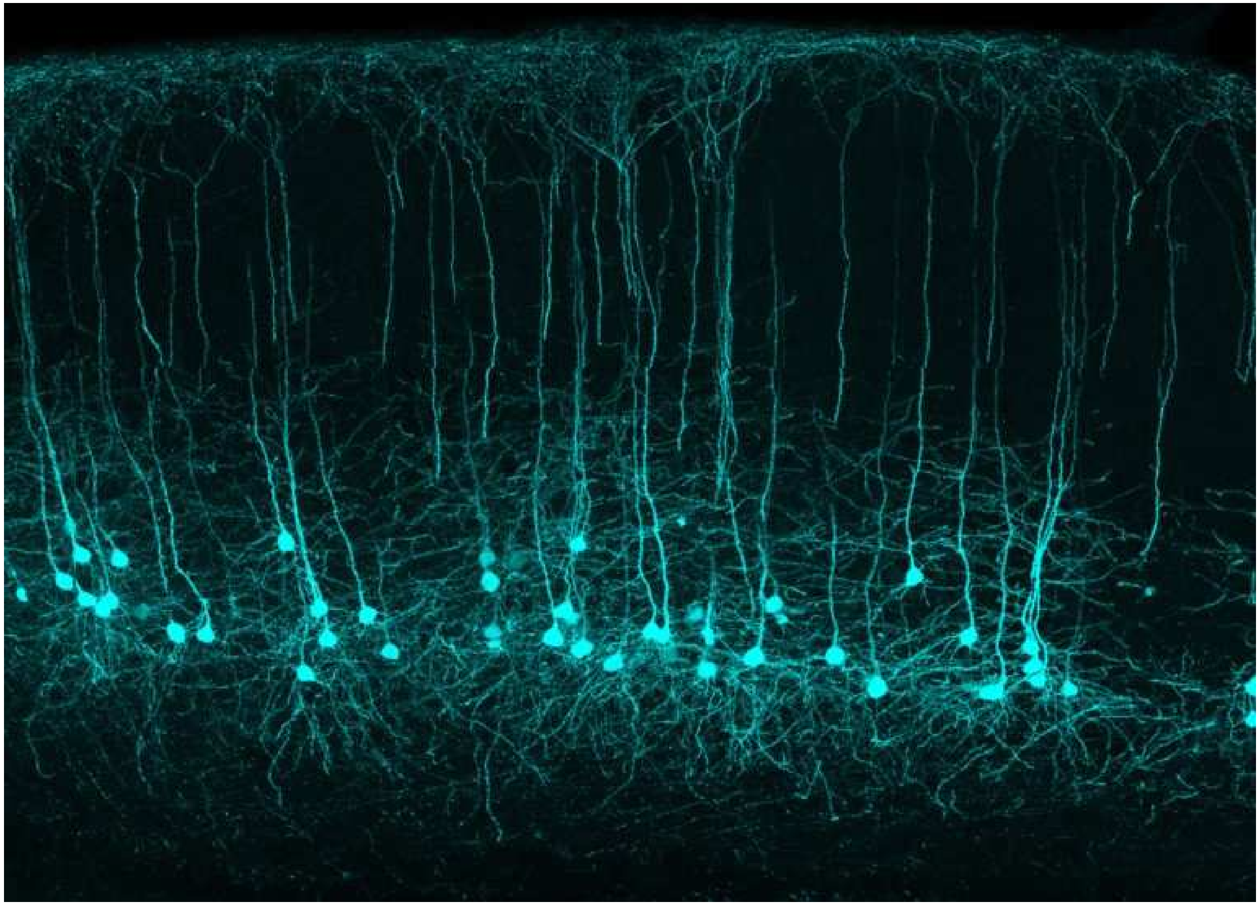
Neuron’s biology

CONCEPT	A neuron is a cell of the nervous system and is an electrically excitable cell that receives, processes, and transmits information through electrical and chemical signals

FUNCTION	It passes information on to organism

PARTS	Body, Axon and Dendrite

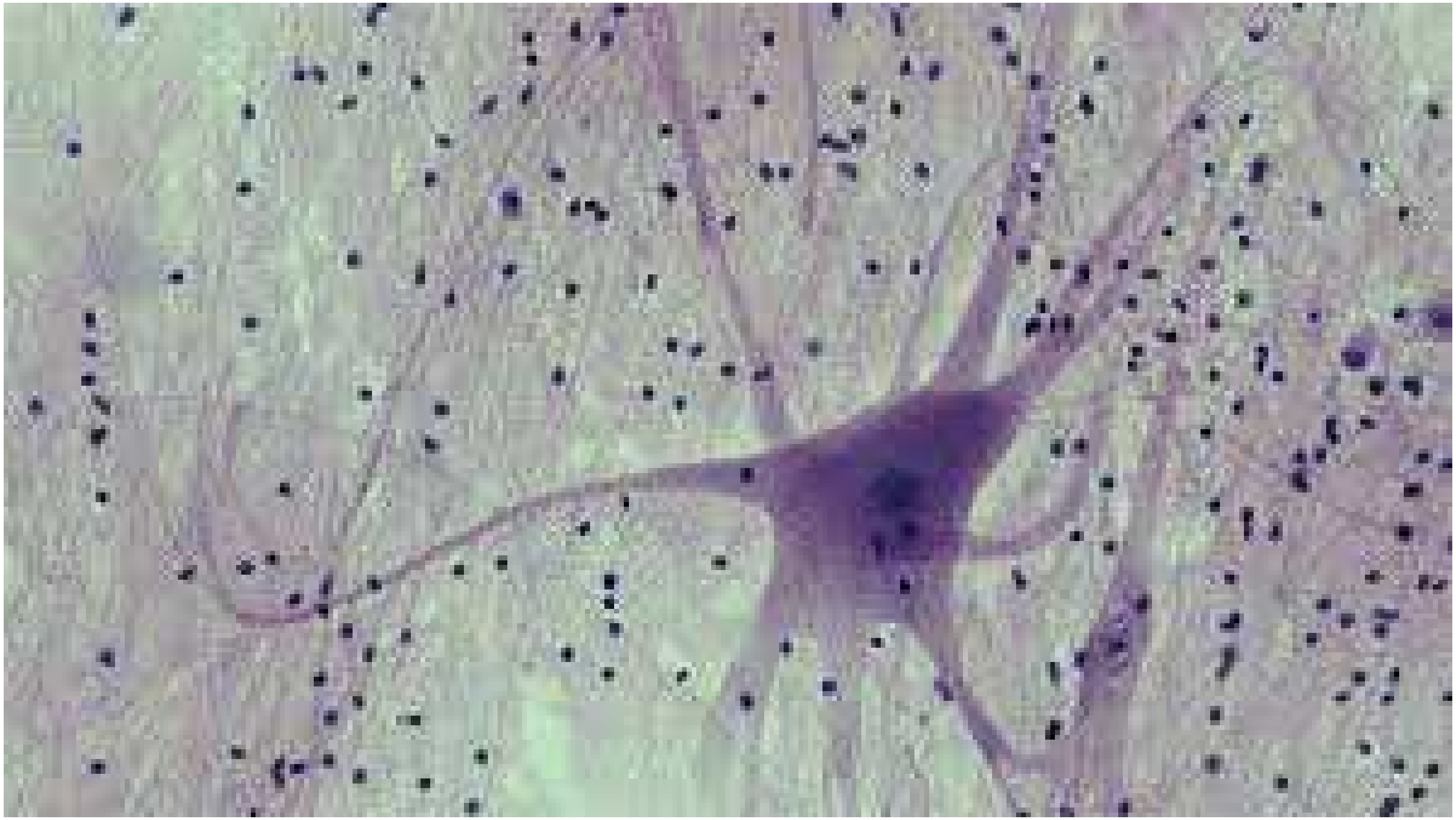
Neuron's biology



Numerous neurons of the cerebral cortex

Image by the Max Planck Florida Institute for Neuroscience

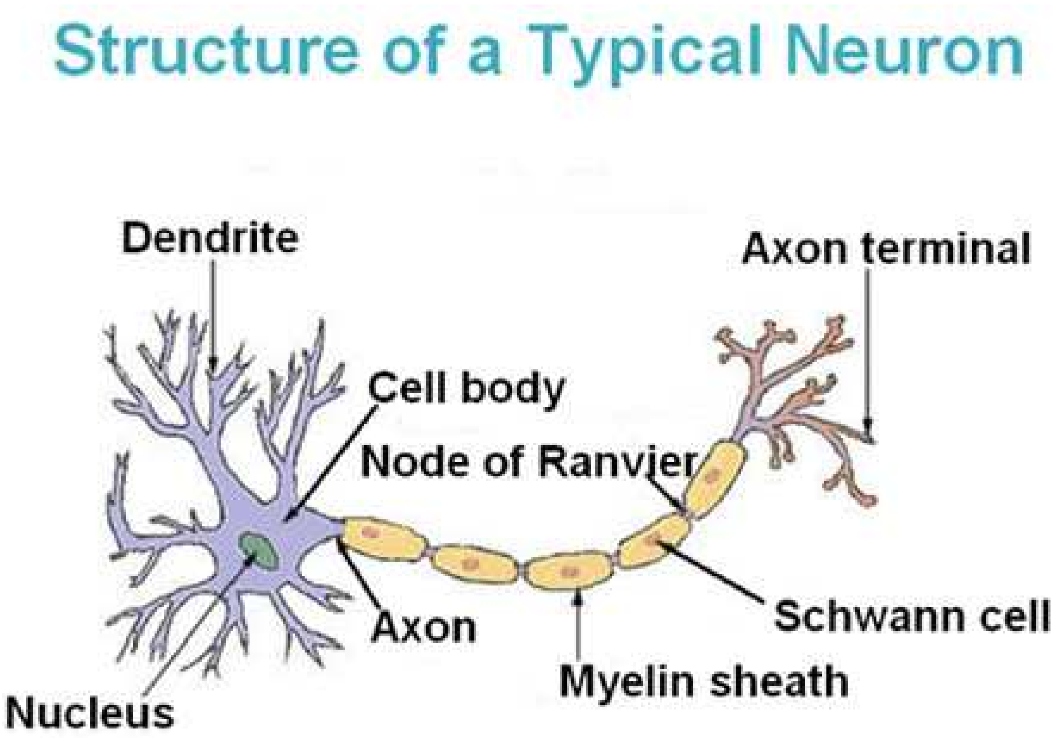
Neuron's biology



Motor neurons

Berkshire community college bioscience image library

Neuron's biology



Picture from the Wikimedia Commons

- Dendrites are thin structures that arise from the cell body, branching multiple times, as a complex "dendritic tree"
- An axon (also called a nerve fiber) is a special cellular extension that arises from the cell body at a site called the axon hillock

Neuron's biology

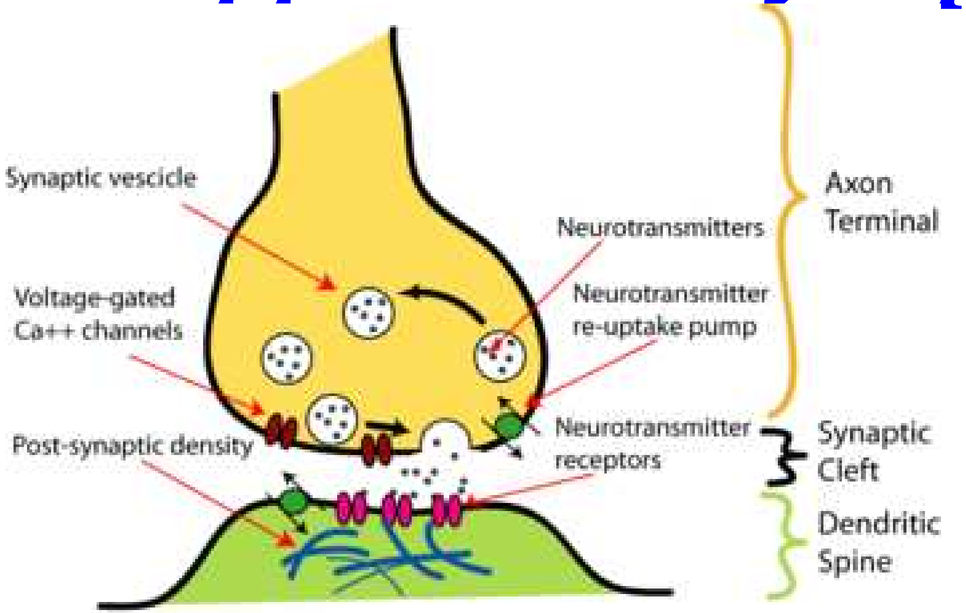
How do neurons connect?

Neuron's biology

SYNAPSE

- From *synaptein* (Charles Scott Sherrington), from the Greek *syn-* (together) and *haptein* (to clasp)
- Specialized junctions through which neurons signal to each other and to non-neuronal cells such as those in muscles or glands
- Crucial to the biological computations that underlie perception and thought
- A huge number in human brain:
  - 10^{15} in young children
  - $10^{14} - 5 \times 10^{14}$ for adults
- It happens at the level of the membranes of the cells

What happens at a synapse?



- Presynaptic: tip of an axon
- Postsynaptic: dendrite or cell body
- Presynaptic neurons secrete neurotransmitters (active zones)
- which bind to receptors from postsynaptic cells
- thanks to cell adhesion proteins in active zones
- and appears the postsynaptic density behind the postsynaptic membrane

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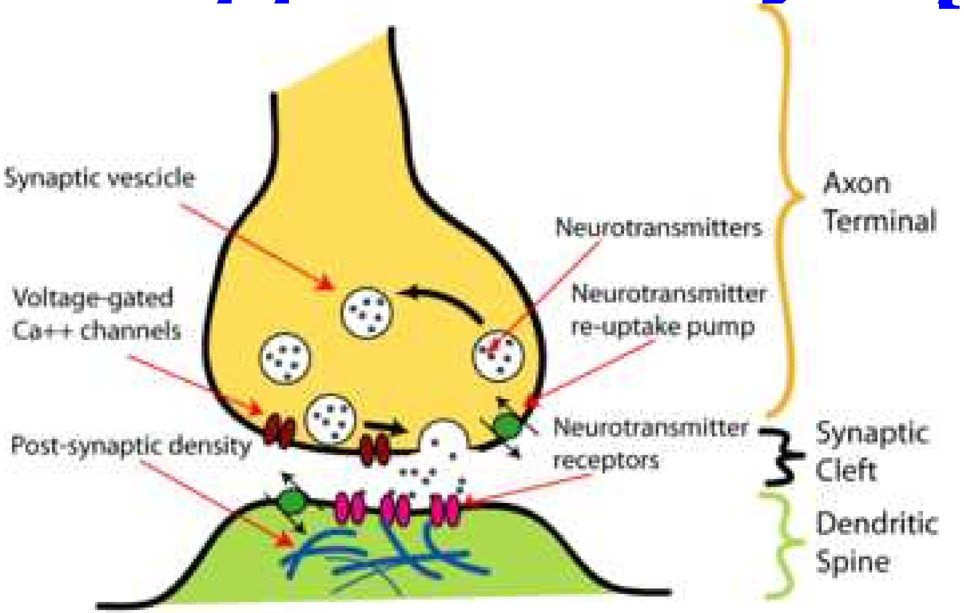
Picture from the Wikimedia Commons

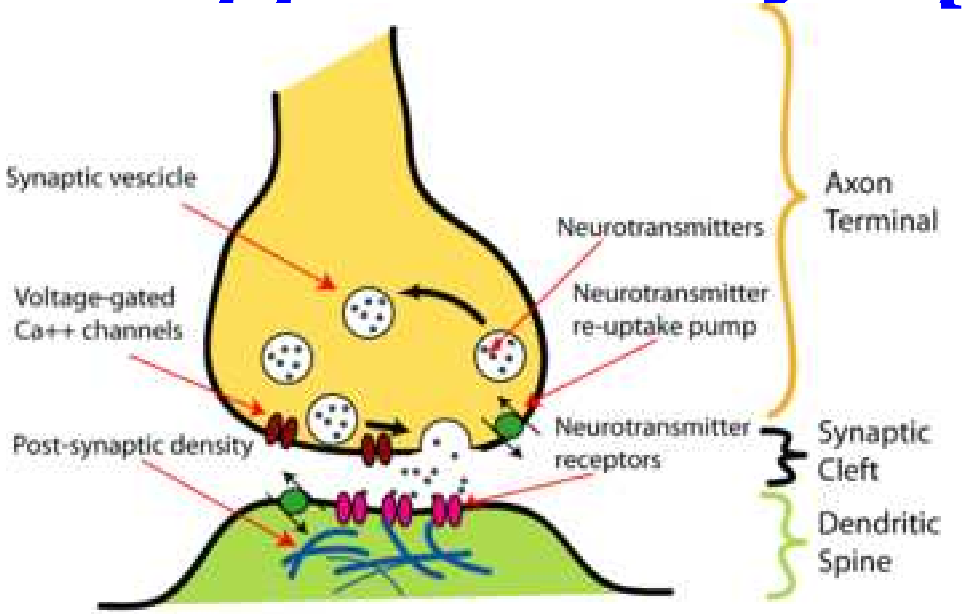
What happens at a synapse?



Why are the neurotransmitters released?

Picture from the Wikimedia Commons

What happens at a synapse?



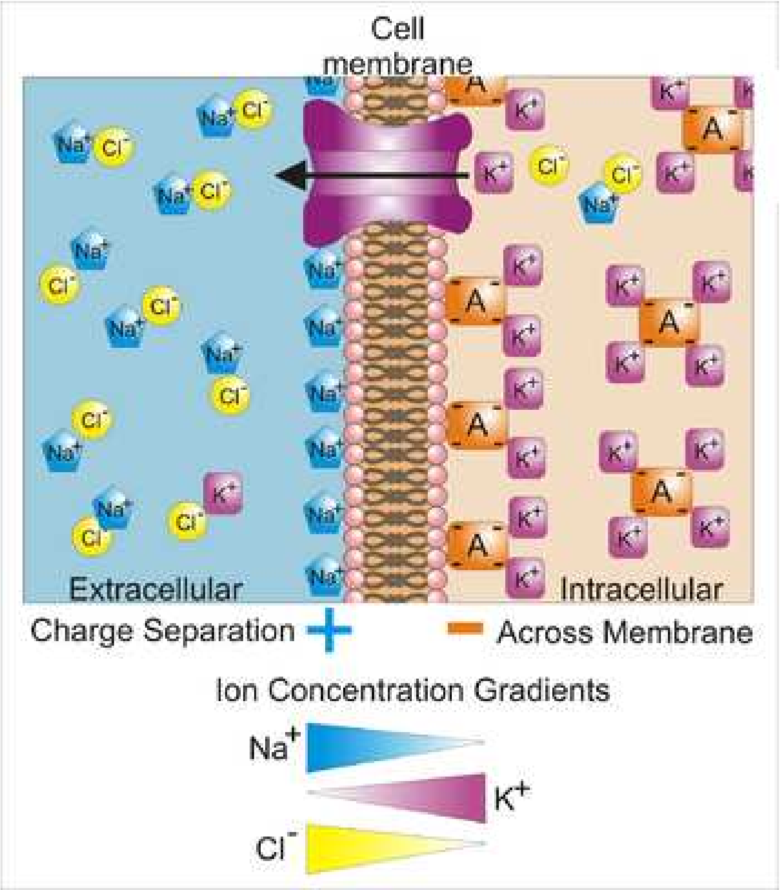
- The neurotransmitters are chemical messengers which transmit signals between neurons
- Stored in synaptic vesicles in the presynaptic axon
- They are released in response to a action potential
- Synaptic vesicles fuse with cell membrane
- And neurotransmitters diffuse and bind to receptors
- Receptors open nearby ion channels in the postsynaptic zone
- and flow of ions in or out changes membrane potential of postsynaptic neuron

How to describe the neural activity with mathematical models?

- Neural activity in terms of the membrane potentials

- Mathematical models to describe the membrane potential

Mathematical models to describe the membrane potential



Picture from the Wikimedia Commons

- Membrane potential:
  $V = V_{inside} - V_{outside}$
- Typical values in the range -40 mV to -70 mV
- Different ions: Potassium, Sodium, Chloride . . .
  - Threshold potential

    ↘

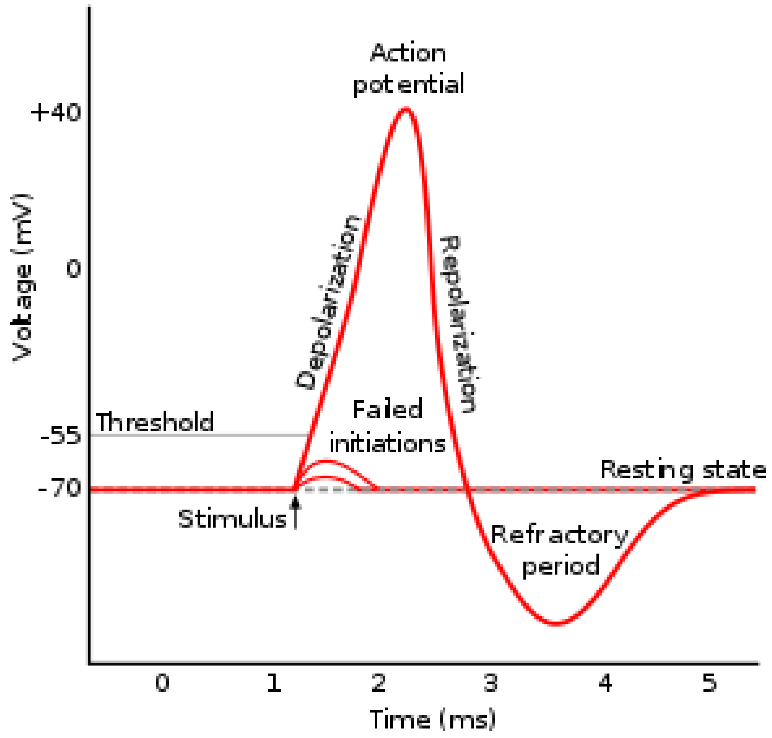
    Action potential

    ↘

    Spikes

Mathematical models to describe the membrane potential

Action potential



video

Picture from the Wikimedia Commons

- The membrane potential starts out at -70mV (Resting potential)
- A stimulus is applied
- The membrane potential rapidly rises to a peak potential
- Then drops below the resting potential
- Remains in a refractory period
- Resting potential is reestablished

Mathematical models to describe the membrane potential

How to model membrane potential?

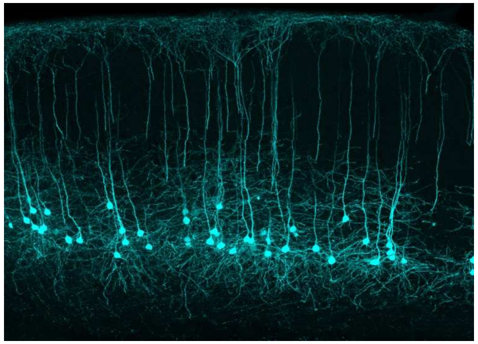
- Membrane potential is the electric potential difference across a cell's plasma membrane
- Membrane is polarized due to different charges inside and outside of the cell
- Influences in the membrane potential:
    - Permeability of the different ions
    - Different concentrations of the different ions
    - Ion pumps

Membrane potential can be modeled as an electric circuit

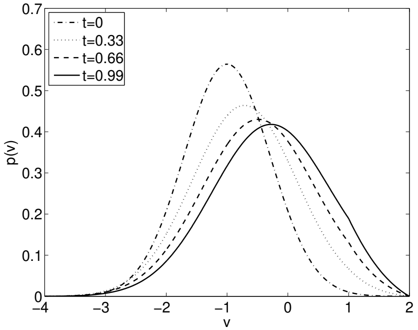
Mathematical models to describe the membrane potential

Different scales

- Microscopic (Particle Description): Very huge number of equations
- Probability density description: $f(t, x, v)$ Particle density at time t in variables (x, v) (in kinetic theory: position x with velocity v, in neuroscience, for instance: conductance x and voltage v)
- Macroscopic (Hydrodynamic Description): System for the macroscopic quantities: momentum of f (in kinetic theory: density, momentum and temperature, in neuroscience, for instance: firing rate)



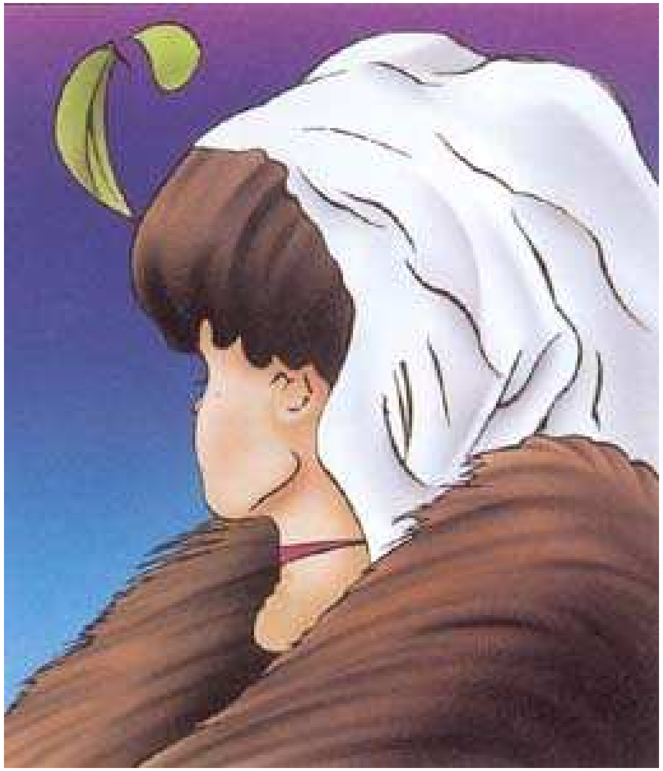
By the Max Planck Florida Institute for Neuroscience



Electroencepalogram from the Wikimedia Commons

Neurophysiological phenomena

Relationship between neurophysiological phenomena and properties of the solutions of mathematical models



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- Self-sustained oscillations are found in many brain areas, like the visual cortex and the olfactory cortex.
- Synchronization/asynchronization of the network:
  - blow-up
  - periodic solutions
  - asymptotic stability
- Epilepsy maybe related with blow up
- Multi-stability is related with:
  - visual perception
  - decision making

How to propose mathematical models to describe neurons?

How to model membrane potential?

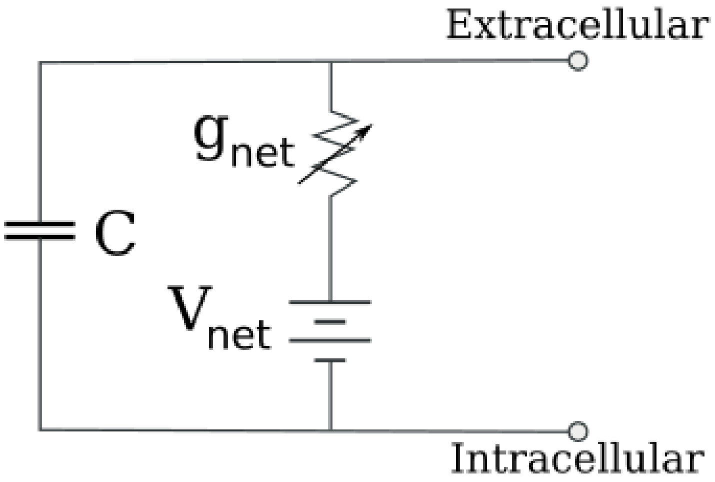
Neuronal model of L. Lapicque (1907)

by Roman Biernacki

With experiments on the frog sciatic nerve
(with platinum plated electrodes)
discovers

Membrane potential can be modeled as an electric circuit

How to model membrane potential?



Picture from the Wikimedia Commons

- The circuit consists of
  - conductors or resistors, representing the **ion channels**
  - batteries, representing the concentration gradients of the ions
  - **capacitors, representing the ability of the membrane to store charge**
- Relationship between the charge stored Q and potential V

  $Q = CV$ $\quad C$ is a proportionality constant
- Current is time derivative of charge
- *Kirchhoff's current* law states that the total current into the cell must sum to zero

How to model membrane potential?

Ohm's Law:

$$V = RI$$

V Potential difference (Voltage): Volts

R Electrical Resistence: Ohms

I Electric Current: Amperes

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Rewritten as:

$$CV = I$$

$C = \frac{1}{R}$ Electrical Conductance: Siemens

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Therefore, the evolution in time: $C\frac{dV}{dt} = \frac{dI}{dt}$ equivalently

$$C_m \frac{dV}{dt} = I_{apply} \left(= \frac{dQ}{dt} \right)$$

C_m	Capacitance: Faraday$(= sS)$
I_{apply}	Applied Current: Amperes
Q	Electric charge: Culombios

How to model membrane potential?

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$$\boxed{\text{Who is } I_{apply}\text{?}}$$

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I_{apply}	Applied Current: Amperes
Q	Electric charge: Culombios

$$\boxed{I_{apply} = -I_{leakage} - I_{ions} + I_{ext}}$$

Ordinary Differential Equations

(microscopic description)

Microscopic level: different models

- **Hodgkin-Huxley model**
- **Morris-Lecar model**
- **FitzHugh-Nagumo model**
- **Integrate-and-fire model**

Hodgkin-Huxley model

- Model propused by **Alan Lloyd Hodking** and **Andrew Fielding Huxley**
- Both **together with John Carew Eccles** were awarded the **1963 Nobel Prize in Physiology or Medicine** "for their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane"
- Their model describe the **ionic mechanisms underlying the initiation and propagation of action potentials** in the squid giant axon
- Video squid giant axon

Hodgkin-Huxley model

They considered experiments using the **voltage-clamping technique**:

- The potential across the membrane is kept fixed at various voltages
- The mechanisms in the cell then react to this potential, and the short-time potential changes needed to counter them are then measured

Hodgkin-Huxley model

$$C_m \frac{dV}{dt} = I_{apply} = -I_{leakage} - I_{ions} + I_{ext}$$

Hodgkin-Huxley model

$$C_m \frac{dV}{dt} = I_{apply} = -I_{leakage} - I_{ions} + I_{ext}$$

- $I_{leakage}(V) = g_L(V - V_L)$,

  g_L: leakage conductance (constant)

  V_L: resting potential

Hodgkin-Huxley model

$$C_m \frac{dV}{dt} = I_{apply} = -I_{leakage} - I_{ions} + I_{ext}$$

- $I_{leakage}(V) = g_L(V - V_L)$,

  g_L: leakage conductance (constant)

  V_L: resting potential

- $I_{ion}(V) = I_{Na}(V) + I_K(V)$
  - $I_{Na}(V) = g_{Na}(V - V_{Na})$,

    g_{Na}: Na conductance (depending on V)

    V_{Na}: reversal potential for Na
  - $I_K(V) = g_K(V - V_K)$,

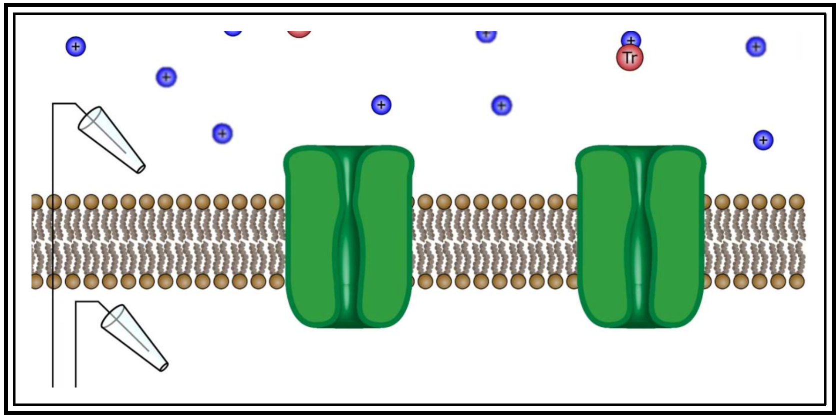
    g_k: K conductance (depending on V)

    V_K: reversal potential for K

Hodgkin-Huxley model

Voltage-gated ion channels

- Ion channels can be thought of as having gates that open or close to regulate the flow of ions through them
- We can consider that the gates follow a Markov process, with transition rates from closed to open α, and from open to closed β



Wikipedia movie

Hodgkin-Huxley model

Evolution on time of the fraction of open channels f is given by

$$\frac{\mathrm{d}f}{\mathrm{d}t} = \alpha(1-f) - \beta f = \alpha - (\alpha+\beta)f = \frac{f_\infty - f}{\tau},$$

with $f_\infty = \frac{\alpha}{\alpha+\beta}$ and $\tau = \frac{1}{\alpha+\beta}$.
Moreover, transition rates depend on the potential difference V:

$$\alpha = \alpha_0 e^{-\tilde{\alpha}V}, \quad \beta = \beta_0 e^{-\tilde{\beta}V} \quad \tilde{\alpha}, \tilde{\beta} > 0,$$

and then $f_\infty(V) == \frac{1}{1+e^{\frac{-(V-V_0)}{S_0}}}$ with

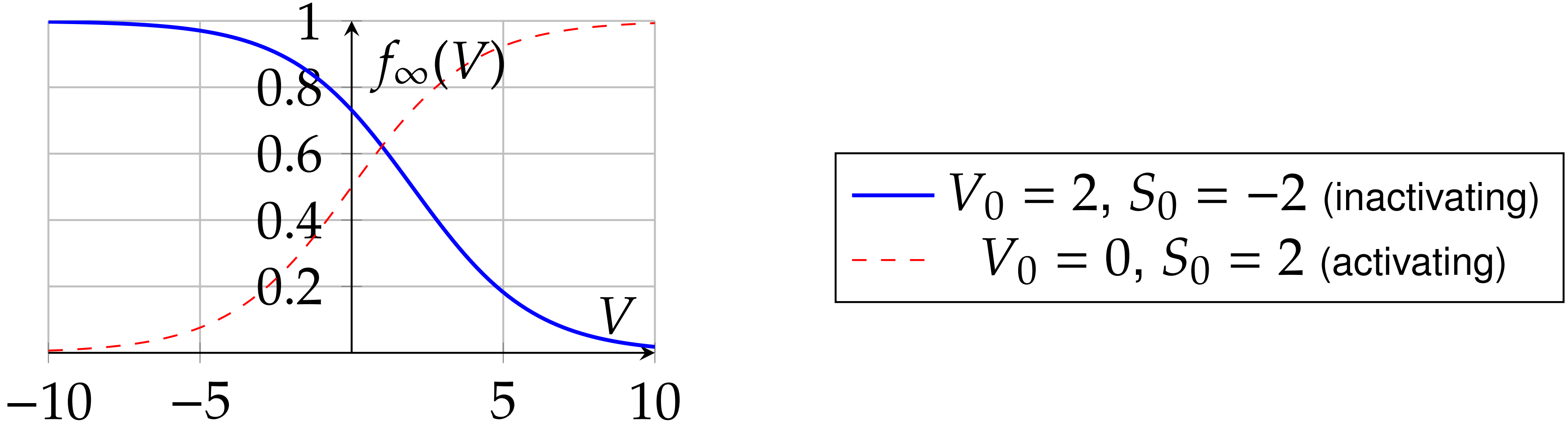
$$S_0 = \frac{1}{\tilde{\beta}-\tilde{\alpha}}, \quad \text{and} \quad V_0 = S_0 \ln\left(\frac{\beta_0}{\alpha_0}\right) = \frac{1}{\tilde{\beta}-\tilde{\alpha}} \ln\left(\frac{\beta_0}{\alpha_0}\right).$$

Hodgkin-Huxley model

Evolution on time of the fraction of open channels f is given by

$$\frac{\mathrm{d}f}{\mathrm{d}t} = -\beta f + \alpha(1-f) = \alpha - (\alpha+\beta)f = \frac{f_\infty - f}{\tau},$$

We observe that $f_\infty = \frac{1}{1+e^{\frac{-(V-V_0)}{S_0}}}$ has a sigmoidal form and therefore the gates can either be activating (if $S_0 > 0$) or inactivating (if $S_0 < 0$). In this sense V_0 can be considered as the threshold and S_0 the sensitivity of channel opening.



Hodgkin-Huxley model

$$C_m \frac{dV}{dt} = I_{apply} = -I_{leakage} - I_{Na} - I_K + I_{ext}$$

- $I_{leakage}(V) = g_L(V - V_L)$,
- $I_{Na}(V) = \bar{g}_{Na} m^3(V) h(V)(V - V_{Na})$
- $I_K(V) = \bar{g}_K n(V)^4 (V - V_K)$

$\bar{g}_{Na}$ and $\bar{g}_K$ maximal value of the conductances

m and n activation variables, and h inactivation variable (between 0 and 1) of the ions channels

$$\frac{dh}{dt} = \alpha_h(V)(1-h) - \beta_h(V)h$$
$$\frac{dm}{dt} = \alpha_m(V)(1-m) - \beta_m(V)m$$
$$\frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n$$

$\alpha(V)$ and $\beta(V)$ are obtained experimentally using the voltage-clamping technique

Hodgkin-Huxley model

$$C_m \frac{dV}{dt} = -g_L(V - V_L) - \bar{g}_{Na} m^3 h(V)(V - V_{Na}) - \bar{g}_K n(V)^4 (V - V_K) + I_{ext}$$

$$\frac{dh}{dt} = \alpha_h(V)(1-h) - \beta_h(V)h$$
$$\frac{dm}{dt} = \alpha_m(V)(1-m) - \beta_m(V)m$$
$$\frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n$$

$\bar{g}_{Na}$ and $\bar{g}_K$ maximal value of the conductances

m, n and h activation/inactivation variables (between 0 and 1) of the ions channels

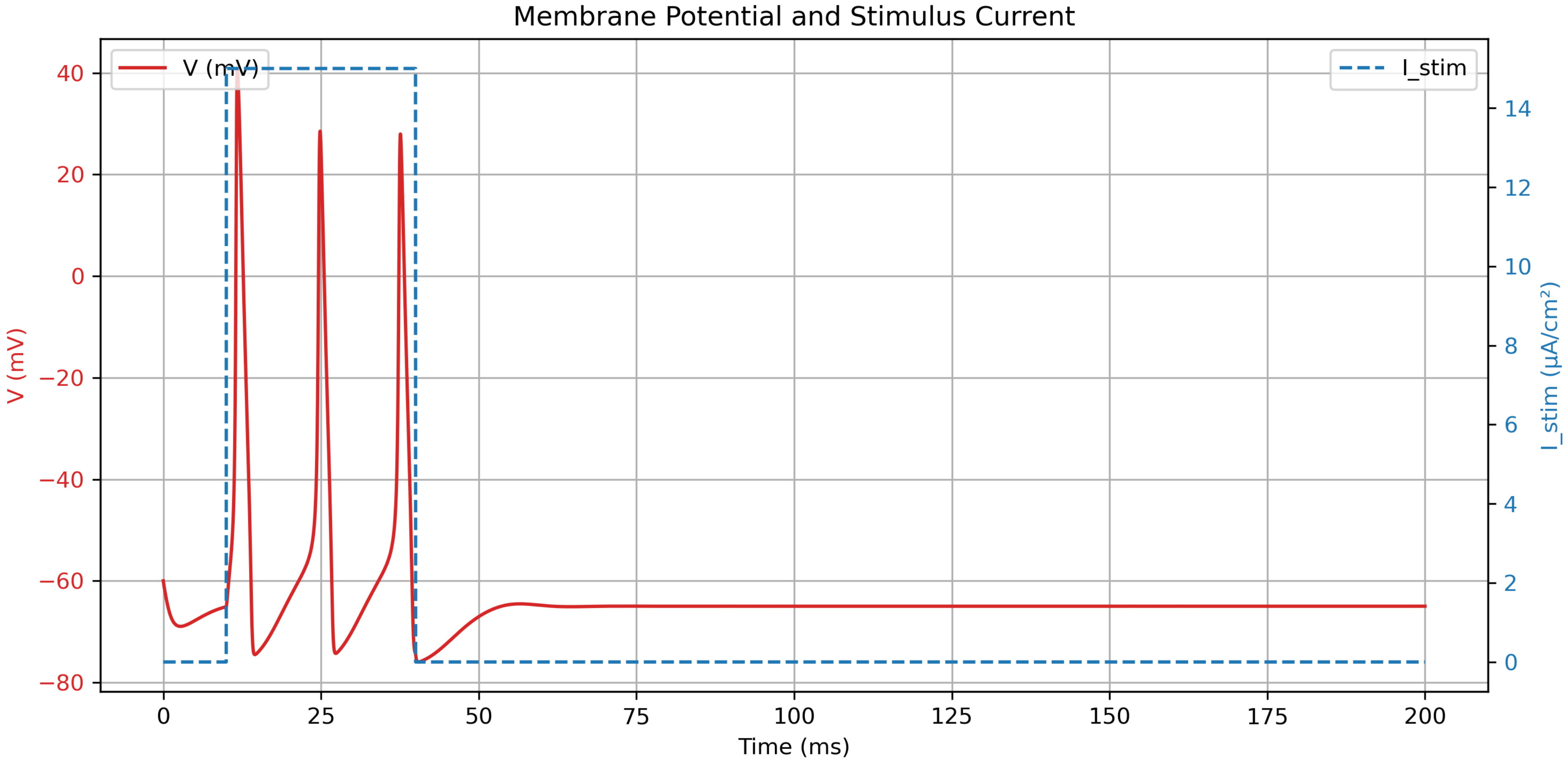
- Nonlinear system unsolved analytically
- Describes the action potential
- To describe the behaviour of a large number of neurons this model is very expensive

Exercise: Numerical study of the model

Hodgkin-Huxley, The J. of Physiology Vol. 116.4, 473-496 (1952)

Hodgkin-Huxley, The J. of Physiology Vol. 117.4, 500-544 (1952)

Hodgkin-Huxley model



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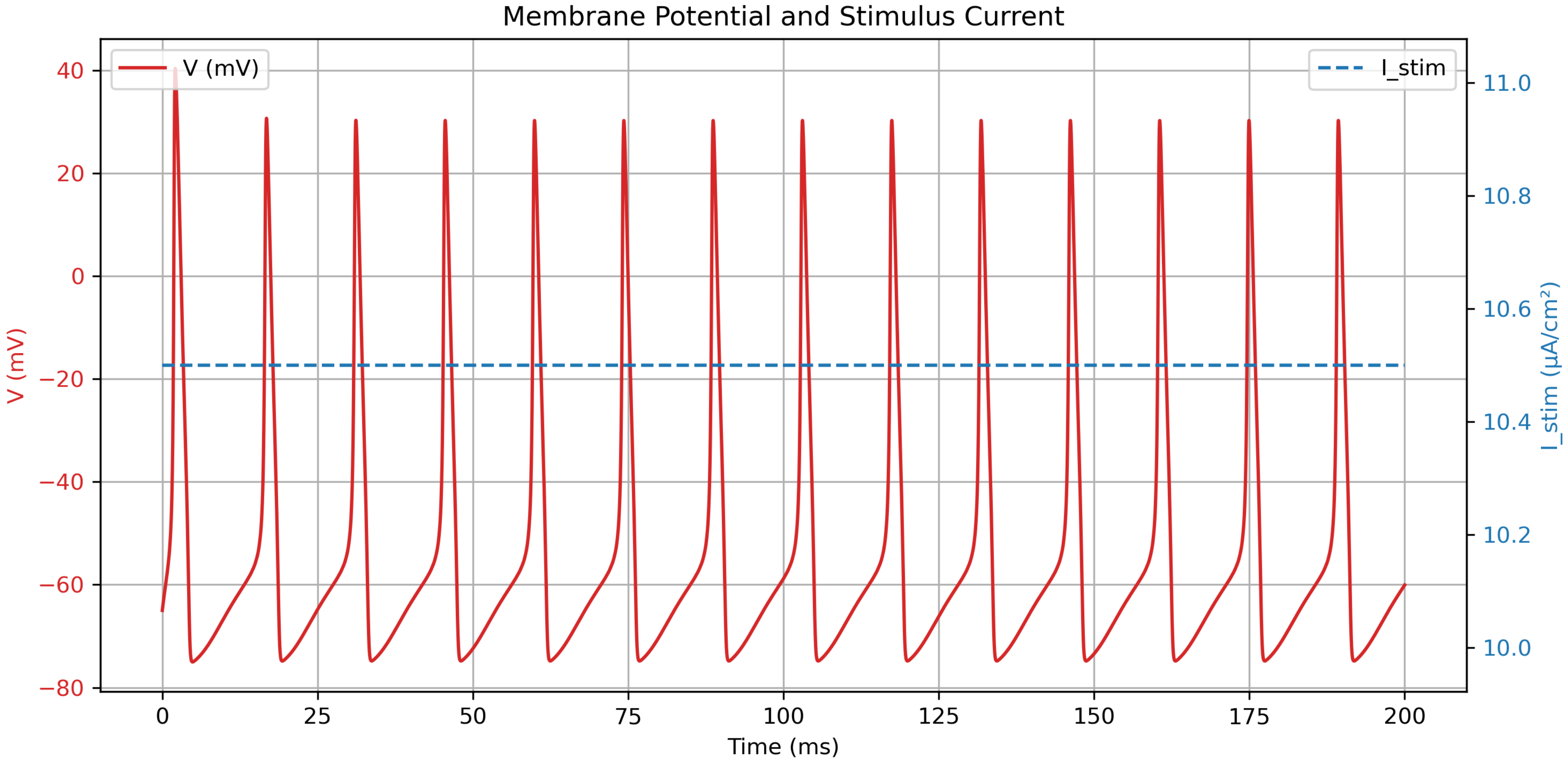

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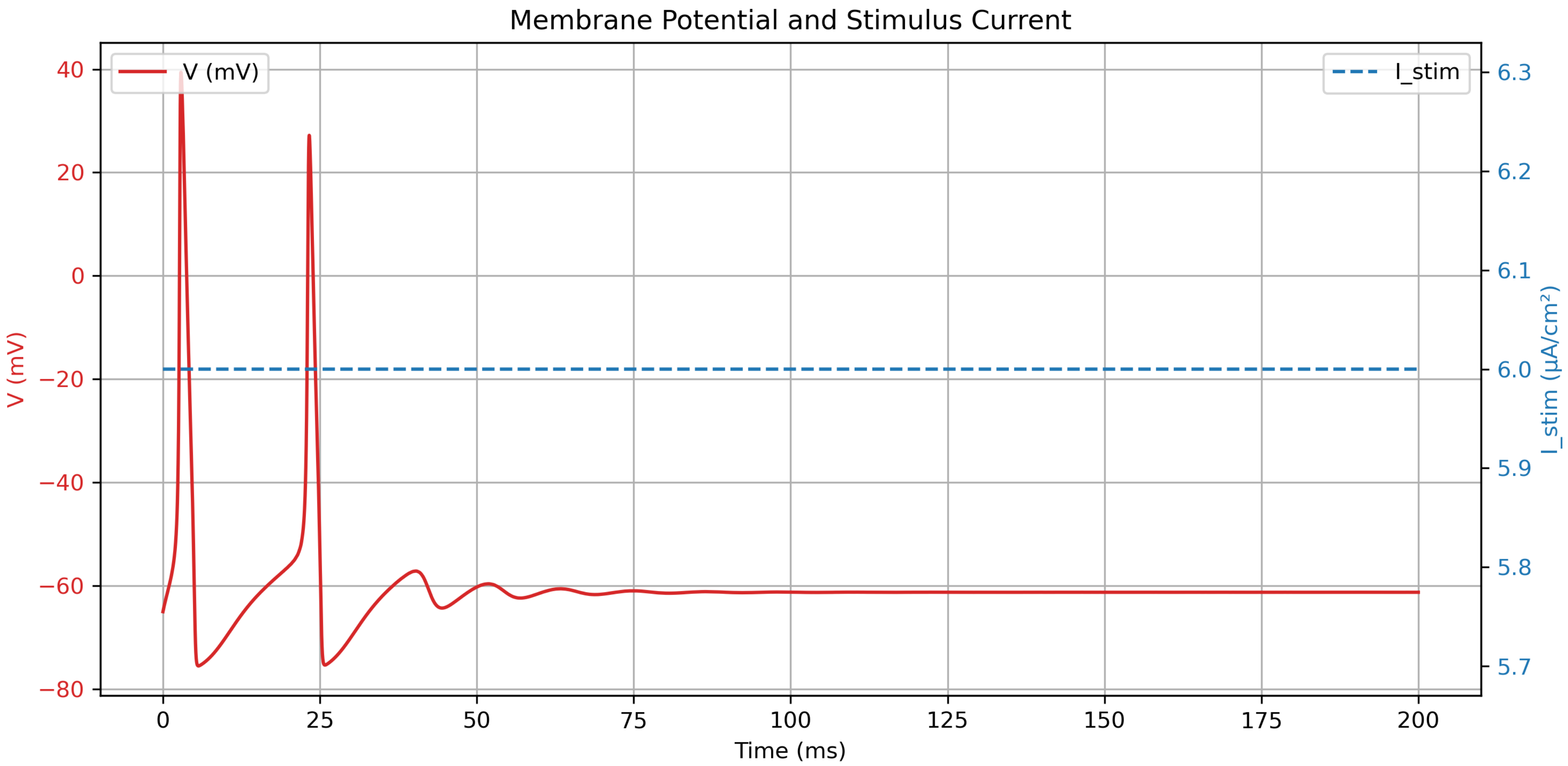

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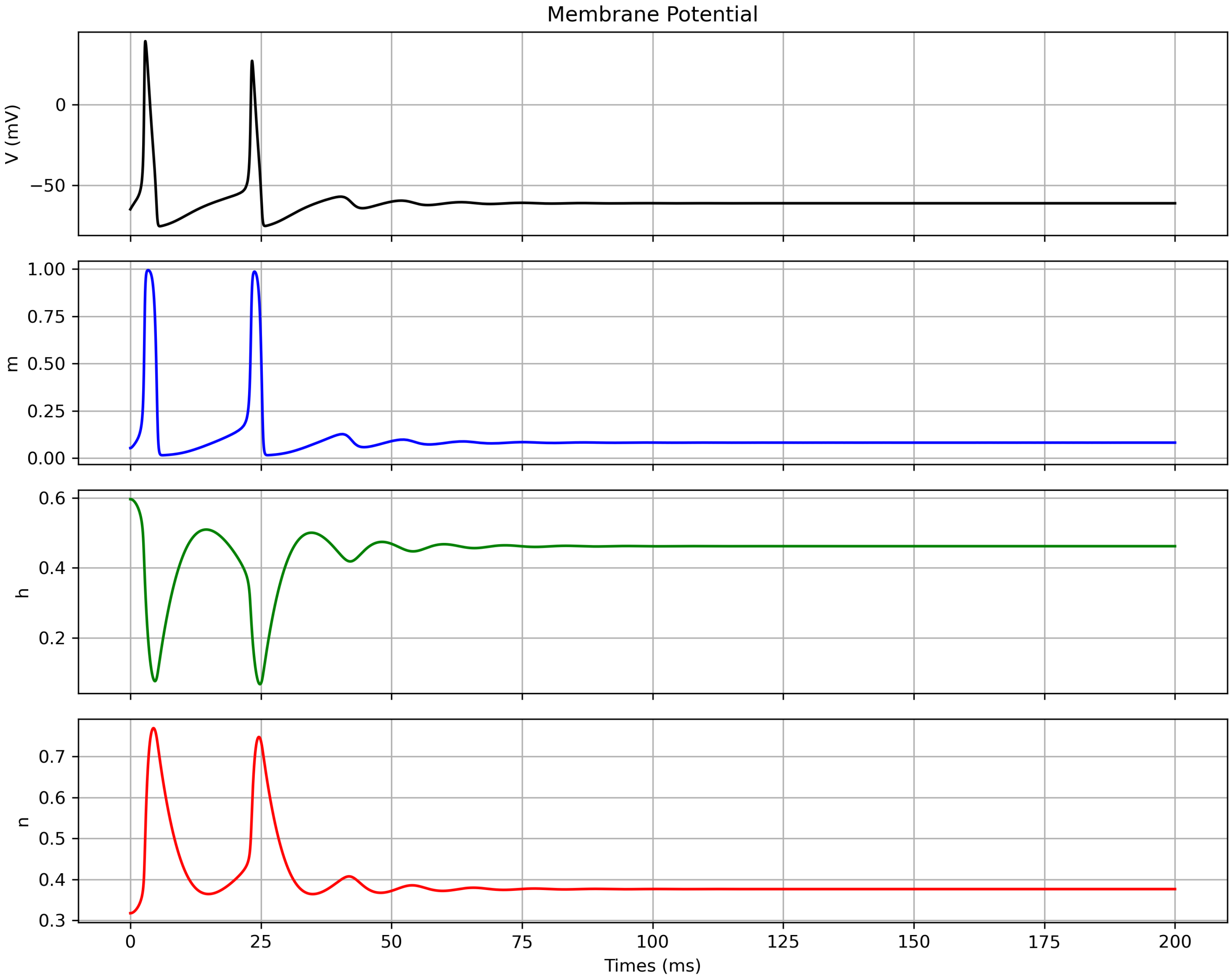

Simplifications of Hodgkin-Huxley model

Morris-Lecar model

Wikimedia Commons

- In 1981 **Catherine Morris** and **Harold Lecar** proposed a simplification of the Hodgkin-Huxley model
- Studing the barnacle muscle fibers subjected to constant current stimulation

Morris-Lecar model

Wikimedia Commons

- In 1981 **Catherine Morris** and **Harold Lecar** proposed a simplification of the Hodgkin-Huxley model
- Studing the barnacle muscle fibers subjected to constant current stimulation

- They consider **two channels** also, but in this case are Calcium and Potassium
- Again the activation variables are obtained experimentally

Morris-Lecar, Biophys. J. Vol. 35(1), 193-213 (1981)

Morris-Lecar model

$$C_m \frac{dV}{dt} = -g_L(V - V_L) - \bar{g}_{Ca} m(V)(V - V_{Ca}) - \bar{g}_K n(V)(V - V_K) + I_{ext}$$

$$\frac{dm}{dt} = \lambda_m(V)(m_\infty(V) - m)$$

$$\frac{dn}{dt} = \lambda_n(V)(n_\infty(V) - n)$$

$m_\infty(V)$ and $n_\infty(V)$ are the fraction of open calcium and potassium channels, respectively, at steady state, and λ_m, λ_n the rate for opening of calcium and potassium channels, respectively, and are obtained experimentally

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$m_\infty(V)$ and $n_\infty(V)$ are the fraction of open calcium and potassium channels, respectively, at steady state, and λ_m, λ_n the rate for opening of calcium and potassium channels, respectively, and are obtained experimentally

- Reduces the Hodgkin-Huxley system to 3 equations
- Reproduces the oscillations of the action potential

Morris-Lecar, Biophys. J. Vol. 35(1), 193-213 (1981)

Morris-Lacar model

The authors propose a further simplification to reduce the system to two equations

$$C_m \frac{dV}{dt} = -g_L(V - V_L) - \bar{g}_{Ca} m_\infty(V)(V - V_{Ca}) - \bar{g}_K n(V)(V - V_K) + I_{ext}$$

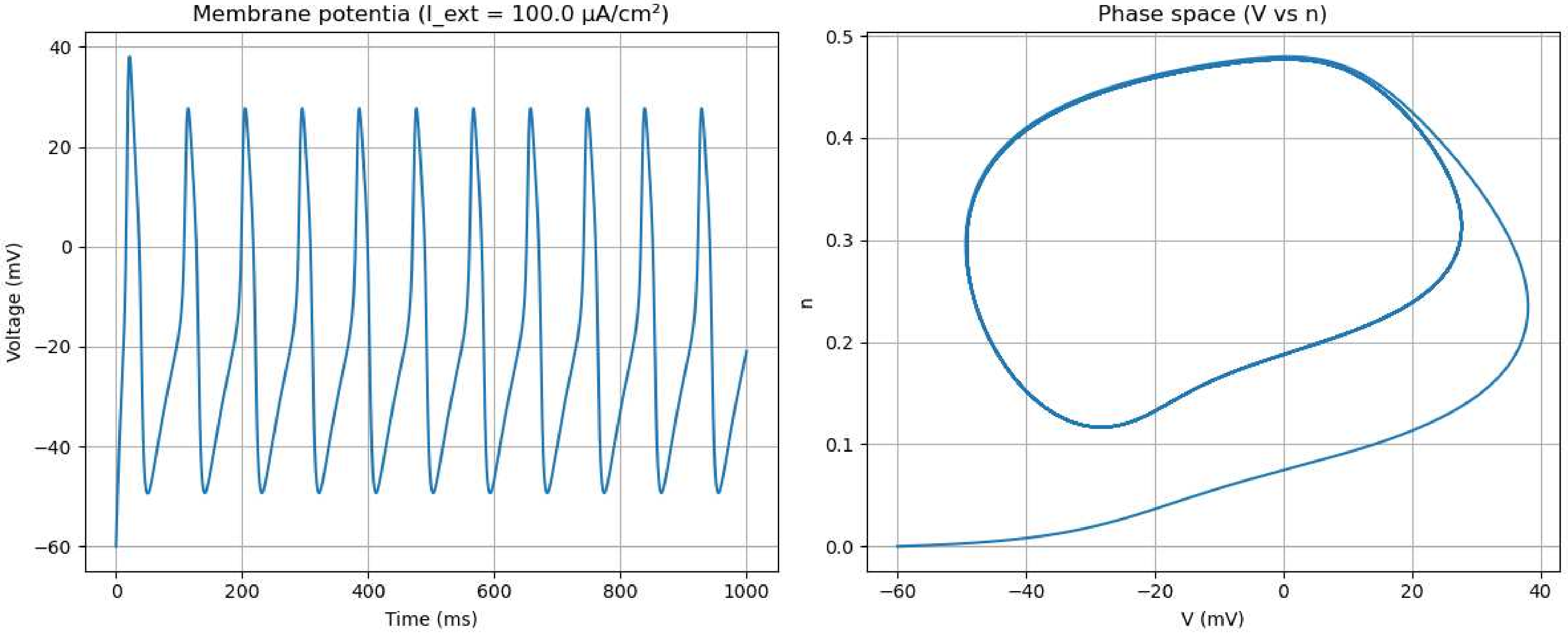
$$\frac{dn}{dt} = \lambda_n(V)(n_\infty(V) - n),$$

where the calcium system is assumed to be so much faster than the potassium system so it is assumed $m(V) = m_\infty(V)$ (stationary)

We observe that the system can be written as

$$\begin{aligned} \frac{dV}{dt} &= f(V,n) \\ \frac{dn}{dt} &= g(V,n) \end{aligned} \qquad (-1)$$

Morris-Lacar model



FitzHugh-Nagumo model

- Other simplification is the FitzHugh–Nagumo model, developed by **Richard FitzHugh** in 1961
- and **Jin-Ichi Nagumo et al.** who created the equivalent circuit the following year, describes a prototype of an excitable system
- Previous models arise from the biophysics of neurons
- The origin of this model is phenomenological
- Phenomenological models only seek to capture the essence of the behaviour
- They tend to be more mathematically manageable than the others

FitzHugh-Nagumo model

Richard FitzHugh modified the **van der Pol equations** (he referred to these equations as the Bonhoeffer–van der Pol equations) for an electrical circuit with a linear capacitor, linear inductor, and nonlinear resistor in parallel

$$\begin{aligned} C\frac{dV}{dt} + F(V) + J &= 0 \\ L\frac{dJ}{dt} &= V, \end{aligned}$$

where C is the capacitance, L the inductance, $F(V)$ a nonlinear current depending on the voltage, V , across the capacitor, and J the current through the inductor The system can be written as a second-order differential equation with unknown V

$$CV''(t) + F'(V)V'(t) + \frac{V(t)}{L} = 0$$

which is a modification of the second order linear equation

$$x'' + kx' + x = 0,$$

where instead of the damping coefficient, k, is considered a function of the solution

FitzHugh-Nagumo model

$$
\begin{aligned}
C\frac{dV}{dt} &= V(V-a)(1-V) - w + I_{ext} =: f_1(V,w)\\
\frac{dw}{dt} &= \beta V - w := f_2(V,w)
\end{aligned}
$$

V : proxy for the membrane potential
w : analogous the gating variables in the HH model
$0 < a < 1,\ \beta, C > 0$ and $I_{ext} \in \mathbb{R}$

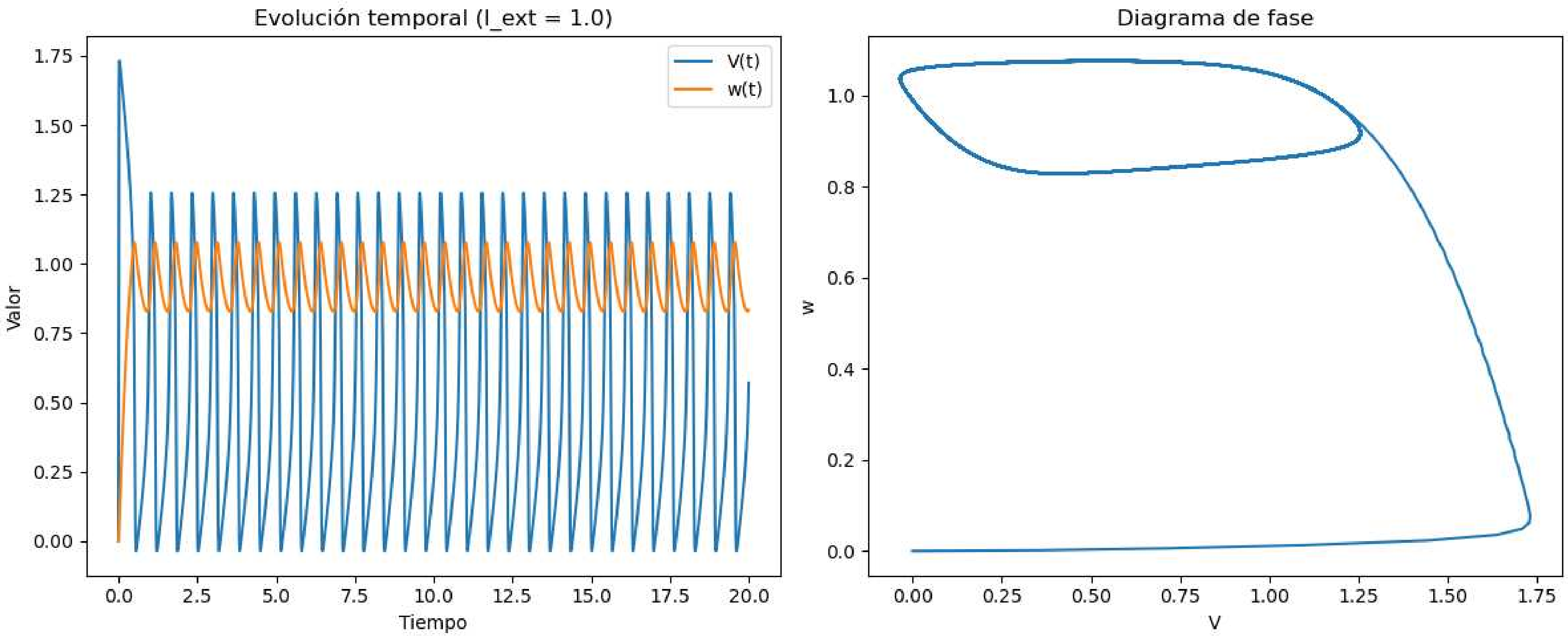
- Reduced system (2 equations) which models activation and desactivation dynamics of a spiking neuron

Exercise: Analysis of this system of two equations

FitzHugh, Biophys. J. Vol. 1, 445-466 (1961)

Nagumo-Arimoto-Yoshizawa, Proc. IRE. Vol. 50, 2061-2070 (1961)

FitzHugh-Nagumo model



Model for nerve fibre

- Previous models describe *local behaviour* of the electrical activity
- They are appropriate for fibres with relatively little spatial variation of biophysical properties, such as the squid giant axon
- To be model more realistic we consider a cell that is shaped as a long cylinder, or cable
- The current flow is along a single spatial dimension, x, the distance along the cable
- The membrane potential depends on the x variable and time t
- The cable equation is a partial differential equation that describes how the membrane potential $V(x,t)$ depends on currents entering, leaving, and flowing within the neuron

Model for nerve fibre

Cable equation

$$C\frac{\partial V(x,t)}{\partial t} = D\frac{\partial^2 V(x,t)}{\partial x^2} - I_{\text{ion}} \quad D > 0$$

**What units does D have?

I_{ion} can be obtained from:

- Hodgkin-Huxley model
- Morris-Lecar model
- FitzHugh-Nagumo model

considering their right hand side in the equation for V

The system with FN model is used to study travelling waves in electrical activity, and have been used to model electrical activity in the heart, for example

FitzHugh's movie of nerve impulse propagation using computer animation techniques available around 1960

Previous models are known as conductance-based models and describe the membrane potential in terms of the ion channels

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These models describe the dynamics of the action potential accurate but they are very difficult to use for a large number of neurons, since they are very expensive

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These models describe the dynamics of the action potential accurate but they are very difficult to use for a large number of neurons, since they are very expensive

We present now Integrate-and-Fire models which do not describe action potential but model the firing rate

Leaky integrate-and-fire model

Recall the equation for the membrane potential

$$C_m \frac{dV}{dt} = I_{apply}$$

considering $I_{apply} = -I_L + I$

$$I_L = g_L(V - V_L)$$

leakage current

- g_L leak conductance
- V_L resting potential

Leaky integrate-and-fire model

$$C_m \frac{dV}{dt} = -g_L(V - V_L) + I$$

Calling $\tau_m = C_m/g_L \approx 2ms$

Leaky integrate-and-fire model

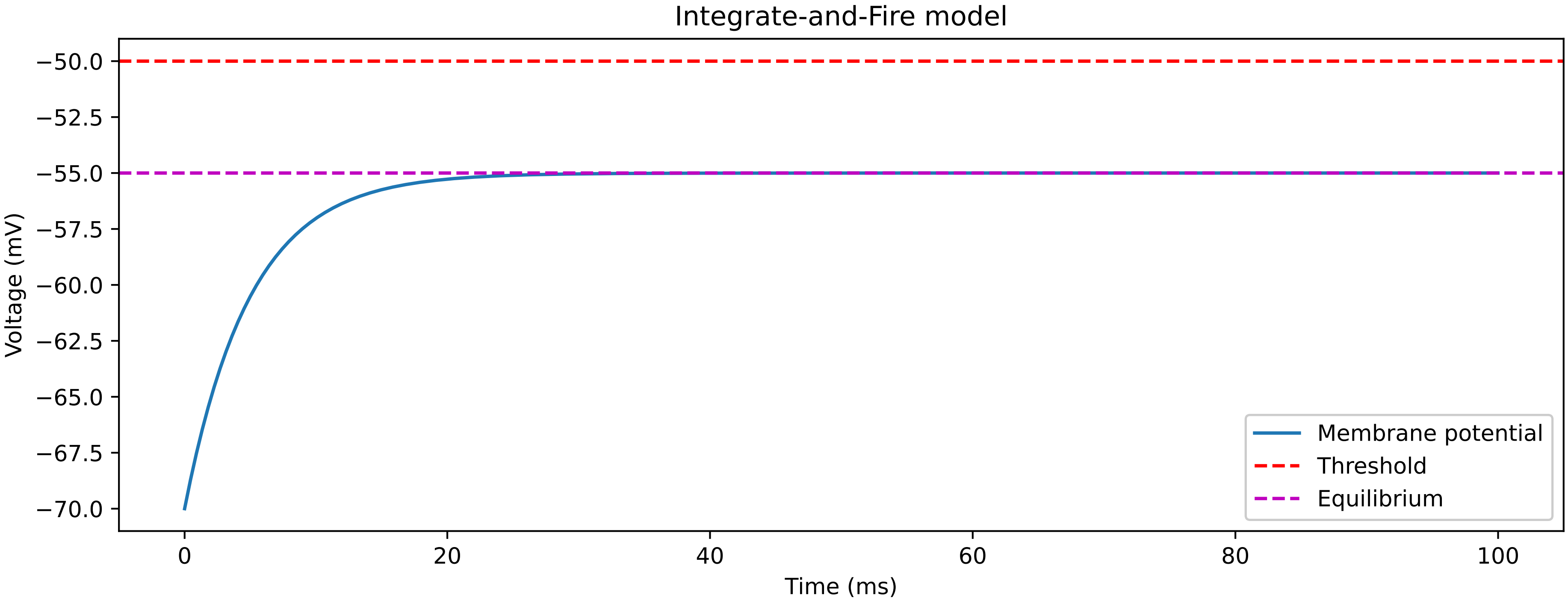
$$\boxed{\tau_m \frac{dV}{dt} = -(V - V_L) + \frac{I}{g_L}}$$

Leaky integrate-and-fire model

$$\boxed{\tau_m \frac{dV}{dt} = -(V - V_L) + \frac{I}{g_L}}$$

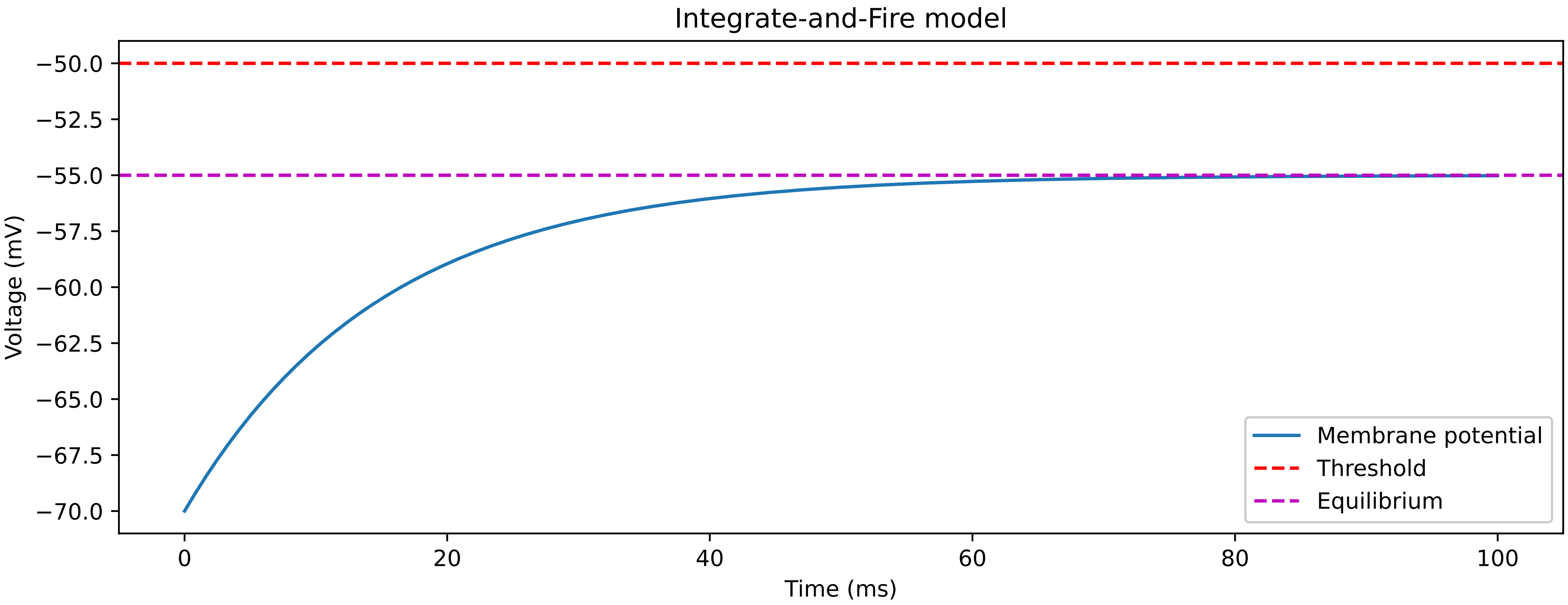
- There are firing times t_{spike}: $V(t_{spike}) = V_{threshold}$
- Inmediately after t_{spike} the potential is reset: $V(t^+_{spike}) = V_{reset}$
- $V_L < V_{reset} < V_{threshold}$
- Typically $V_L \approx -70mV$, $V_{reset} \approx -60mV$ and $V_{threshold} \approx -50mV$
- Equilibrium: $V_\infty = V_L + \frac{I}{g_L}$
- If $V_\infty < V_{threshold}$ there are no spikes

Leaky integrate-and-fire model



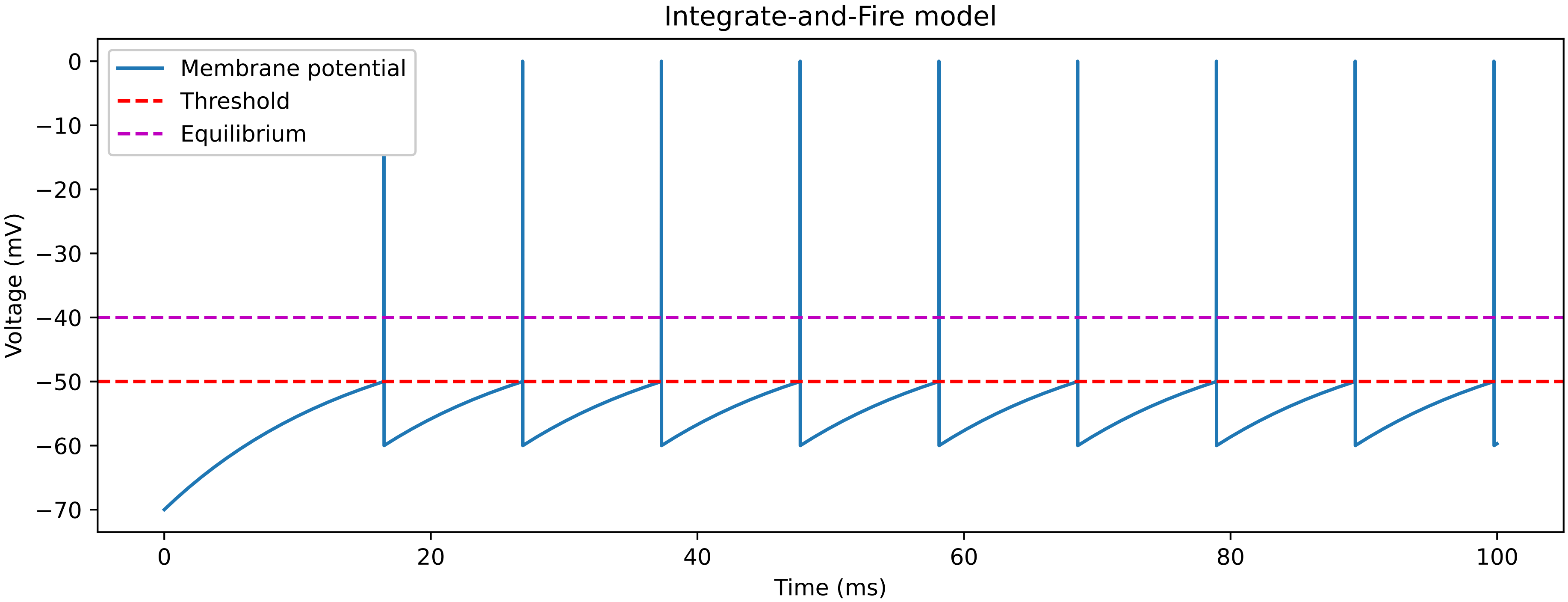
$$\tau = 5,\ I = 1.5,\ \frac{1}{g_L} = 10$$

Leaky integrate-and-fire model



$$\tau = 15,\ I = 1.5,\ \frac{1}{g_L} = 10$$

Leaky integrate-and-fire model



$$\tau = 15,\ I = 1.5,\ \frac{1}{g_L} = 20$$

Noise

Neurons live in a noisy enviroment

Noise

- The above models describe a deterministic behaviour
- However opening and closing of channels is a probablistic event
- A spontaneous release of neurotransmitters occurs, leading to a random bombardment of small depolarizations and hyperpolarizations
- Noise in neural systems has been the subject of research since the early 1960s

See G. Bard Ermentrout & David H. Terman *Mathematical Foundations of Neuroscience* and references therein for further details

Leaky integrate-and-fire model *with noise*

$$\boxed{\tau_m \frac{dV}{dt} = -(V - V_L) + \frac{I}{g_L}}$$

$$+$$

White noise

$$\boxed{dV = \tau_m \left(\frac{I}{g_L} - (V - V_L)\right) dt + \sigma dB_t}$$

We can simulate that **stochastic system** with this scheme

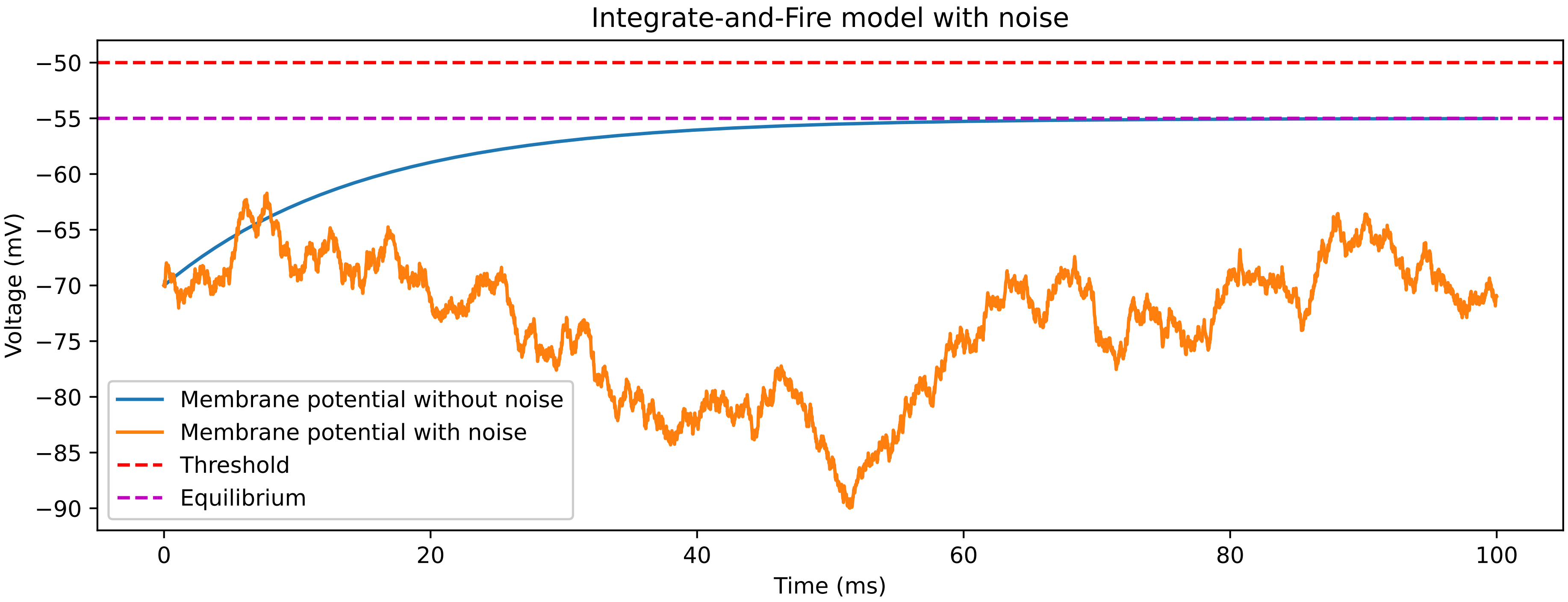
$$V_{n+1} = V_n + \tau_m \left(\frac{I}{g_L} - (V_n - V_L)\right) dt + \sigma \sqrt{dt} \mathcal{N}(0, 1)$$

Leaky integrate-and-fire model *with noise*

The noise allows neurons to fire in the presence of subthreshold inputs

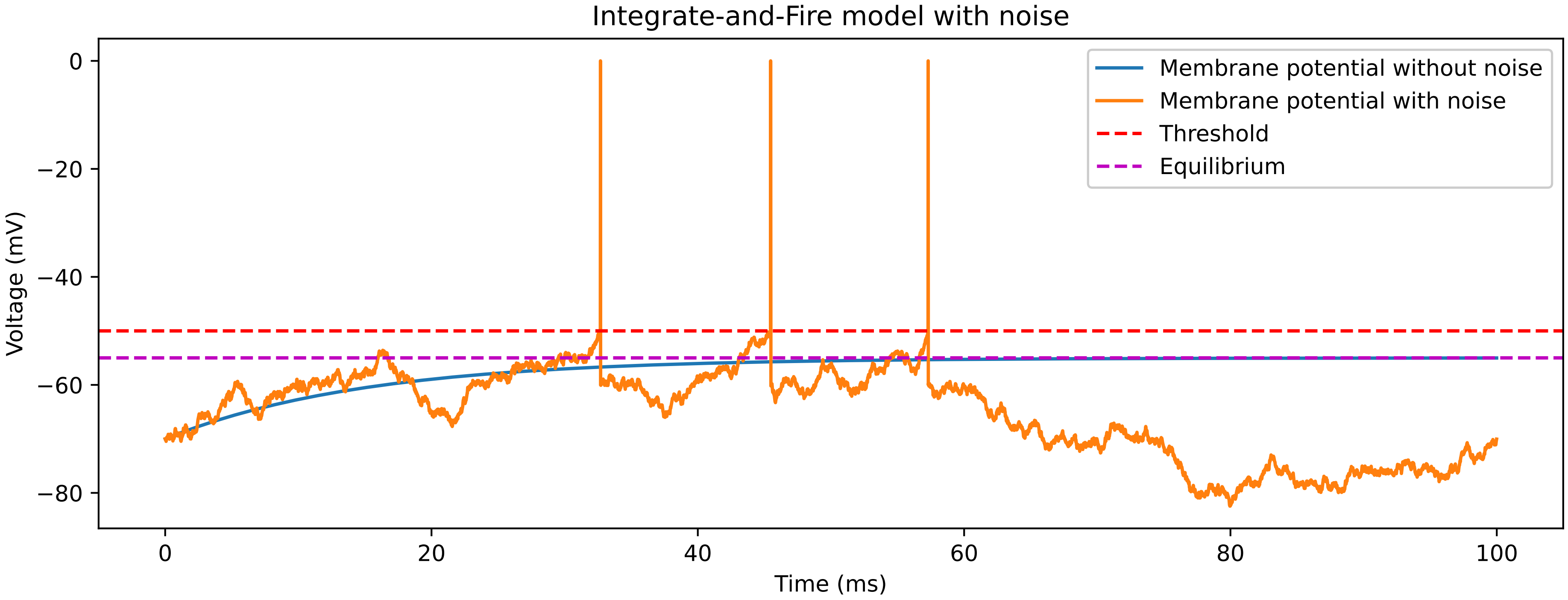
If a current is applied that will not cause the deterministic model to fire, the addition of zero mean noise can induce the neuron to fire

Leaky integrate-and-fire model *with noise*



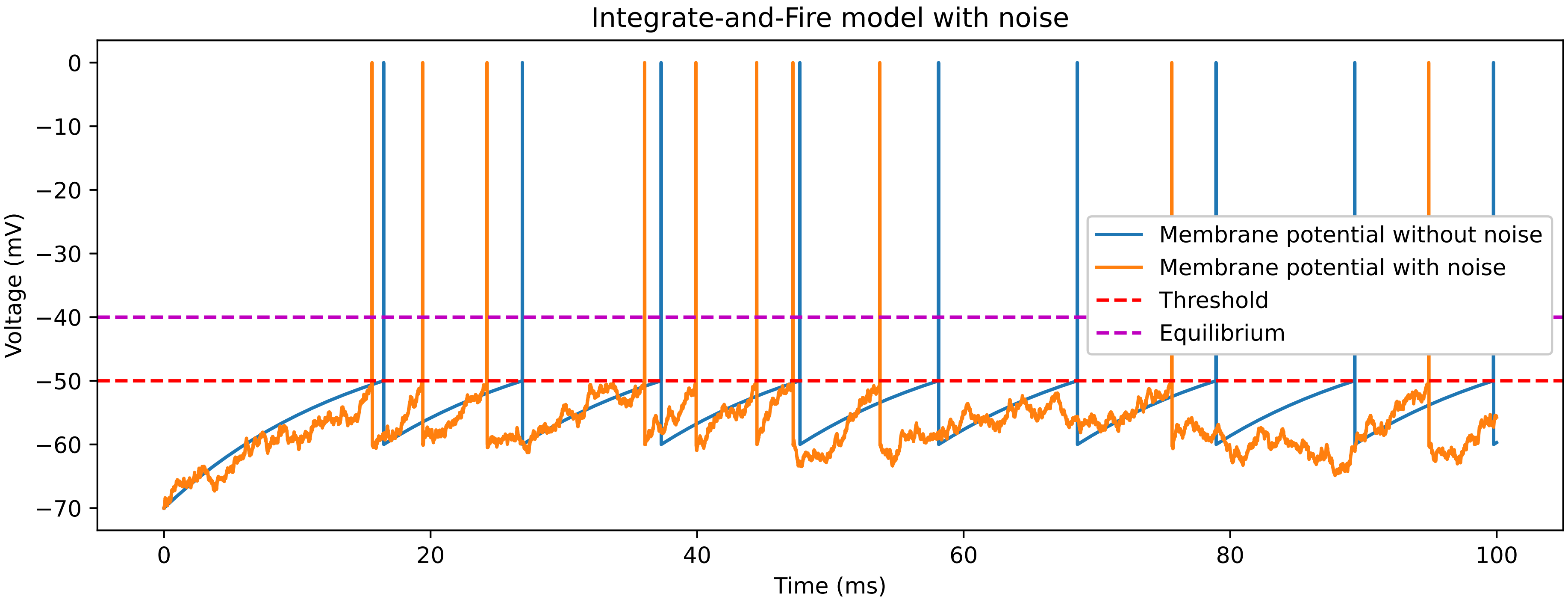
$$\tau = 15,\ I = 1.5,\ \frac{1}{g_L} = 10,\ \sigma = 2$$

Leaky integrate-and-fire model *with noise*



$$\tau = 15,\ I = 1.5,\ \frac{1}{g_L} = 10,\ \sigma = 2$$

Leaky integrate-and-fire model *with noise*



$$\tau = 15, \; I = 1.5, \; \frac{1}{g_L} = 20, \; \sigma = 2$$

Leaky integrate and fire model *with interaction*

How to take into account the interaction between neurons?

$$\boxed{C_m \frac{dV}{dt} = -g_L (V - V_L)}$$

+

Interactions

$$\boxed{C_m \frac{dV}{dt} = -g_L (V - V_L) + I(t)}$$

- $I(t)$: Interactions of the neuron with the network (synapse)
- No constant input

Leaky integrate and fire model with interaction

$$\boxed{C_m \frac{dV}{dt} = -g_L (V - V_L) + I(t)}$$

- $I(t) = J_E \sum_{i=1}^{C_E} \sum_j \delta(t - t^i_{Ej} - d) - J_I \sum_{i=1}^{C_I} \sum_j \delta(t - t^i_{Ij} - d)$
  - E, I: Excitatory, Inhibitory neurons
  - J_E, J_I: strength of the synapses
  - C_E, C_I: total number of presynaptic neurons
  - t^i_{Ej}, t^i_{Ij}: times of the j^{th}-spike coming from the i^{th}-presynaptic neuron
  - d: transmission delay

- The incoming synaptic current is a stochastic process
- Noisy leaky integrate and fire model

Partial Differential Equations

(Probability density description-mesoscopic description)

Mean-field models

- **What is the behaviour of a large number of neurons?**
- Mesoscopic description in terms of **density of neurons**
- The unknown, p, is the probability of finding a neuron at time t
  - with voltage v
  - with 'state' s. 'state' is the *time elapsed* since last spike
  - ...
- **If the number of neurons is very large, is p a solution to any equation?**
- If the answer is yes, the equation is called a mesoscopic o mean-field

Mesoscopic models

Advantages of mesoscopic models

- Drastic reduction of the number of equations
- The mesoscopic equation is easier to study than the microscopic system
- The computational cost to numerically solve the mesoscopic equation is lower than that required to solve the macroscopic system
- It is possible to obtain macroscopic quantities

Mean field limits for 'particles' systems, where particles could be:

- Physics: gases, electrons, . . .
- Biology: cells, virus, . . .
- Economy: agents in a market, . . .

Mesoscopic models

Example 1

Particle system

$$C_m \frac{dV_i}{dt} = I \quad i = 1, \ldots, N$$

The density of neurons $p(t, v)$ satisfies

$$C_m \partial_t p + I \partial_v p = 0$$

which is independent on N, so the limit equation with $N \to \infty$ is the same equation

For each i: $V_i(t) = \frac{V_i(0)+It}{C_m}$, therefore $p(V_i(t), t) = p(V_i(0), 0)$

$$0 = \frac{dp(V_i(t), t)}{dt} = \partial_t p(V_i(t), t) + \frac{I}{C_m} \partial_v p(V_i(t), t) = 0$$

Mesoscopic models

Example 2

Particle system

$$C_m \frac{dV_i}{dt} = I - gV_i \quad i = 1, \dots, N$$

Mesoscopic model

$$C_m \partial_t p + \partial_v \left((I - gv)p \right) = 0$$

Mesoscopic models

With noise

- Particle systems is a stochastic system
- Probability density of neurons is the density of a stochastic process
- Does the probability density of neurons become deterministic as the number of neurons tends to ∞? (**propagation of chaos**)
- If the case, does it satisfy a PDE?

Example

Particle system: $\frac{dV_i}{dt} = \sigma dB_t^i \quad i = 1, \ldots, N$

Mesoscopic model: $\partial_t p - \frac{\sigma^2}{2}\partial_v^2 p = 0$

Some PDE models

The unknown, p, is the probability of finding a neuron at time t

- If **spike trains** follow Poisson processes $\rightsquigarrow$ **Nonlinear Fokker-Planck equations**
    - ◇ $p(v,t)$ is the probability of finding a neuron at time t with voltage v

Some PDE models

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Brunel-Hakim, Neural Comp. Vol. 11, 1621-1671 (1999)

Mattia-Del Giudice, Phys. Rev. E, Vol. 66, 051917 (2002)

Renart-Brunel-Wang, Mathematical Biology and Medicine Series (2004)

Sirovich-Omurtag-Lubliner, Network: Computation in Neural Systems, Vol. 17, 3-29, (2006)

Liu-Wang-Zhang-Zhou, Siam J. Math. Anal. Vol54(1), (2022)

Jabin-Zhou, preprint 2023

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- If **spike trains** follow point processes $\rightsquigarrow$ **age-structured partial differential equations** (Pakdaman-Perthame-Salort)
  - ◇ $p(s,t)$ is the probability of finding a neuron at time t with 'state' s. 'state' is the *time elapsed* since last spike

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Chevallier-C-Doumic-Reynaud-Bouret, M3AS, Vol. 25,14, 2669-2719, (2015)

Chevallier, Stochastic Processes and their Applications, (2017)

Quiñinao,Acta Applicandae Mathematicae, 146:29–55, (2016)

Some PDE models

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Dumont, Henry and Tarniceriu give some relationships between both PDE models

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Dumont-Henry-Tarniceriu, J. Theor Biol, 406, 31-41. (2016)

Dumont-Henry-Tarniceriu, Journal of mathematical biology, 73(6-7), 1413-1436. (2016)

Nonlinear Noisy Leaky Integrate and Fire (NNLIF)

(Nonlinear Fokker-Planck equations)

Neural phenomena

- Networks are composed of **excitatory and inhibitory neurons**
- When the membrane potential reaches a **threshold value $\mathbf{V_F}$**, the neurons emit an action potential (**spike**) and their voltage values return to a **reset value $\mathbf{V_R}$**. $(V_R < V_F)$
- Between the emission and reception of the spikes among neurons there are some *transmission delays*
- During a certain time (*refractory period*) the neurons do not respond to stimuli

There is a family of NNLIF models in terms of the different phenomena that take into account

Neural phenomena

Let's start with

- Networks are on average excitatory or inhibitory
- When the membrane potential reaches a **threshold value V_F**, the neurons emit an action potential (**spike**) and their voltage values return to a **reset value V_R**. ($V_R < V_F$)
- Between the emission and reception of the spikes among neurons there are some *transmission delays*
- ~~During a certain time (*refractory period*) the neurons do not respond to stimuli~~

Noisy Leaky Integrate-and-fire model

NLIF Model

- $I(t)$: Interactions of the neuron with the network (synapse)

Noisy Leaky Integrate-and-fire model

NLIF Model

- $I(t)$: Interactions of the neuron with the network (synapse)
- $I(t) = J_E \sum_{i=1}^{C_E} \sum_j \delta(t - t^i_{Ej}) - J_I \sum_{i=1}^{C_I} \sum_j \delta(t - t^i_{Ij})$
  - ◇ E, I: Excitatory, Inhibitory neurons
  - ◇ J_E, J_I: strength of the synapses
  - ◇ C_E, C_I: total number of presynaptic neurons
  - ◇ t^i_{Ej}, t^i_{Ij}: times of the j^{th}-spike coming from the i^{th}-presynaptic neuron

Noisy Leaky Integrate-and-fire model

NLIF Model

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  - C_E, C_I: total number of presynaptic neurons
  - t^i_{Ej}, t^i_{Ij}: times of the j^{th}-spike coming from the i^{th}-presynaptic neuron
- Stochastic process.-
  - Each neuron spikes according to a stationary Poisson process with constant probability of emitting a spike per unit time ν
  - All these processes are assumed to be independent between neurons
  - $\mu_C = b\nu$ average value of the current ($b = C_E J_E - C_I J_I$)
  - $\sigma^2_C = (C_E J^2_E + C_I J^2_I)\nu$ variance of the current

Noisy Leaky Integrate-and-fire model

Any typical neuron of the network:

$$dV = (-V + V_L + \mu_c)\,dt + \sigma_C\,dB_t$$

$(\mu_C = b\nu,\ \sigma_C^2 = (C_E J_E^2 + C_I J_I^2)\nu,$
$C_m = g_L = 1)$

$V(t^-_{spike}) = V_F$ and $V(t^+_{spike}) = V_R$,
t_{spike} the firing time

Assuming:

- Diffusion approximation of the synaptic current with the same mean and variance as the Poissonian spike-train process
- A **network sparse random connectivity**
- **Small synaptic strength** compared to the firing threshold

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Mattia-Del Giudice, Phys. Rev. E, Vol. 66, 051917 (2002)

Noisy Leaky Integrate-and-fire model

- Diffusion approximation $(\mu_C = b\nu,\ \sigma_C^2 = (C_E J_E^2 + C_I J_I^2)\nu,\ C_m = g_L = 1)$

$$dV = (-V + V_L + \mu_c)\,dt + \sigma_C\,dB_t$$

- Firing rate: Probability of firing per unit time of the Poissonian spike train

$$\nu = \nu_{ext} + N(t-d)$$

$N(t)$ mean firing rate of the network

- $N(t)$ is computed as the flux of neurons across the threshold or firing voltage $V_{threshold} = V_F$
- d is the transmission delay

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NNLIF model with $d = 0$

$$\frac{\partial p}{\partial t}(v,t) + \frac{\partial}{\partial v}\left[h\left(v, N(t)\right)p(v,t)\right] - a\left(N(t)\right)\frac{\partial^2 p}{\partial v^2}(v,t) = \delta(v - V_R)N(t)$$

NNLIF model with $d = 0$

$$\frac{\partial p}{\partial t}(v,t) + \frac{\partial}{\partial v}\left[h\left(v, N(t)\right)p(v,t)\right] - a\left(N(t)\right)\frac{\partial^2 p}{\partial v^2}(v,t) = \delta(v - V_R)N(t)$$

- $v \in (-\infty, V_F]$ V_R: **Reset potential** V_F: **Threshold potential**
- $h(v, N) = -v + bN(t)$
- $a(N) = a_0 + a_1 N \quad a_0 > 0,\, a_1 \geq 0$

NNLIF model with $d = 0$

$$\frac{\partial p}{\partial t}(v,t) + \frac{\partial}{\partial v}\left[h\left(v, N(t)\right)p(v,t)\right] - a\left(N(t)\right)\frac{\partial^2 p}{\partial v^2}(v,t) = \delta(v - V_R)N(t)$$

- $v \in (-\infty, V_F]$ V_R: **Reset potential** V_F: **Threshold potential**
- $h(v, N(t)) = -v + \boxed{b} N(t)$ excitatory/inhibitory network (b>0 or b<0)
- $a(N) = a_0 + a_1 N$ $a_0 > 0,\ a_1 \geq 0$ **we generally consider** $\boxed{a(N) = a = 1}$

NNLIF model with $d = 0$

$$\frac{\partial p}{\partial t}(v,t) + \frac{\partial}{\partial v}\left[h\,(v,N(t))p(v,t)\right] - a\,(N(t))\frac{\partial^2 p}{\partial v^2}(v,t) = \delta(v - V_R)N(t)$$

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- $a(N) = a_0 + a_1 N$ $a_0 > 0,\ a_1 \geq 0$ **we generally consider** $\boxed{a(N) = a = 1}$

Boundary conditions

- $p(V_F,t) = 0$
- $p(-\infty,t) = 0$
- $\frac{\partial p}{\partial v}(V_R^-,t) - \frac{\partial p}{\partial v}(V_R^+,t) = \frac{N(t)}{a(N(t))}$

NNLIF model with $d = 0$

$$\frac{\partial p}{\partial t}(v,t) + \frac{\partial}{\partial v}\left[h\left(v, N(t)\right)p(v,t)\right] - a\left(N(t)\right)\frac{\partial^2 p}{\partial v^2}(v,t) = \delta(v - V_R)N(t)$$

- $v \in (-\infty, V_F]$ $\qquad$ V_R: **Reset potential** $\qquad$ V_F: **Threshold potential**
- $h(v, N(t)) = -v + \boxed{b} N(t)$ excitatory/inhibitory network (b>0 or b<0)
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Boundary conditions

- $p(V_F, t) = 0$
- $p(-\infty, t) = 0$
- $\frac{\partial p}{\partial v}(V_R^-, t) - \frac{\partial p}{\partial v}(V_R^+, t) = \frac{N(t)}{a(N(t))}$
- $N(t) := -a\Big(N(t)\Big)\frac{\partial p}{\partial v}(V_F, t) \geq 0 \quad \Longleftarrow$ Nonlinear system!

Firing rate $\qquad$ Conservation of mass $\int_{-\infty}^{V_F} p(v,t)dv = 1$ **Exercise**

Brunel-Hakim, Neural Comp. Vol. 11, 1621-1671 (1999)

C-Carrillo-Perthame, The Journal of Mathematical Neuroscience, 1:7. (2011)

NNLIF model with $d > 0$

$$\frac{\partial p}{\partial t}(v,t) + \frac{\partial}{\partial v}\Big[\ \underbrace{h(v, N(t-d))}_{\text{transmission delay}}\ p(v,t)\Big] - \underbrace{a(N(t-d))}_{\text{transmission delay}}\ \frac{\partial^2 p}{\partial v^2}(v,t) = \delta(v - V_R)N(t)$$

- $v \in (-\infty, V_F]$ V_R: **Reset potential** V_F: **Threshold potential**
- $h(v, N(t)) = -v + \boxed{b} N$ excitatory/inhibitory network (b>0 or b<0)
- $a(N) = a_0 + a_1 N$ $a_0 > 0,\ a_1 \geq 0$ **we generally consider** $a(N) = a = 1$

Boundary conditions

- $p(V_F, t) = 0$
- $p(-\infty, t) = 0$
- $\frac{\partial p}{\partial v}(V_R^-, t) - \frac{\partial p}{\partial v}(V_R^+, t) = \frac{N(t)}{a(N(t-d))}$
- $N(t) := -a\big(N(t-d)\big)\frac{\partial p}{\partial v}(V_F, t) \geq 0$ $\Longleftarrow$ Nonlinear system!

Firing rate

Conservation of mass $\int_{-\infty}^{V_F} p(v,t)dv = 1$ **Exercise**

Analytical properties

- Blow up
- Transmission delay avoids blow up
- Existence results
- Steady states
- Long time behaviour

Blow up

Blow up

Theorem (C-Carrillo-Perthame, 2011) *Assuming:*

- $h(v, N) + v \geq bN$, $0 < a_m \leq a(N)$ *($-\infty < v \leq V_F$ and $N \geq 0$)*
- $b > 0$ *average-excitatory network*

If the initial data is concentrated enough around $v = V_F$ there are

no global-in-time weak solutions

Blow up

Theorem (C-Carrillo-Perthame, 2011) *Assuming:*

- $h(v,N) + v \geq bN$, $0 < a_m \leq a(N)$ *($-\infty < v \leq V_F$ and $N \geq 0$)*
- $b > 0$ *average-excitatory network*

If the initial data is concentrated enough around $v = V_F$ there are no global-in-time weak solutions

The solutions blow up when ...

- For b fixed: the initial condition is concentrated enough around V_F
- For p^0 fixed: b, the connectivity parameter, is large enough

Concentrated enough around V_F

$$\int_{-\infty}^{V_F} e^{\mu v} p^0(v)\, dv \geq \frac{e^{\mu V_F} - e^{\mu V_R}}{b\,\mu} =: \lambda$$

choosing $\mu > \max(\frac{V_F}{a_m}, \frac{1}{b})$

proof

Roux-Salort, 2021: All solutions blow-up if b is large enough

Blow up

Carrillo-González-Gualdani-Schonbek* analyze
the global existence of classical solutions ($d = 0$ and $a = 1$)

- For inhibitory networks: Global classical solutions
- For excitatory networks: Local well-posedness of classical solutions
- Blow up criterium:

$$T^* = \sup\{t > 0 \,:\, N(t) < \infty\}$$

T^*: maximal existence time

  - ◇ For inhibitory networks: $T^* = \infty$
  - ◇ For excitatory networks: there exist classical solutions which blow up at finite time T^* and N diverges

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*Carrillo-González-Gualdani-Schonbek, Comm. in PDEs, Vol. 38(3), 385-409, (2013)

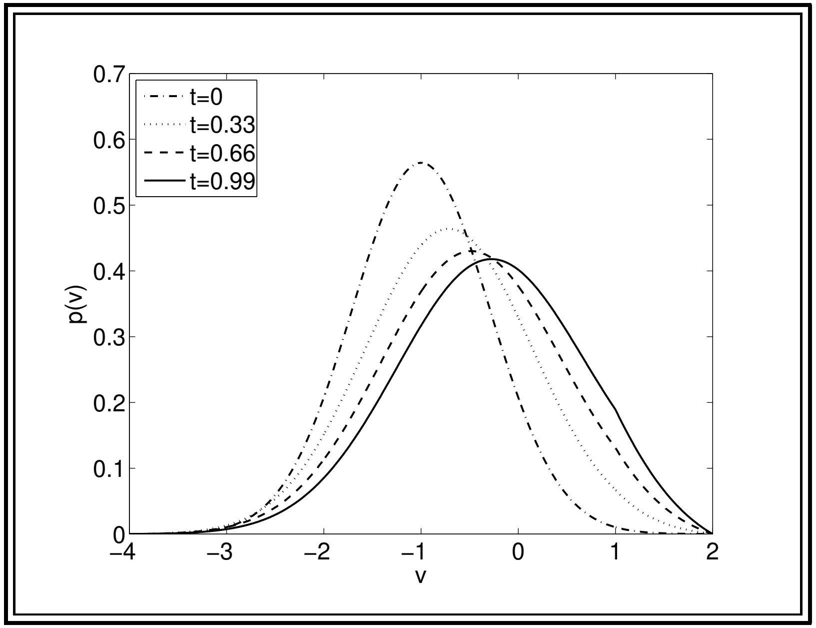
Delarue-Inglis-Rubenthaler-Tanré, The Annals of Applied Probability, 25(4), 2096-2133 (2015).

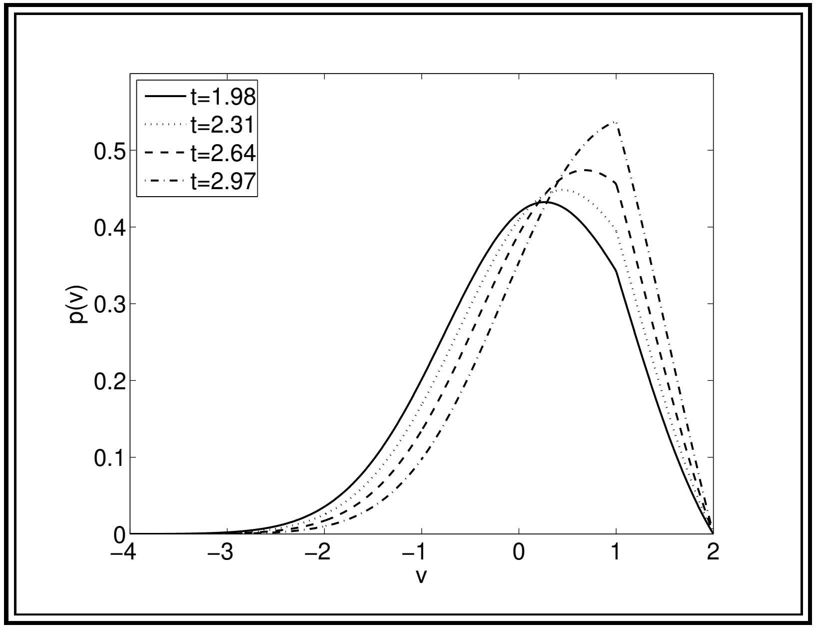
Delarue-Inglis-Rubenthaler-Tanré, Stoch. Proc. Appl., 125(6), 2451-2492 (2015)

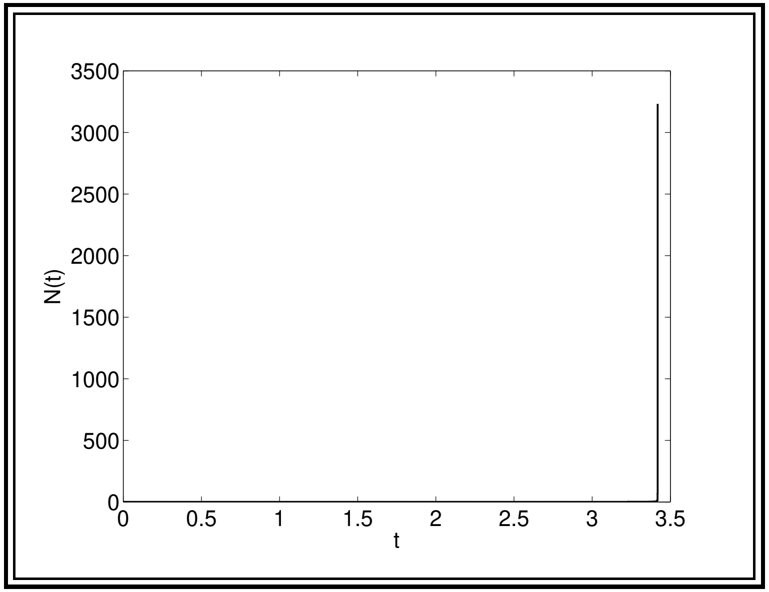
Blow up

Blow-up

Distribution functions $p(v,t)$ for $a \equiv 1$ and $b = 3$ at different times







Delay avoids the blow-up

$$\frac{\partial p}{\partial t}(v,t) + \frac{\partial}{\partial v}\left[h\left(v, N(t)\right)p(v,t)\right] - a\left(N(t)\right)\frac{\partial^2 p}{\partial v^2}(v,t) = \delta(v - V_R)N(t)$$

- $v \in (-\infty, V_F]$
- $h(v, N(t)) = -v + bN$
- $a(N) = a_0 + a_1 N \quad a_0 > 0,\, a_1 \geq 0$

Delay avoids the blow-up

$$\frac{\partial p}{\partial t}(v,t)+\frac{\partial}{\partial v}\left[h\left(v,N(t-d)\right)p(v,t)\right]-a\left(N(t-d)\right)\frac{\partial^2 p}{\partial v^2}(v,t)=\delta(v-V_R)N(t)$$

- $v \in (-\infty, V_F]$
- $h(v,N(t-d)) = -v + bN(t-d)$
- $a(N(t-d)) = a_0 + a_1 N(t-d) \quad a_0 > 0,\ a_1 \geq 0$

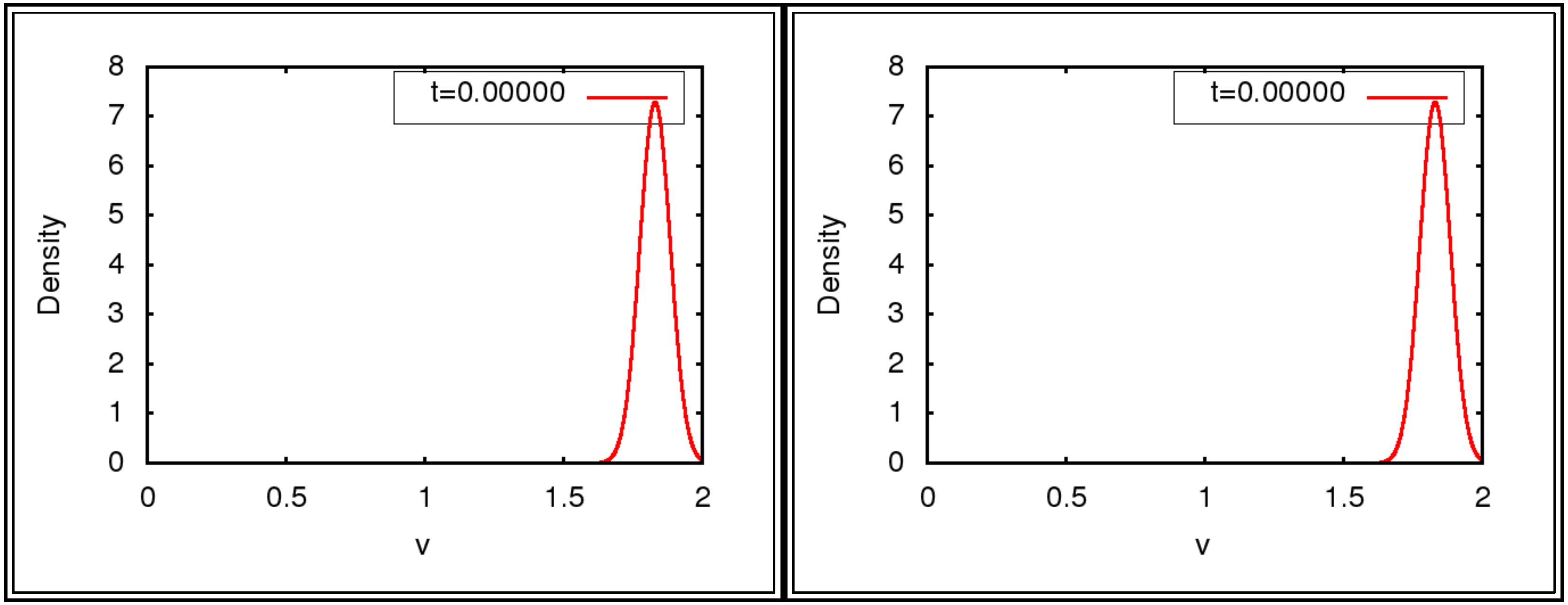
$d \geq 0$ is the transmission delay

C-Schneider, ESAIM: M2AN, Vol 52(5), 1733-1761, (2018)

C-Roux-Salort-Schneider, Commun Part Diff Eq, Vol 44(12), 1358-1386 (2019)

Delay avoids the blow-up

$a \equiv 1$ and $b = 0.5$

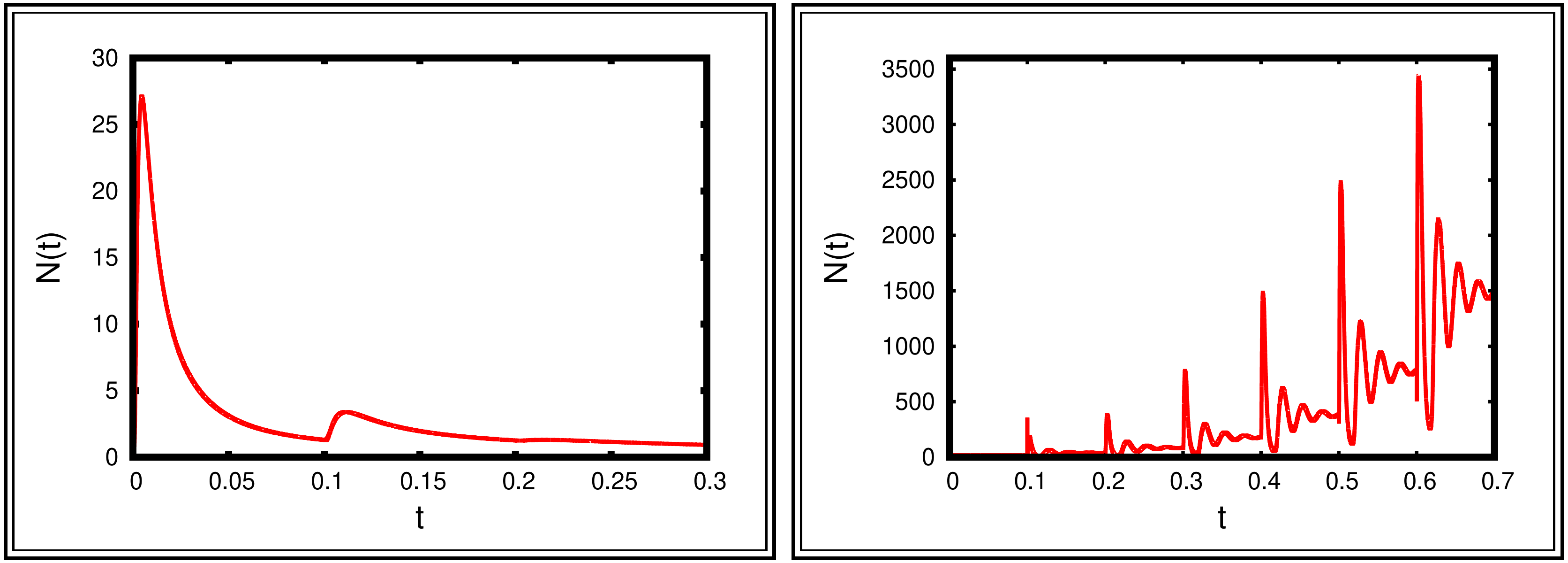


$d = 0$

$d > 0$

Delay avoids the blow-up

Firing rate with delay, $d > 0$ for two different situations: b small (only one steady state) and b large (no steady states)



C-Schneider, ESAIM: M2AN, Vol 52(5), 1733-1761, (2018)

C-Roux-Salort-Schneider, Commun Part Diff Eq, Vol 44(12), 1358-1386 (2019)

Delay avoids the blow-up

Difficulty to prove the global existence

- **Inhibitory case**: The criterium for the maximal time of existence directly derives that the firing rate is uniformly bounded for every time, obtaining the global existence of solution

- **Excitatory case:** The previous procedure is not possible, since the firing rate sometimes is not uniformly bounded.

C-Roux-Salort-Schneider, Commun Part Diff Eq, Vol 44(12), 1358-1386 (2019)

Carrillo-González-Gualdani-Schonbek, Comm. in PDEs, Vol. 38(3), 385-409, (2013)

Carrillo-Perthame-Salort-Smets, Nonlinearity 28 3365 (2015)

Delay avoids the blow-up

Proof of the global existence of solution ($d > 0$)

1. Rewriting as a Stefan like problem
2. Local existence by means of
   - Integral formulation
   - Fixed point theorem
3. Key result: Maximal time of existence
4. super solutions and global existence result

C-Roux-Salort-Schneider, Commun Part Diff Eq, Vol 44(12), 1358-1386 (2019)

Steady states

Steady states

We will focus on the case of $a(N) = a$ constant

$$\frac{\partial p}{\partial t}(v,t) + \frac{\partial}{\partial v}\left[(-v + bN(t-d))\, p(v,t)\right] - a\frac{\partial^2 p}{\partial v^2}(v,t) = \delta(v - V_R)N(t)$$

p_∞ steady state satisfies

$$\frac{\partial}{\partial v}\left[(v - bN)p + a\frac{\partial}{\partial v}p(v) + NH(v - V_R)\right] = 0$$

in the sense of distributions, with H being the Heaviside function

Steady states

Therefore,

$$(v - bN_\infty)p_\infty + a\frac{\partial p_\infty}{\partial v} + N_\infty H(v - V_R) = C$$

Steady states

Therefore,

$$(v - bN_\infty)p_\infty + a\frac{\partial p_\infty}{\partial v} + N_\infty H(v - V_R) = C$$

Definition of N_∞ + Dirichlet boundary condition $\Longrightarrow$ $C = 0$

Then (*easy exercise*)

$$p_\infty(v) = \frac{N_\infty}{a} e^{-\frac{(v-bN_\infty)^2}{2a}} \int_v^{V_F} e^{\frac{(w-bN_\infty)^2}{2a}} H[w - V_R]dw$$

Steady states

$$p_\infty(v) = \frac{N_\infty}{a} e^{-\frac{(v-bN_\infty)^2}{2a}} \int_{\max(v,V_R)}^{V_F} e^{\frac{(w-bN_\infty)^2}{2a}}\, dw$$

To determine p_∞ **we need to know** N_∞

Steady states

$$p_\infty(v) = \frac{N_\infty}{a} e^{-\frac{(v-bN_\infty)^2}{2a}} \int_{\max(v,V_R)}^{V_F} e^{\frac{(w-bN_\infty)^2}{2a}} \, dw$$

Using the conservation law, $\int_{\infty}^{V_F} p_\infty(v)\, dv = 1$, we obtain the following implicit equation for N_∞

$$\frac{a}{N_\infty} = \int_{-\infty}^{V_F} \left[e^{-\frac{(v-bN_\infty)^2}{2a}} \int_{\max(v,V_R)}^{V_F} e^{\frac{(w-bN_\infty)^2}{2a}} dw \right] dv$$

Steady states

Linear case ($b = 0$)

$$\frac{a}{N_\infty} = \int_{-\infty}^{V_F} \left[e^{-\frac{v^2}{2a}} \int_{\max(v,V_R)}^{V_F} e^{\frac{w^2}{2a}} \, dw \right] dv$$

and there is **unique stationary state** p_∞ given by

$$p_\infty(v) = \frac{N_\infty}{a} e^{-\frac{v^2}{2a}} \int_{\max(v,V_R)}^{V_F} e^{\frac{w^2}{2a}} \, dw$$

with

$$N_\infty = \frac{a}{\int_{-\infty}^{V_F} \left[e^{-\frac{v^2}{2a}} \int_{\max(v,V_R)}^{V_F} e^{\frac{w^2}{2a}} \, dw \right] dv}$$

Steady states

Non-linear case ($b \neq 0$)

Question: Number of solutions to

$$\frac{a}{N} = \int_{-\infty}^{V_F} \left[e^{-\frac{(v-bN)^2}{2a}} \int_{\max(v,V_R)}^{V_F} e^{\frac{(w-bN)^2}{2a}} dw \right] dv \quad ?$$

$$N = \frac{1}{I(N)} \iff NI(N) = 1 \iff \frac{1}{N} = I(N),$$

with

$$I(N) := \frac{1}{a} \int_{-\infty}^{V_F} \left[e^{-\frac{(v-bN)^2}{2a}} \int_{\max(v,V_R)}^{V_F} e^{\frac{(w-bN)^2}{2a}} dw \right] dv$$

Steady states

With the change of variables:

$$z = \frac{v-bN}{\sqrt{a}}, \quad u = \frac{w-bN}{\sqrt{a}}, \qquad w_F = \frac{V_F-bN}{\sqrt{a}}, \quad w_R = \frac{V_R-bN}{\sqrt{a}}$$

$$I(N) = \int_{-\infty}^{w_F} \left[e^{-\frac{z^2}{2}} \int_{\max(z,w_R)}^{w_F} e^{\frac{u^2}{2}} du \right] dz.$$

And with the new change $s = \frac{z-u}{2}$ and $\bar{s} = \frac{z+u}{2}$

$$I(N) = \int_0^{\infty} e^{-s^2/2} e^{-\frac{sbN}{\sqrt{a}}} \frac{e^{\frac{s\,V_F}{\sqrt{a}}} - e^{\frac{s\,V_R}{\sqrt{a}}}}{s} ds$$

Thus we find the steady states if find N solution to

$$\begin{cases} \dfrac{1}{N} = I(N), \\ I(N) = \int_0^{\infty} e^{-s^2/2} e^{-\frac{sbN}{\sqrt{a}}} \frac{e^{\frac{s\,V_F}{\sqrt{a}}} - e^{\frac{s\,V_R}{\sqrt{a}}}}{s} ds. \end{cases}$$

(*The details can be computed as exercise*)

Steady states

Properties of $I(N)$

- $I(0) < \infty$
- For all integers $k \geq 1$,

$$I^{(k)}(N) = (-1)^k \left(\frac{b}{\sqrt{a}}\right)^k \int_0^\infty e^{-s^2/2} s^{k-1} \left(e^{s\, w_F} - e^{s\, w_R}\right) ds\,.$$

- $b < 0$: I is an increasing strictly convex function and $\lim_{N\to\infty} I(N) = \infty$
- $b > 0$: I is a decreasing convex function and $\lim_{N\to\infty} I(N) = 0$, $\lim_{N\to\infty} N\, I(N) = \frac{V_F - V_R}{b}$.

  So when $N \to \infty$:
  - ◇ $I(N) < \frac{1}{N}$ if $\frac{V_F - V_R}{b} < 1$
  - ◇ $I(N) > \frac{1}{N}$ if $\frac{V_F - V_R}{b} > 1$

Exercise: prove these properties. (Hint: follow steps in C-Carrillo-Perthame, 2011)

Steady states

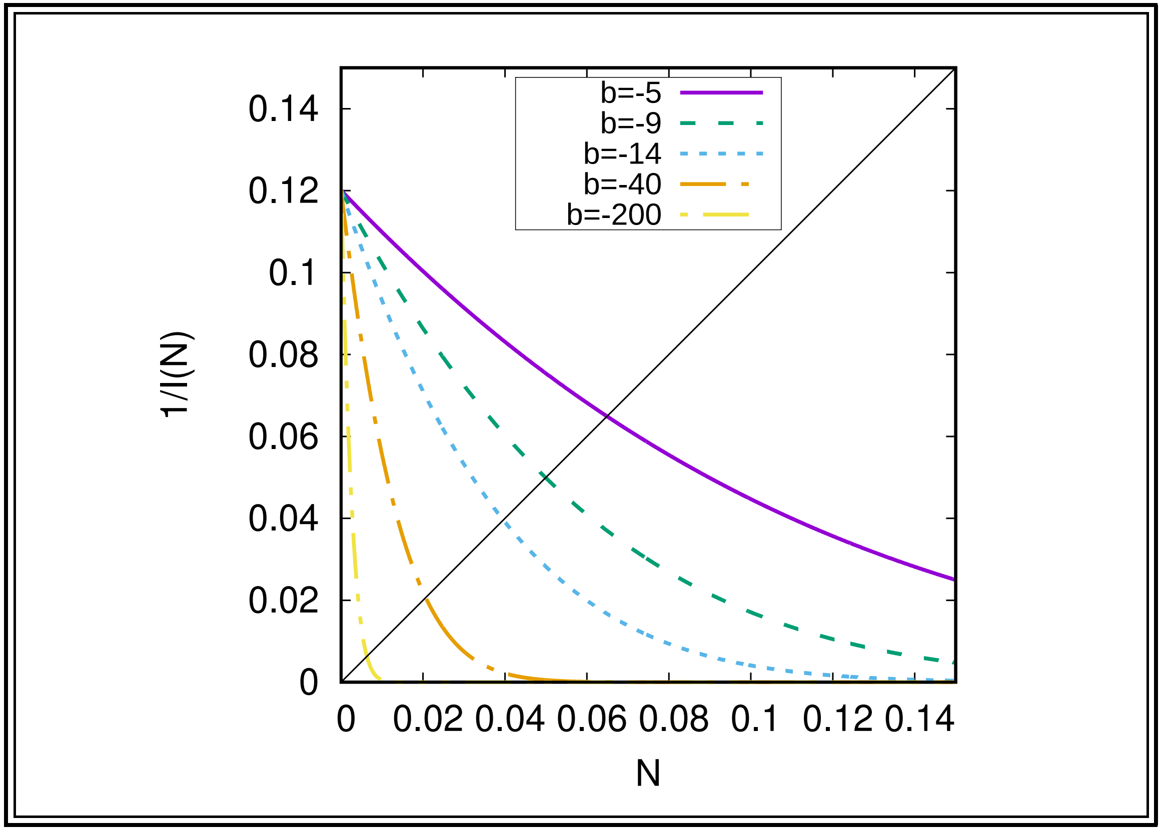
Number of steady states in terms of connectivity parameter b

(C-Carrillo-Perthame, 2011):

- Average-inhibitory network ($b < 0$): there is a unique steady state
- Average-excitatory network ($b > 0$):
  - High connectivity: there is no steady state
  - Small connectivity: there is a unique steady state
  - Between small and high connectivity: at least one or at least two steady states

Steady states

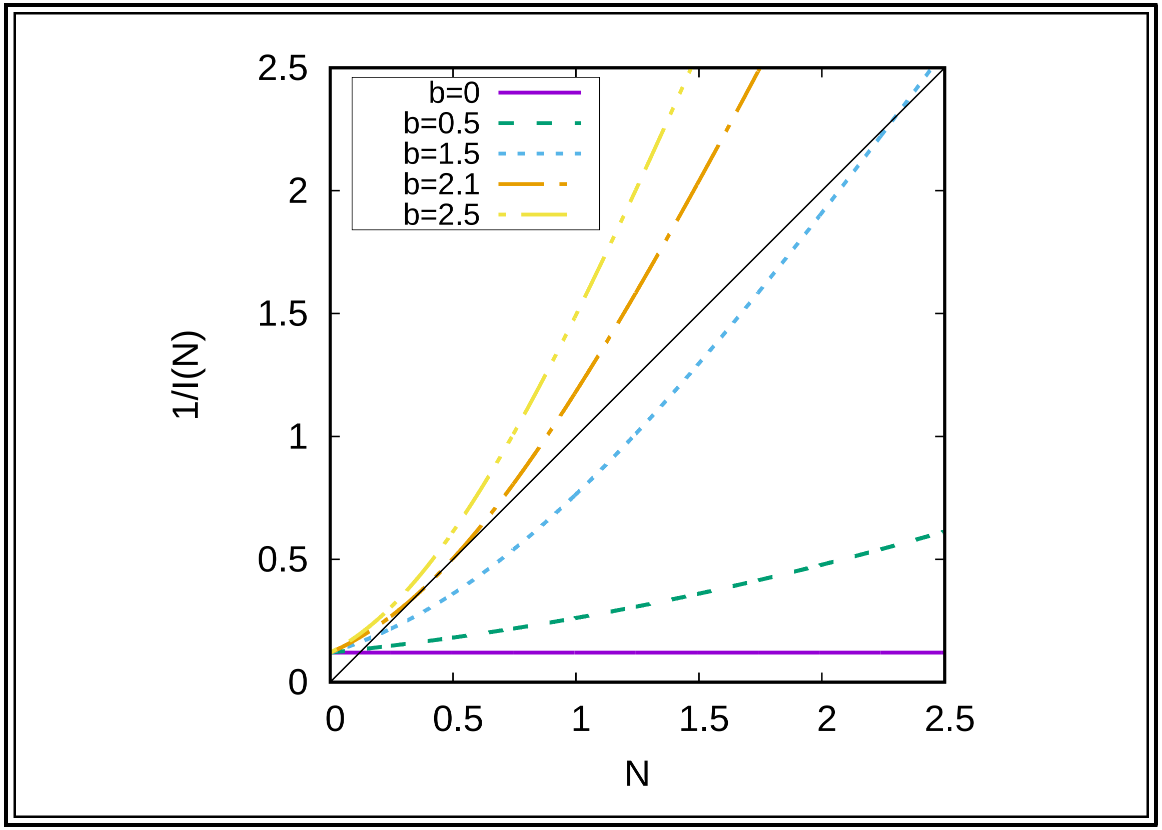
Function $\frac{1}{\text{I(N)}}$ is plotted against the function N for $b < 0$



$a \equiv 1,\ V_R = 1,\ V_F = 2$

Steady states

Function $\frac{1}{\text{I(N)}}$ is plotted against the function N for $b > 0$



$a \equiv 1,\ V_R = 1,\ V_F = 2$

Steady states

Theorem *Assume* $a(N) = a$ *is constant*

i) *For* $b < 0$ *and* $b > 0$ *small enough there is a unique steady state*

ii) *Under either the condition* $0 < b < V_F - V_R$ *or the condition* $0 < 2ab < (V_F - V_R)^2 V_R$ *, there exists at least one steady state solution*

iii) *If both* $0 < 2ab < (V_F - V_R)^2 V_R$ *and* $b > V_F - V_R$ *hold, then there are at least two steady states*

iv) *There is no steady state under the high connectivity condition* $b > \max(2(V_F - V_R), 2V_F I(0))$

Exercise: Proof. (Hint: follow steps in C-Carrillo-Perthame, 2011)

Are the steady states stable?

Entropy dissipation method

- Entropy dissipation method is a technique for studying the **long-term behaviour** of some PDE systems

- The idea is to find decreasing functionals (**Lyapunov functionals**)

- Originally it had a physical basis, **physical entropy**
  (H-Theorem for Boltzmann equation (gases dynamics))
  - ◇ For physicists, the functional is increasing

Entropy dissipation method

- The convergence is proved in terms of this functional: the **distance to the equilibrium is given by the relative entropy**

- Can it be traumatic for mathematicians whose preferred distance is L^1 norm?
  - Sometime is posible to prove that convergence in terms of the entropy implies convergence in L^1
  - Csizár-Kullback-Pinsker inequality:

$$\frac{1}{2}\|f-g\|_{L^1}^2 \leq \int f \log \frac{f}{g}$$

$H(f|g) := \int f \log \frac{f}{g}$ relative entropy

(See these notes of Jose Cañizo for more details about this inequality)

Entropy dissipation method

Scheme

- Consider a *entropy functional*, $E(f(t,\cdot))$, which can be applied to any function, solution or not of the equation, such that, if f is a solution of the system,
  - ◇
    $$\frac{d}{dt}E(f(t,\cdot)) = -D(f(t,\cdot)) \leq 0,$$
    $D((f,\cdot))$ is called **entropy production**
  - ◇ it has a unique minimum at the equilibrium $f_\infty(\cdot)$

- Consider the *relative entropy* $E[f|f_\infty](t) := E(f(t,\cdot)) - E(f_\infty(\cdot)) \geq 0$

- Try to control entropy production by the entropy (**entropy-entropy production inequality**)
  $$D(f) \geq \Phi(E[f|f_\infty])$$
  with $H \mapsto \Phi(H)$ some continuous function, strictly positive when $H > 0$

Finally

$$\boxed{\frac{d}{dt}E[f|f_\infty](t) = -D(f(t,\cdot)) \leq -\Phi(E[f|f_\infty])}$$

Entropy dissipation method

$$\frac{d}{dt}E[f|f_\infty](t) = -D(f(t,\cdot)) \leq -\Phi(E[f|f_\infty])$$

- Example 1: $\Phi(H) = \alpha H$

$$\frac{d}{dt}E[f|f_\infty](t) =\leq -\Phi(E[f|f_\infty]) = -\alpha E[f|f_\infty] \Rightarrow E[f|f_\infty] \leq E[f|f_\infty](0)e^{-\alpha t}$$

- Example 2: $\Phi(H) = CH^{1+\alpha}$, $C, \alpha > 0$
  Then the entropy going down like $O(t^{-1/\alpha})$ (polynomial rate of convergence to equilibrium)

- **Example 3: we study the linear NNLIF equation**

Entropy dissipation method

Relative entropy

$$E(t) := \int_{-\infty}^{V_F} p_\infty(v) G\left(\frac{p(v,t)}{p_\infty(v)}\right) dv$$

G **convex function**

- $\frac{dE(t)}{dt} \leq 0$ Entropy production
- Control the entropy production in terms of the entropy

$$\frac{dE(t)}{dt} \leq -\mu E(t), \quad \mu > 0$$

In this step Poincaré's inequality (see these notes of Jose Cañizo) helps (considering $G(x) = (x-1)^2$)

$$\gamma \int_{-\infty}^{V_F} p_\infty(v) \left(\frac{p(v,t)}{p_\infty(v)} - 1\right)^2 dv \leq \int_{-\infty}^{V_F} p_\infty(v) \left(\frac{\partial}{\partial v} \frac{p(v,t)}{p_\infty(v)}\right)^2 dv$$

- Gronwall's inequality gives the result:

$$E(t) \leq e^{-\mu t} E(0), \quad \mu > 0$$

Case linear b=0

For any smooth convex function $G : \mathbb{R}^+ \longrightarrow \mathbb{R}$

$$-\frac{d}{dt}\int_{-\infty}^{V_F} p_\infty(v) G\left(\frac{p(v,t)}{p_\infty(v)}\right) dv =$$

$$N_\infty\left[G\left(\frac{N(t)}{N_\infty}\right) - G\left(\frac{p(v,t)}{p_\infty(v)}\right) - \left(\frac{N(t)}{N_\infty} - \frac{p(v,t)}{p_\infty(v)}\right) G'\left(\frac{p(v,t)}{p_\infty(v)}\right)\right]\Big|_{V_R}$$

$$+a_0 \int_{-\infty}^{V_F} p_\infty(v)\, G''\left(\frac{p(v,t)}{p_\infty(v)}\right) \left[\frac{\partial}{\partial v}\left(\frac{p(v,t)}{p_\infty(v)}\right)\right]^2 dv \geq 0$$

Exercise: Proof

Case linear b=0

Theorem [Exponential decay] (C-Carrillo-Perthame)
Fast-decaying solutions verifying $p^0(v) \leq C^0 p_\infty(v)$ *for some* $C^0 > 0$, *satisfy*

$$\int_{-\infty}^{V_F} p_\infty(v) \left(\frac{p(v,t) - p_\infty(v)}{p_\infty(v)} \right)^2 dv \leq$$

$$e^{-2a_0 \nu t} \int_{-\infty}^{V_F} p_\infty(v) \left(\frac{p^0(v) - p_\infty(v)}{p_\infty(v)} \right)^2 dv.$$

(considering $G(x) = (x-1)^2$)

Case non linear $b \neq 0$

- C-Carrillo-Perthame: Numerical analysis

- Carrillo-Perthame-Salort-Smets: Local asymptotic stability for stationary states for $|b|$ small

- C-Roux-Salort-Schneider: Local asymptotic stability for stationary states for $|b|$ small and $d > 0$

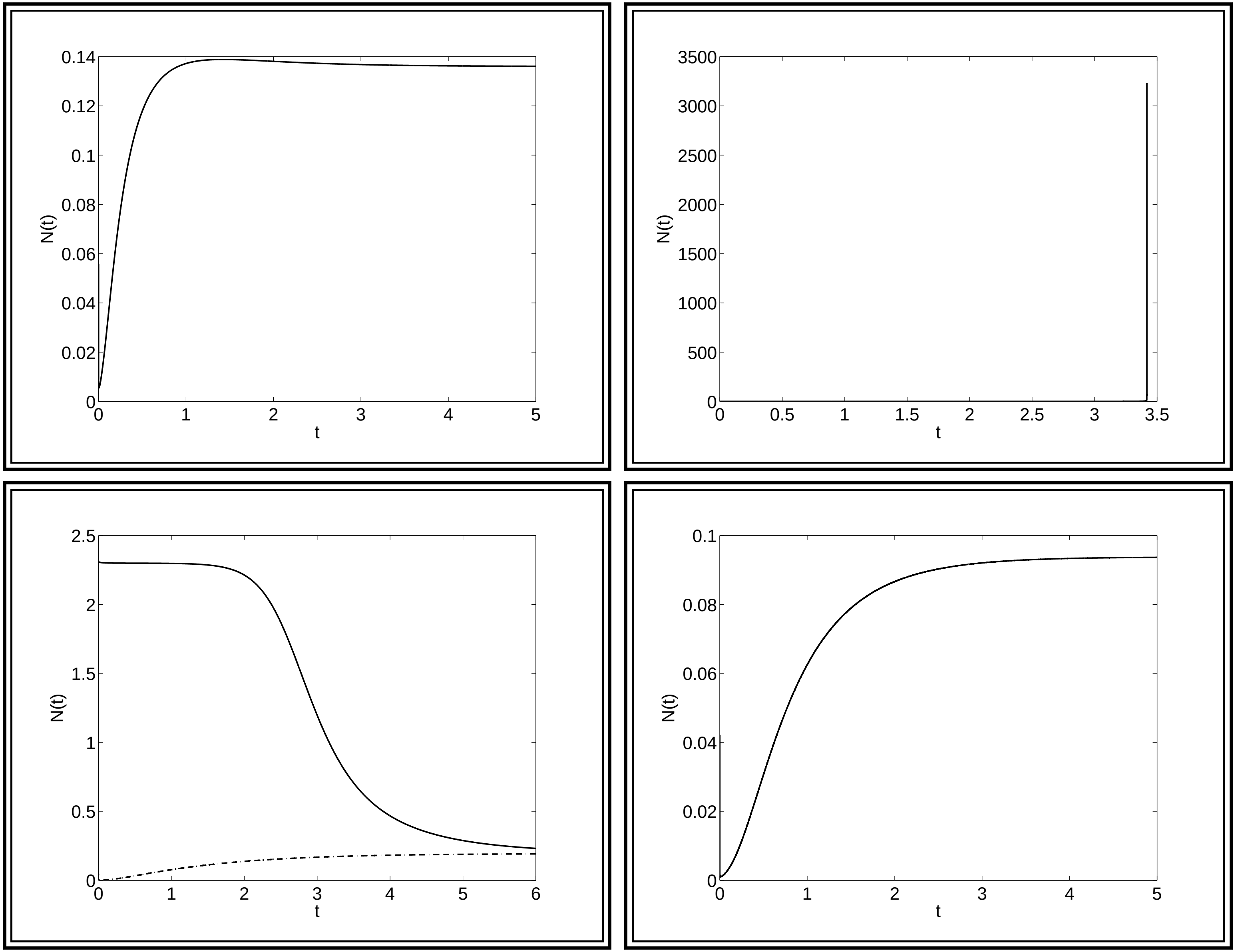
Exercise: Compute $\frac{d}{dt}\int_{-\infty}^{V_F} p_\infty(v) G\left(\frac{p(v,t)}{p_\infty(v)}\right) dv$ in the nonlinear case ($b \neq 0$) (G convex smooth function)

Carrillo-Perthame-Salort-Smets, Nonlinearity 28.9 (2015): 3365.

C-Roux-Salort-Schneider, Commun Part Diff Eq, Vol 44(12), 1358-1386 (2019)

Numerical results

Firing rates $N(t)$ for $a \equiv 1,\ d = 0$



Top left: $b = 0.5$ Top right: $b = 3$ Bottom left: $b = 1.5$ Bottom right: $b = -1.5$

What happens when the connectivity is high?

$$\frac{dE(t)}{dt} = \underbrace{-\text{Positive}\,(t)}_{\text{Linear part}} + \underbrace{2b(N(t-d)-N_\infty)\int_{-\infty}^{V_F} p\frac{\partial}{\partial v}\left(\frac{p(v,t)}{p_\infty(v)}\right)}_{\text{nonlinear part: without sign}}$$

Considering $G(x) = (x-1)^2$ and controlling the nonlinear term with L^2 estimates on N:

No answer using entropy method

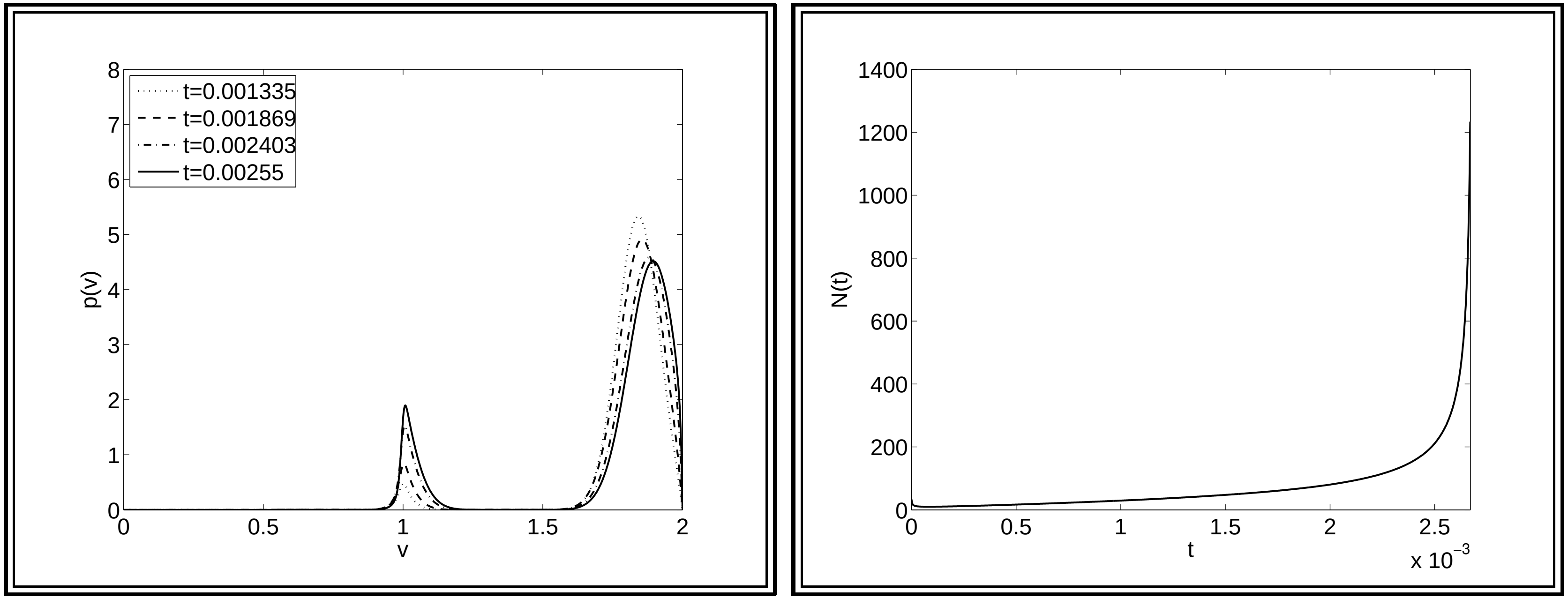
- Without delay $d = 0$ and $|b|$ small: Carrillo-Perthame-Salort-Smets, 2015
- With delay $d > 0$ and $|b|$ small: C-Roux-Salort-Schneider, 2019

To answer the question, we first analyzed this other one

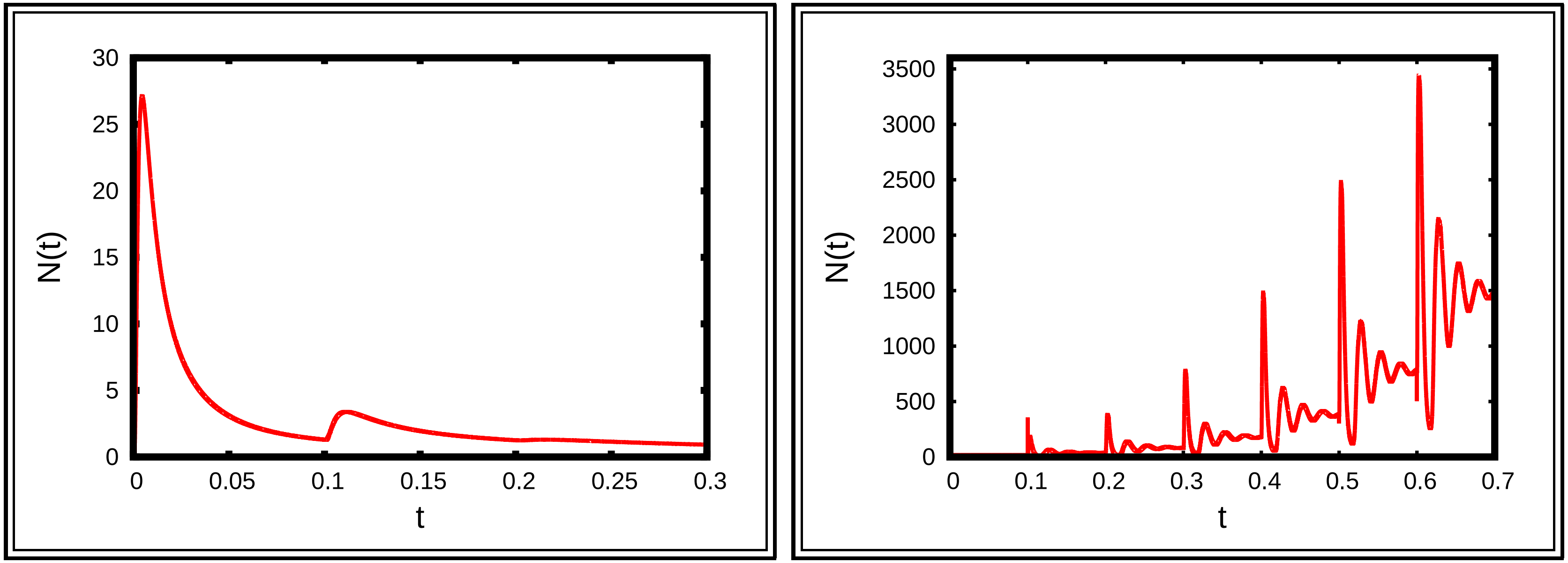
What happens after the blow-up phenomenon?

PDE description: blow-up situations

Without delay



With delay



After the blow-up

To answer we have to go back to the microscopic description

Any typical neuron of the network becomes

$$dV(t) = -\left(V(t) + bN(t-d)\right) dt + \sqrt{2a}dB(t),$$

$B(t)$ the standard Brownian motion

$V(t^-_{spike}) = V_F$ and $V(t^+_{spike}) = V_R$, with t_{spike} the firing time.

After the blow-up

To answer we have to go back to the microscopic description

Any typical neuron of the network becomes

$$dV(t) = -(V(t) + bN(t-d))\,dt + \sqrt{2a}dB(t),$$

$B(t)$ the standard Brownian motion

$V(t_{spike}^{-}) = V_F$ and $V(t_{spike}^{+}) = V_R$, with t_{spike} the firing time.

- $N(t) = e'(t)$
- $e(t) = \lim_{\mathcal{N}\to\infty} \frac{1}{\mathcal{N}} \sum_j^{\mathcal{N}} \sum_k 1_{\{\tau_k^j \le t\}}$ the theoretical expected number of spike times by a typical neuron
- $\left(\tau_k^j\right)_{k\geq 1}$ sequence of spike times

Delarue-Inglis-Rubenthaler-Tanré, Ann. Appl. Probab., 25(4), 2096-2133 (2015)

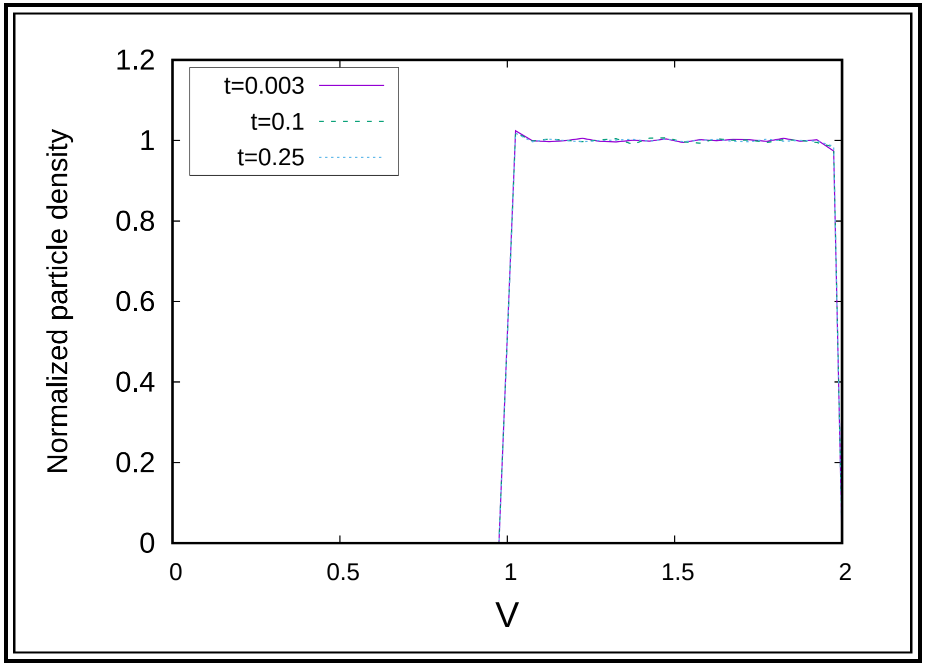
Delarue-Inglis-Rubenthaler-Tanré, Stoch. Proc. Appl., 125(6), 2451-2492 (2015)

After the blow-up

What happens after the blow-up phenomenon?

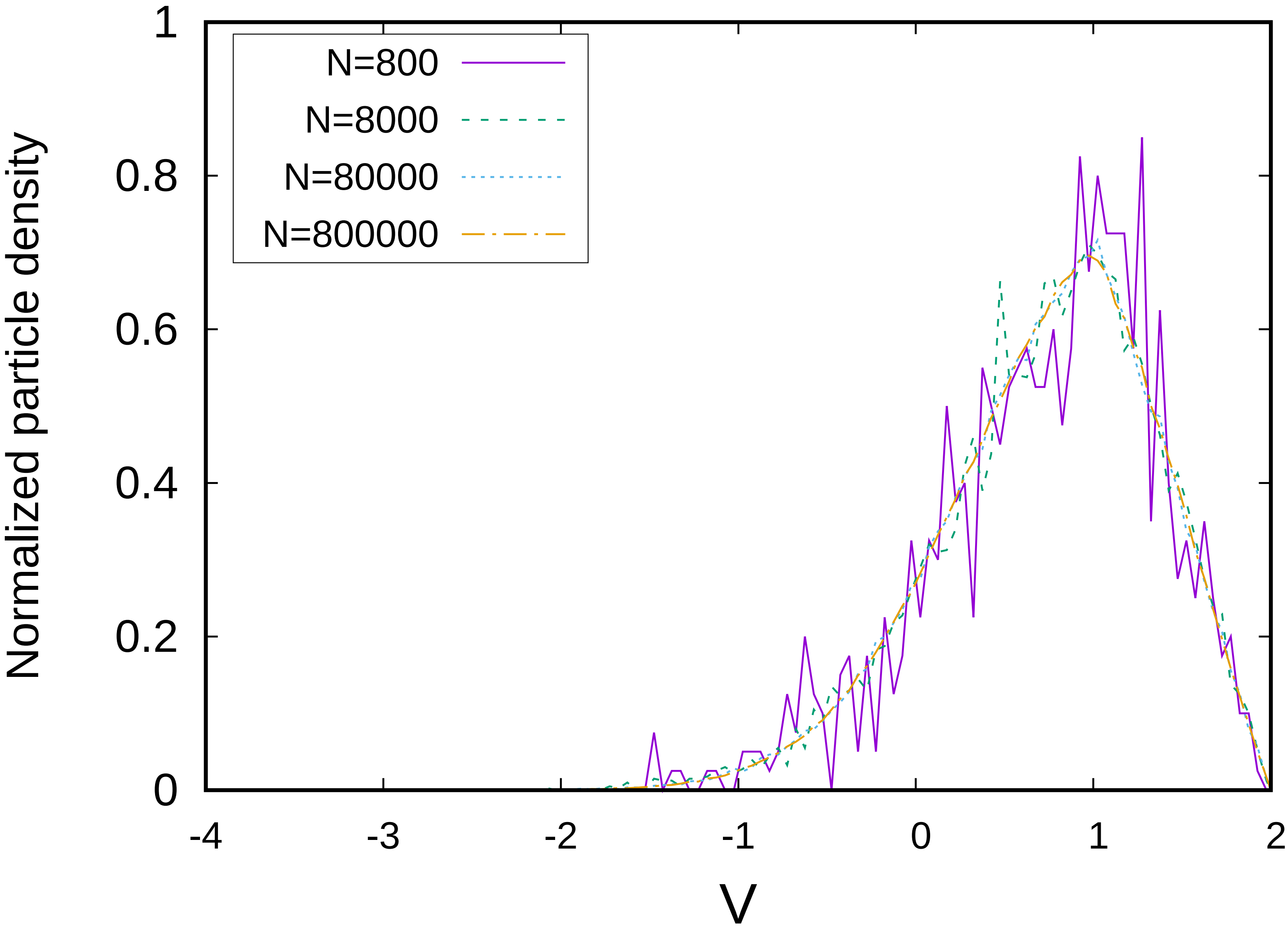
To answer we study the particle system numerically (C-RamosLora, 2021)

Sometimes systems tend to “plateau” distributions after the blow-up, which means that the membranes potential tend to be uniformly distributed in the interval (V_R, V_F)



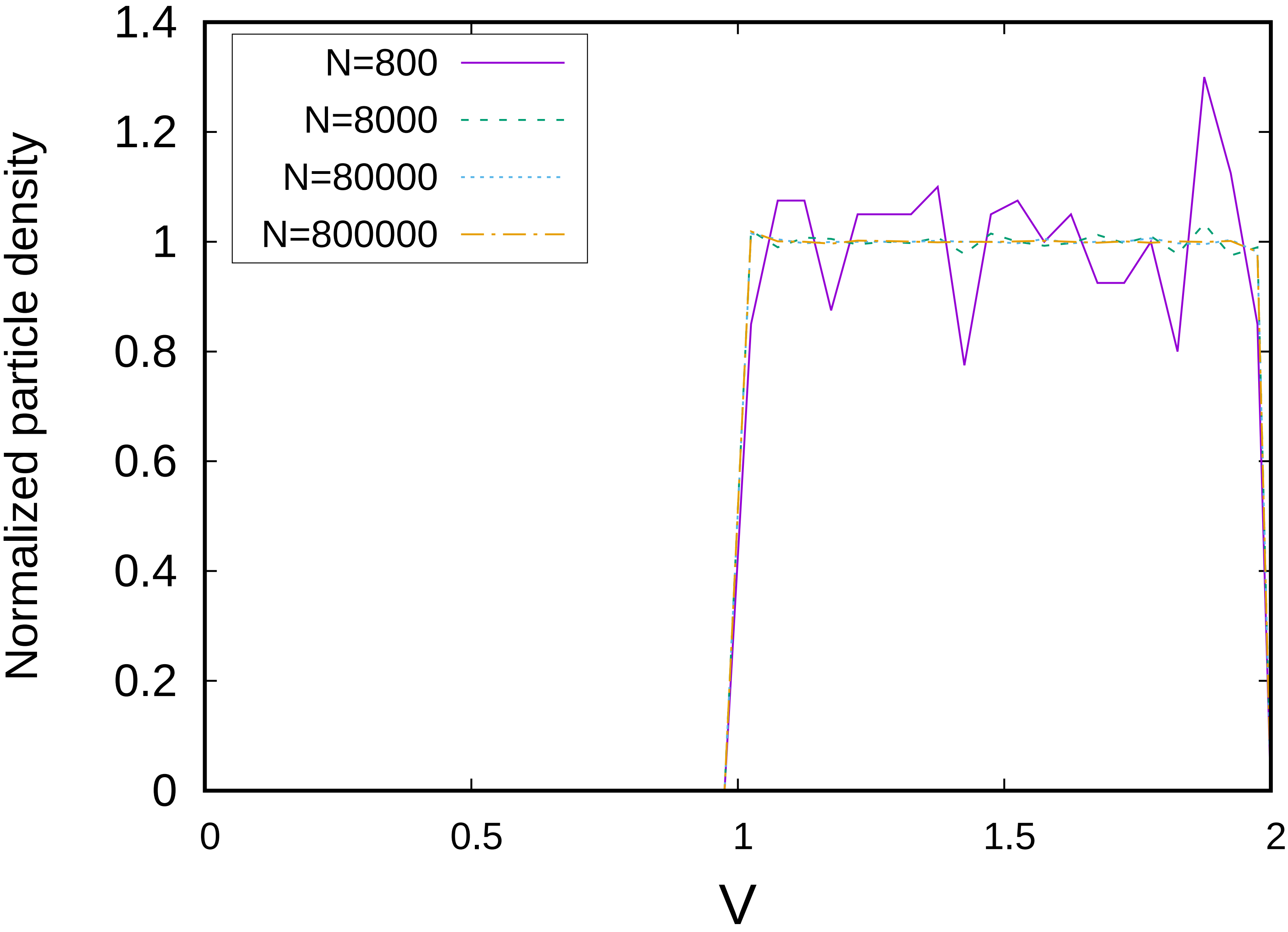
$V_R = 1, V_F = 2$

Numerical tests to set the number of neurons



$b = 1.5$. The system starts with a Gaussian initial condition and evolves towards a steady state. Distribution at time $t = 0.5$

Numerical tests to set the number of neurons



$b = 1$. A very singular situation where neurons are evenly distributed between V_R and V_F.

Distribution at time $t = 0.005$

After the blow-up

System behaviour after the blow-up depends on the connectivity parameter b:

- Weakly connected $(b < V_F - V_R)$: Tends to its unique steady state after blow-up
- Highly connected $(V_F - V_R \leq b)$: “Plateau” distributions appear when synaptic delays are taken into account.
  - ◇ No steady states case: Tends to a “plateau” distribution
  - ◇ Two steady states case: Bistability between the steady state with the lowest firing rate and the “plateau” state
  - ◇ The limiting case $b = V_F - V_R$: Tends to a "plateau" distribution under blow-up situations, either without synaptic delay or with a very small delay value. For a high enough delay the system tends to the stationary state

Relationship with physical solutions **(Delarue-Inglis-Rubenthaler-Tanré, 2015)**

C-RamosLora, CiCP 30, 820-850 (2021)

Physical solutions for SDE model

At microscopic level the notion of solution was extended to **physical solutions** (Delarue-Inglis-Rubenthaler-Tanré):

- Main difference: regularity of the expectation $e(t)$:
  - ◇ Continuous for classical solutions
  - ◇ Can present certain positive jump discontinuities for physical solutions
- Neurophysiologically:
  - ◇ Classical notion: neurons only fire when they reach V_F
  - ◇ Physical notion: neurons can fire if their membrane potentials are close to V_F
- Existence:
  - ◇ Non global existence for classical solutions (without delay)
  - ◇ Global existence even after the blow-up occurs for physical solutions The notion of physical solution make sense for weakly connected network ($b < V_F - V_R$), because neurons cannot fire more than once at the same time

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Delarue-Inglis-Rubenthaler-Tanré, Ann. Appl. Probab., 25(4), 2096-2133 (2015)

Delarue-Inglis-Rubenthaler-Tanré, Stoch. Proc. Appl., 125(6), 2451-2492 (2015)

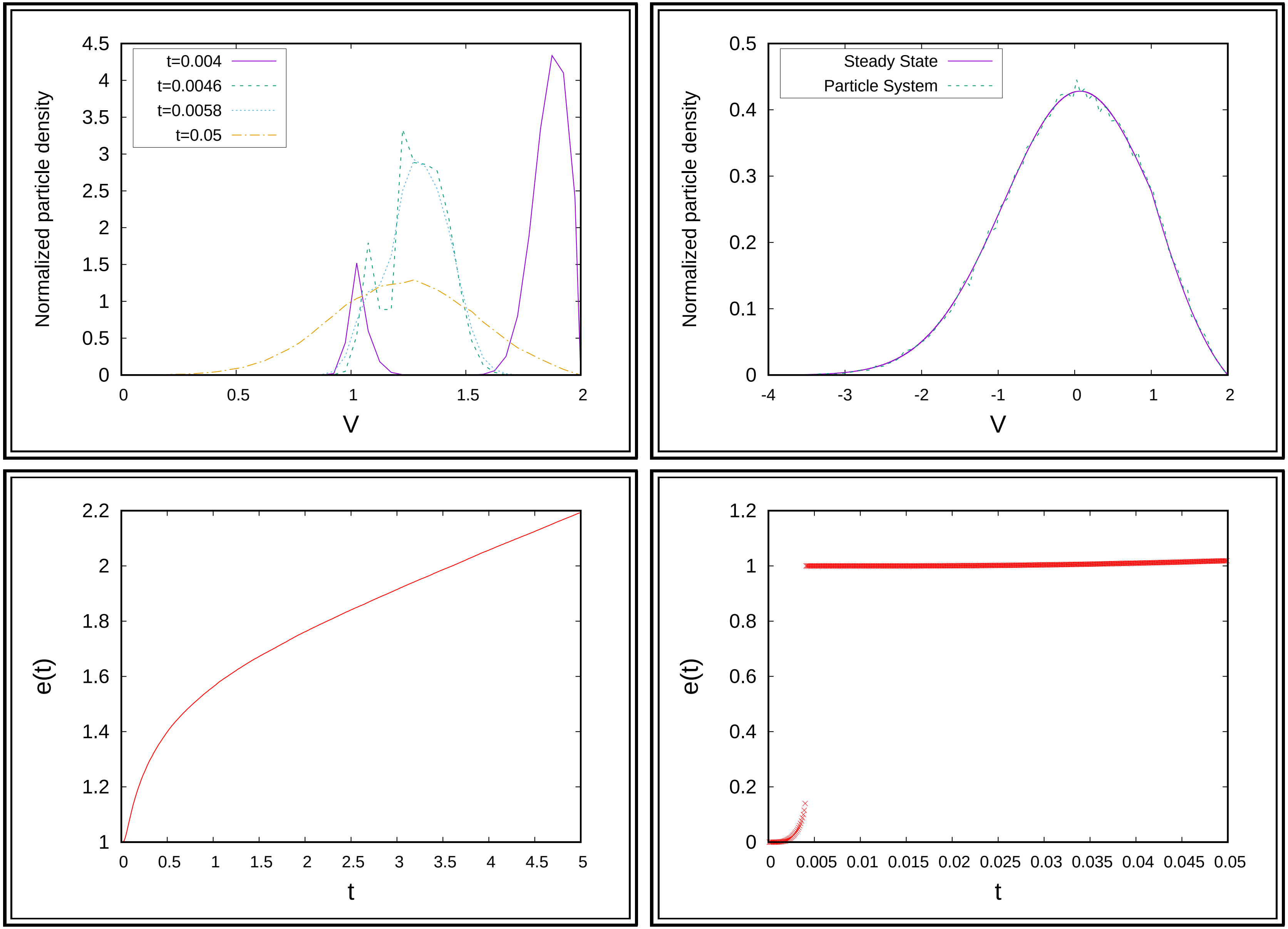
Numerical simulations

What happens after blow-up?

(Fixed parameters: $V_R = 1$, $V_F = 2$, $a = 1$)

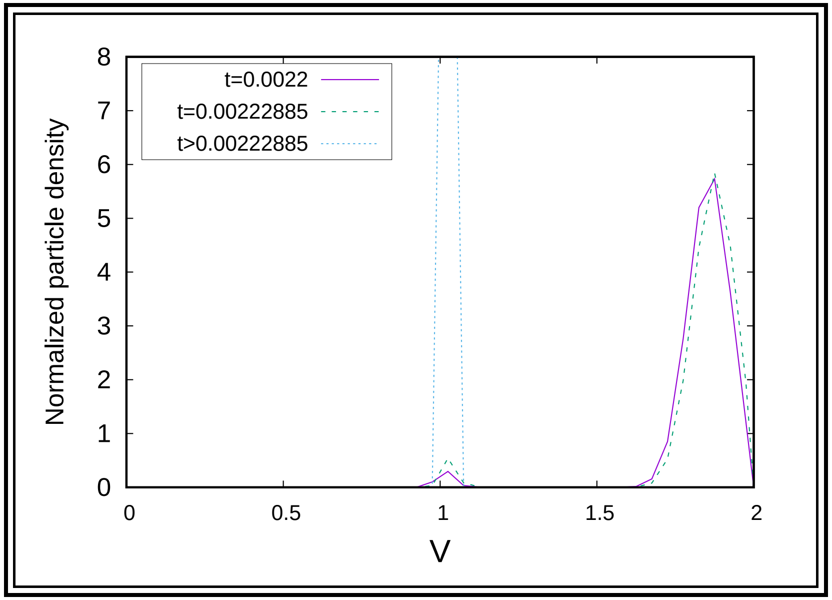
Particle system description

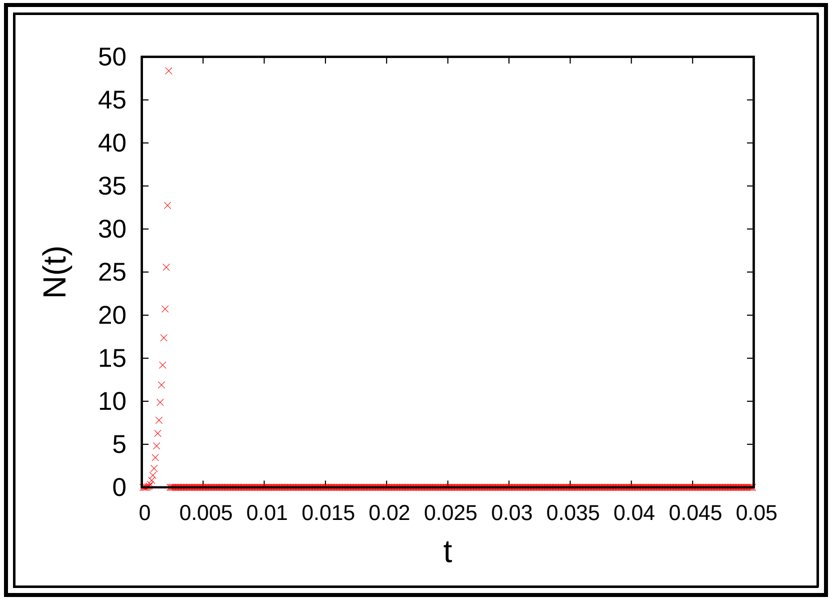
Blow-up situation: $b < V_F - V_R = 1$, $d = 0$. Physical solution



Particle system description

Blow-up situation: $b > V_F - V_R = 1$, $d = 0$. No physical solutions



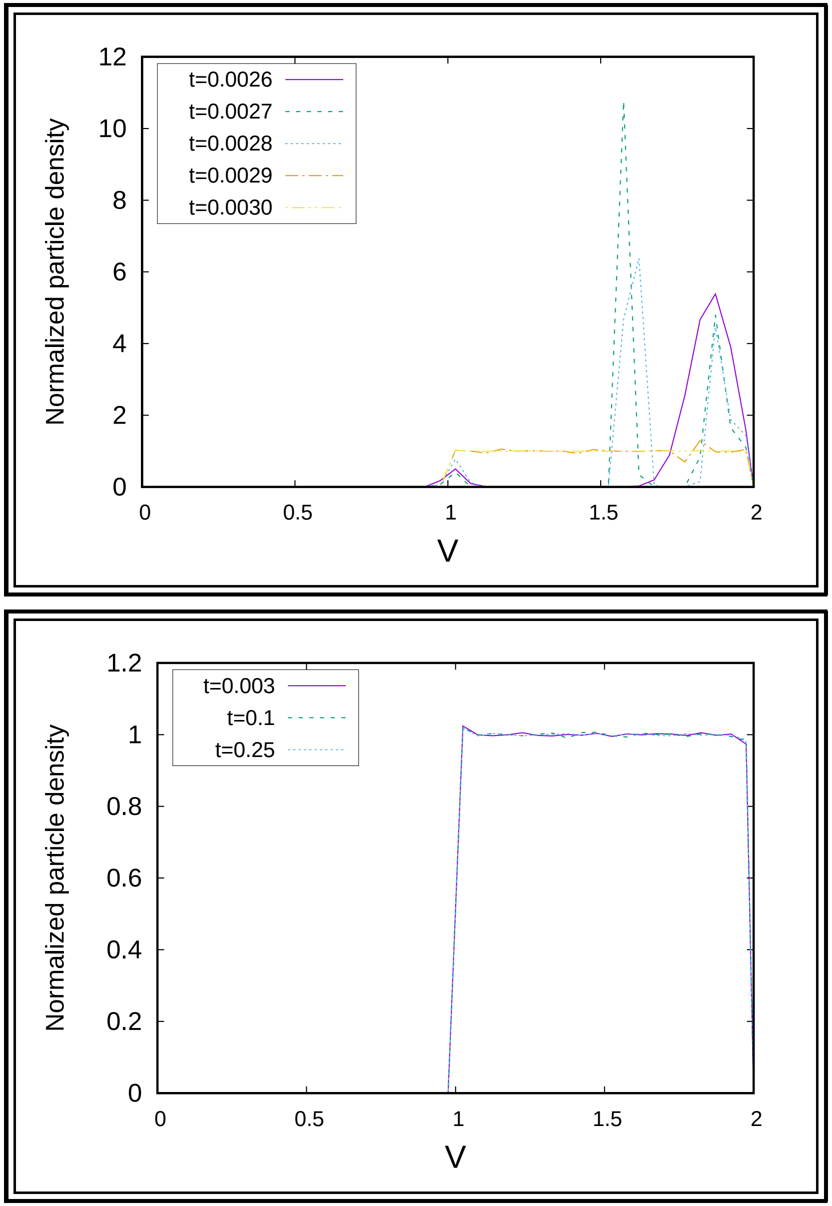


Trivial solutions appears depending on b

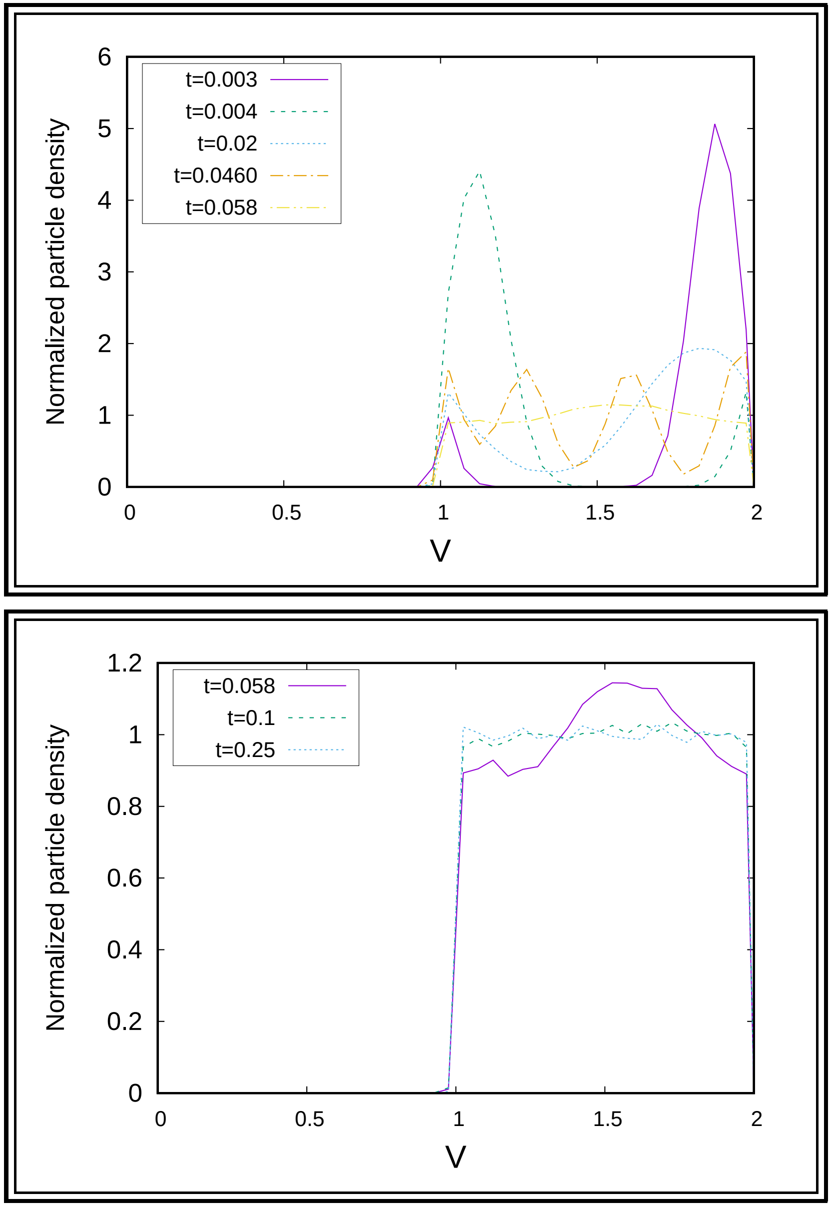
Under what situations do “plateau” states appear?

Particle system description:“Plateau” distributions

Limiting case: $b = V_F - V_R$ video



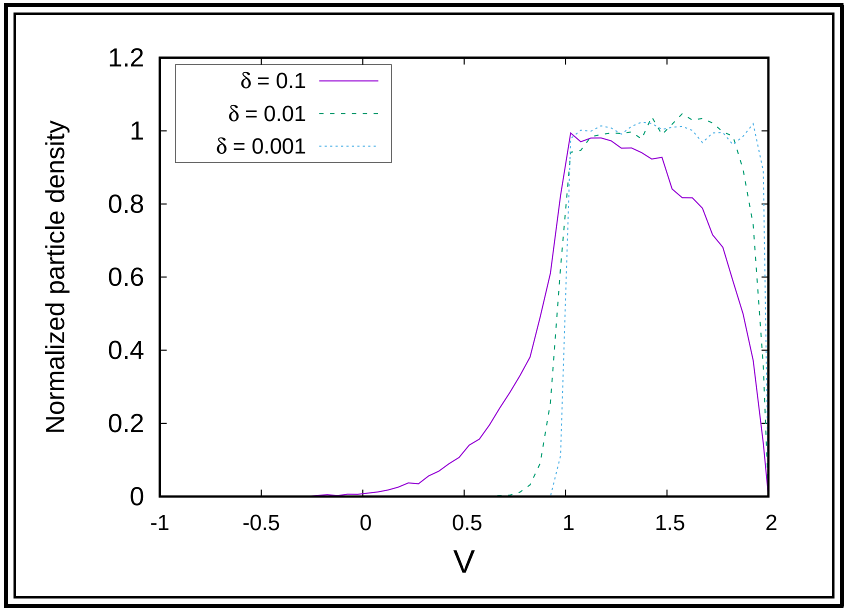
Without delay

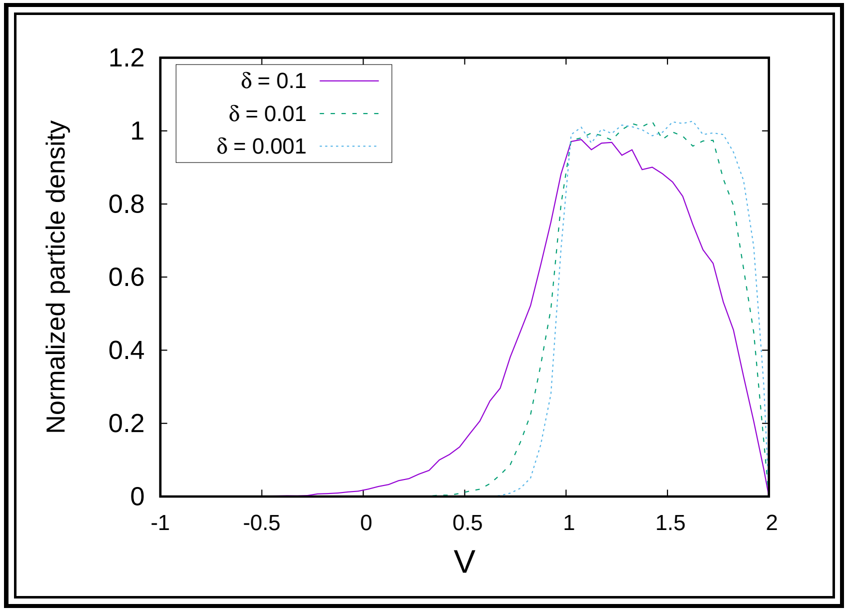


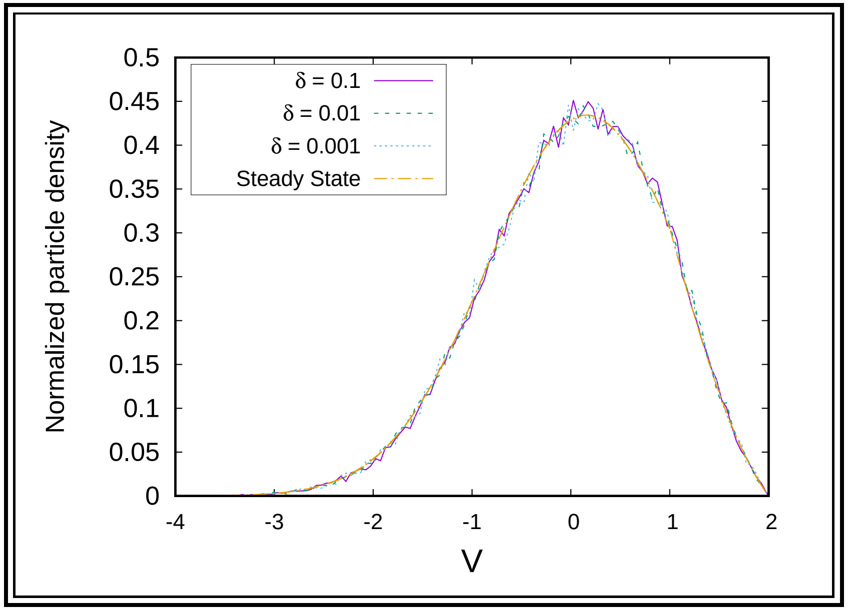
With very small delay=0.0001

Particle system description:"Plateau" distributions

"Plateau" states desappear for large delays if $b = V_F - V_R$

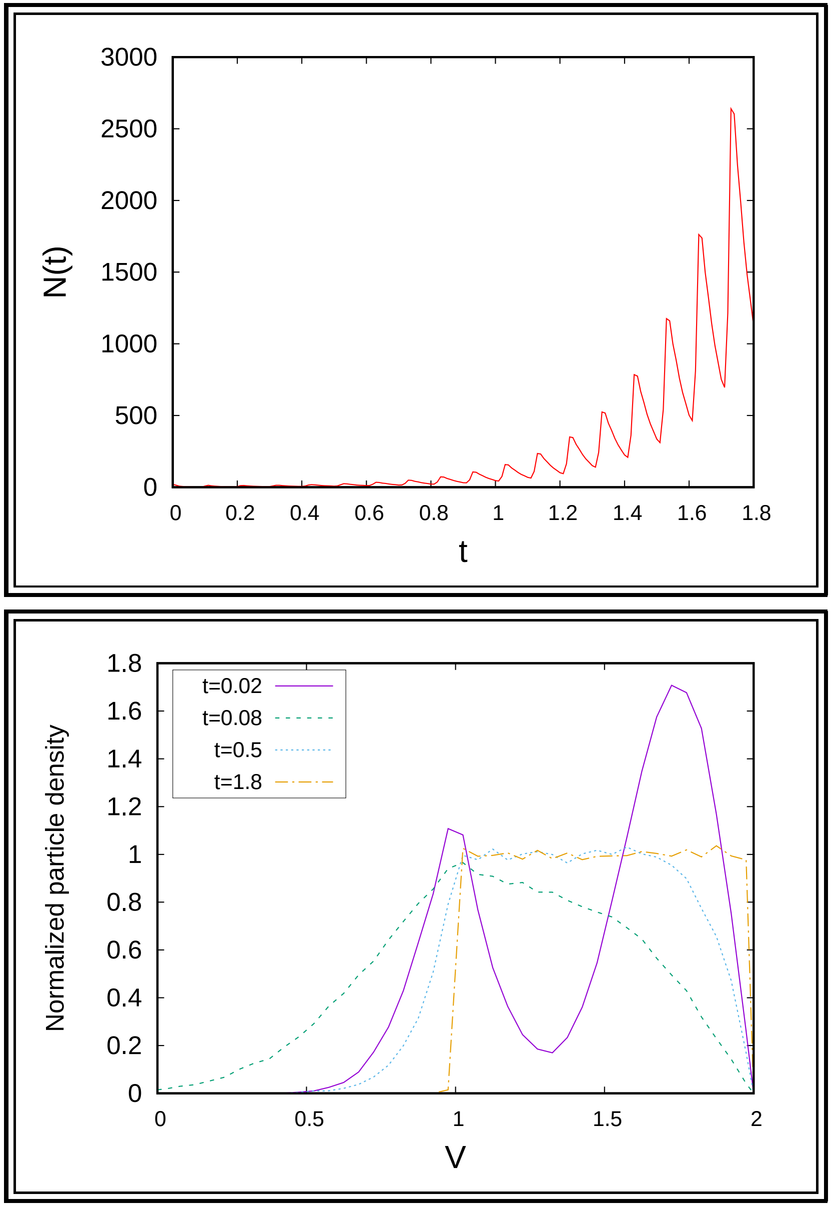




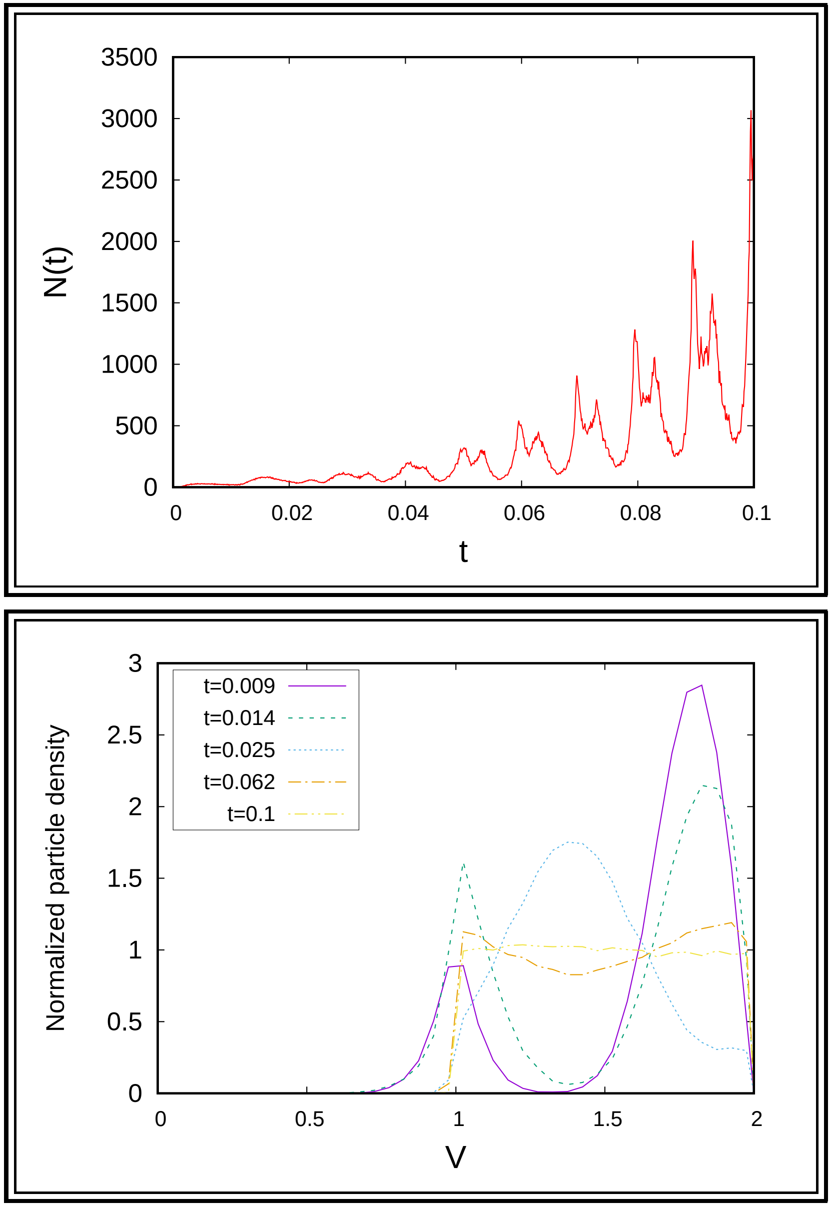


Particle system description:“Plateau” distributions

$b = 1.5 > V_F - V_R$ two steady states **with delay**



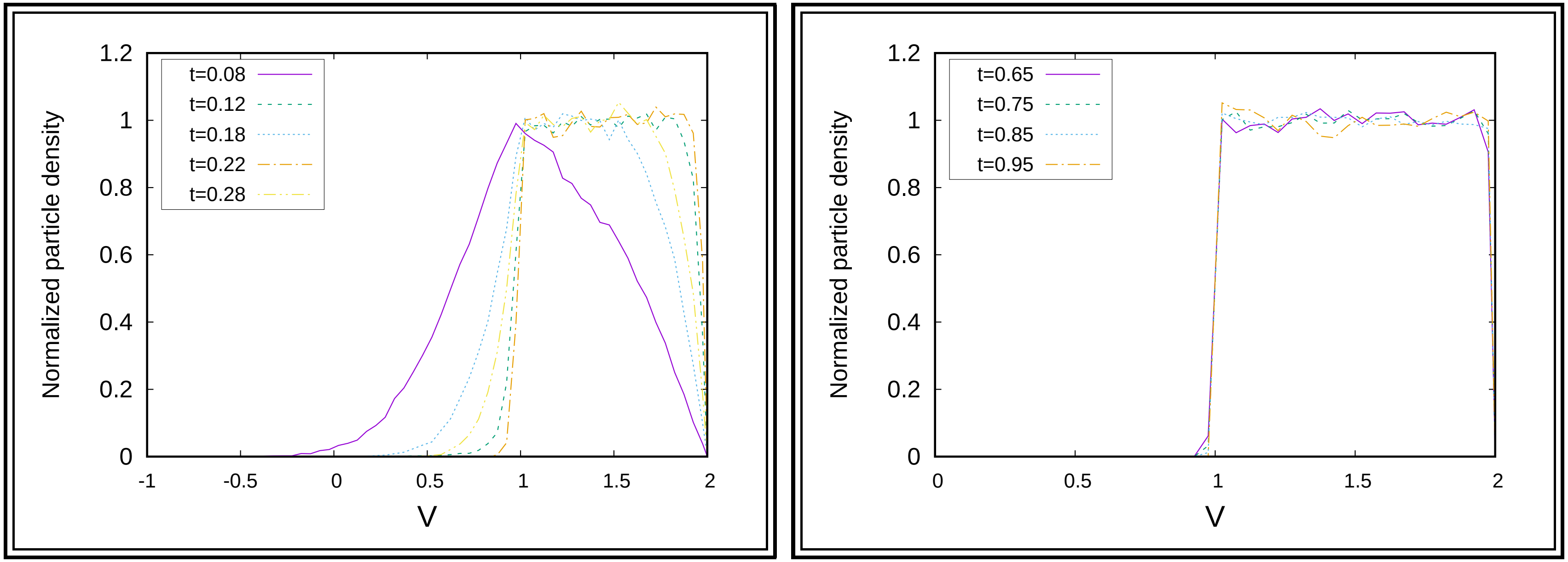
delay=0.1



delay=0.01

Particle system description:"Plateau" distributions

$b = 2.2 > V_F - V_R$ no steady states **with delay**



Numerical simulations show

The notion of physical solution make sense for weakly connected network ($b < V_F - V_R$), because neurons cannot fire more than once at the same time

What happens after system synchronization depends on the connectivity parameter b:

- Without delay:
  - ◇ $b < V_F - V_R$: the system is reset to V_R and tends to the steady state
  - ◇ $b > V_F - V_R$: the system collapse and tends to a “trivial” state.
  - ◇ $b = V_F - V_R$: the system tends to a “plateau” state.
- With delay:
  - ◇ $b > V_F - V_R$: System tends towards a “plateau” distribution, even when there are no steady states
  - ◇ $b = V_F - V_R$: System tends to a “plateau” state, unless the value of the delay is too large, in which case it tends to the steady state

Numerical simulations show

Therefore:

- **Physical solution tends to its unique steady state after blow-up**
- Limiting case $b = V_F - V_R$:
  - ◇ “Plateau” profile coincides with the stationary profile, with $N \to \infty$.
  - ◇ System tends to:
    - ○ a "plateau" distribution under blow-up situations, either without synaptic delay or with a very small delay value
    - ○ the stationary state for a high enough delay

Pseudo equilibria

Discrete description for system with **large transmission delay**

Quick simulations give accurate information about the NNLIF system

Pseudo equilibria: Motivation

$$\frac{\partial p}{\partial t}(v,t) + \frac{\partial}{\partial v}\left[(-v + bN(t-d))p(v,t)\right] - a\frac{\partial^2 p}{\partial v^2}(v,t) = \delta(v - V_R)N(t)$$

Steady states

$$\frac{\partial}{\partial v}\left[(-v + bN_\infty)p_\infty(v)\right] - a\frac{\partial^2 p_\infty}{\partial v^2}(v) = \delta(v - V_R)N_\infty$$

Using boundary conditions and conservation of mass

$$p_\infty(v) = \frac{N_\infty}{a} e^{-\frac{(v-b\,N_\infty)^2}{2a}} \int_{max(v,V_R)}^{V_F} e^{\frac{(w-b\,N_\infty)^2}{2a}} dw,$$

where $N_\infty = \frac{1}{I(N_\infty)}$ (Implicit equation for N_∞)

$$I(N) := a^{-1}\left(\int_{-\infty}^{V_F} e^{-\frac{(v-b\,N)^2}{2a}} \int_{max(v,V_R)}^{V_F} e^{\frac{(w-b\,N)^2}{2a}} dw dv\right)$$

Pseudo equilibria: Motivation

Steady states

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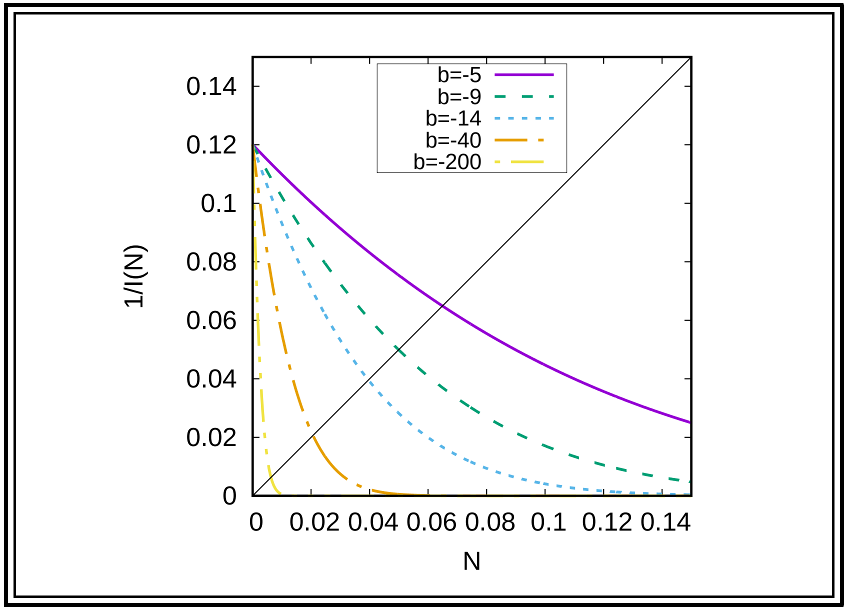
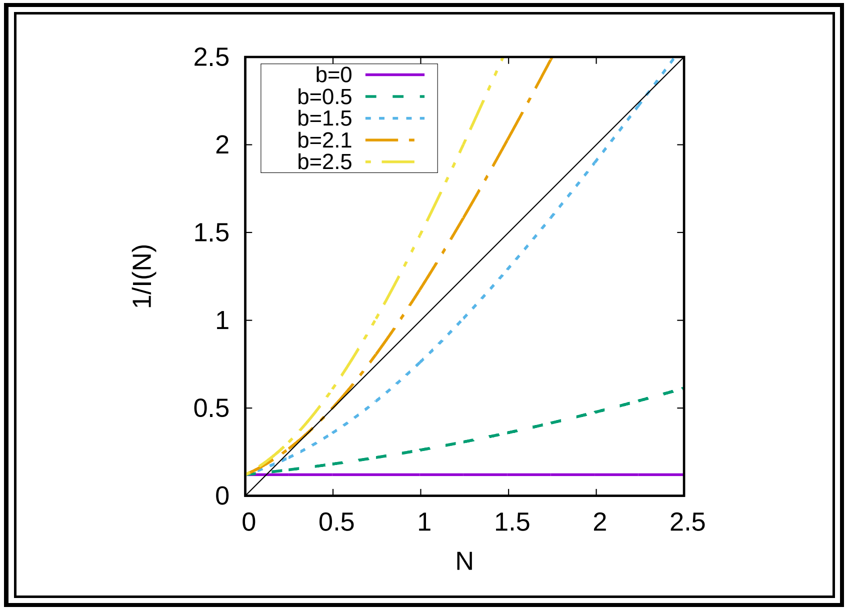




Inhibitory networks: a unique steady state

Excitatory networks: depending on the connectivity parameter b: one, two or none steady state

Pseudo equilibria: Motivation

Pseudo equilibria

$$p_N(v) = \frac{\tilde{N}_\infty}{a} e^{-\frac{(v-bN)^2}{2a}} \int_{max(v,V_R)}^{V_F} e^{\frac{(w-bN)^2}{2a}} dw, \quad N \in \mathbb{R}^+,$$

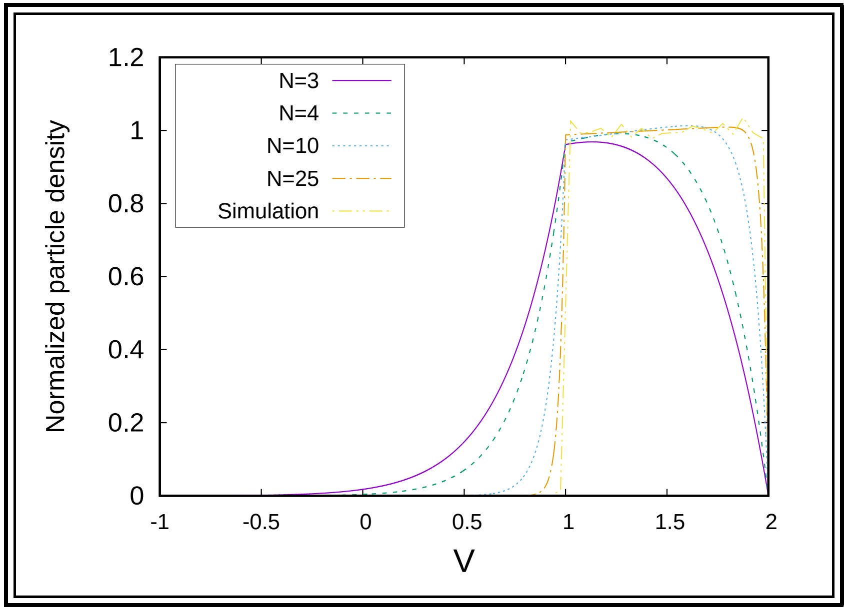
$$\tilde{N}_\infty = a\left(\int_{-\infty}^{V_F} e^{-\frac{(v-bN)^2}{2a}} \int_{max(v,V_R)}^{V_F} e^{\frac{(w-bN)^2}{2a}} dwdv\right)^{-1} = \frac{1}{I(N)}$$

This profile is the equilibrium of the linear equation with given N

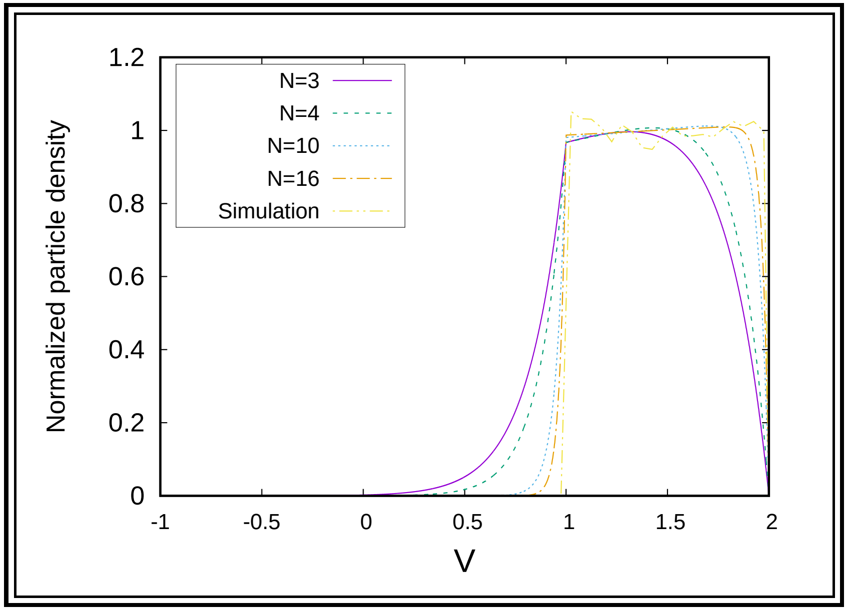
$$\frac{\partial p}{\partial t}(v,t) + \frac{\partial}{\partial v}\left[(-v+bN)p(v,t)\right] - a\frac{\partial^2 p}{\partial v^2}(v,t) = \delta(v-V_R)N(t)$$

Pseudo equilibria: Motivation

Plateau distributions of simulations coincide with pseudo equilibria, for N increasing.



$b = 1.5$



$b = 2.2$

Pseudo-equilibria sequences

Pseudo-equilibria sequence

(C-Cañizo-RamosLora, 2024)

- Firing rates sequence: Given $0 \leq N_0$

$$N_{0,\infty} := N_0 \quad \text{and} \quad N_{k+1,\infty} := \frac{1}{I(N_{k,\infty})} \quad k = 0, 1, 2, \ldots$$

(Recursive equation $N_{k+1,\infty} = f(N_{k,\infty})$ with $f(x) := \frac{1}{I(x)}$)

Remark: Given p_0 if $N_0 := -a\partial_v p_0(V_F)$ and $N_0 = N_\infty$ then $N_{k,\infty} = N_\infty$

- Pseudo-equilibria sequence:

$$p_{k,\infty}(v) = \frac{N_{k+1,\infty}}{a} e^{-\frac{\left(v-bN_{k,\infty}\right)^2}{2a}} \int_{max(v,V_R)}^{V_F} e^{\frac{\left(w-bN_{k,\infty}\right)^2}{2a}} dw.$$

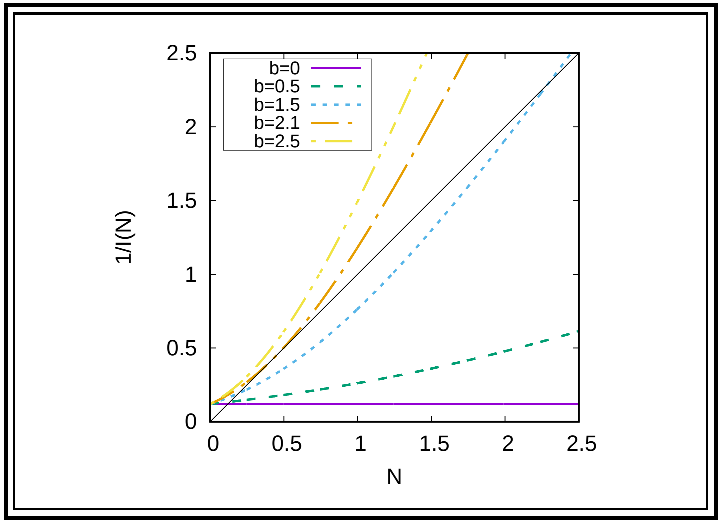
These sequences are independent of the Fokker-Planck equation and depend only on b, V_R, V_F

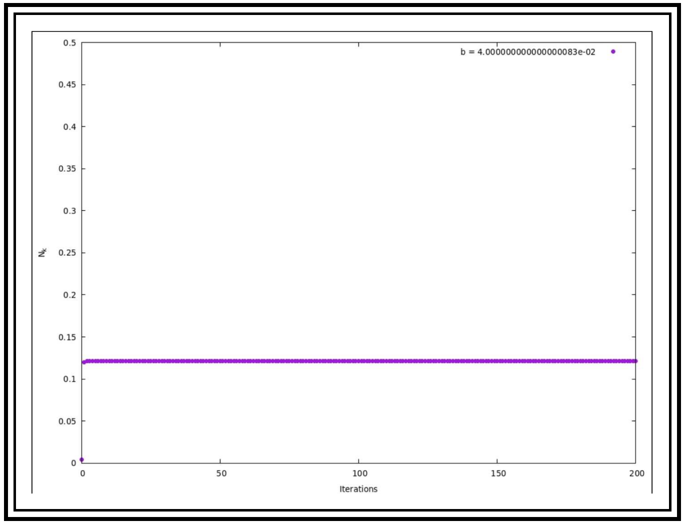
C-Cañizo-RamosLora,Phys. Rev. E 110 (2024)

Pseudo-equilibria sequences

$b > 0$: Monotony of $\{N_{k,\infty}\}_{k\geq 0}$

- If N^* is the only solution of $NI(N) = 1$ thus:
  - If $N^* \leq N_0$ then $\{N_{k,\infty}\}_{k\geq 0}$ is a decreasing sequence which tends to N^*
  - If $N_0 \leq N^*$ then $\{N_{k,\infty}\}_{k\geq 0}$ is a increasing sequence which tends to N^*
- If $NI(N) = 1$ has not solution then $\{N_{k,\infty}\}_{k\geq 0}$ diverges
- If $NI(N) = 1$ has two solutions: N_1^* and N_2^* ($N_1^* < N_2^*$), thus:
  - If $N_0 \leq N_1^*$ then $\{N_{k,\infty}\}_{k\geq 0}$ is a increasing sequence which tends to N_1^*
  - If $N_1^* \leq N_0 \leq N_2^*$ then $\{N_{k,\infty}\}_{k\geq 0}$ is a decreasing sequence which tends to N_1^*
  - If $N_2^* \leq N_0$ then $\{N_{k,\infty}\}_{k\geq 0}$ diverges





see the precise statement of the theorem in

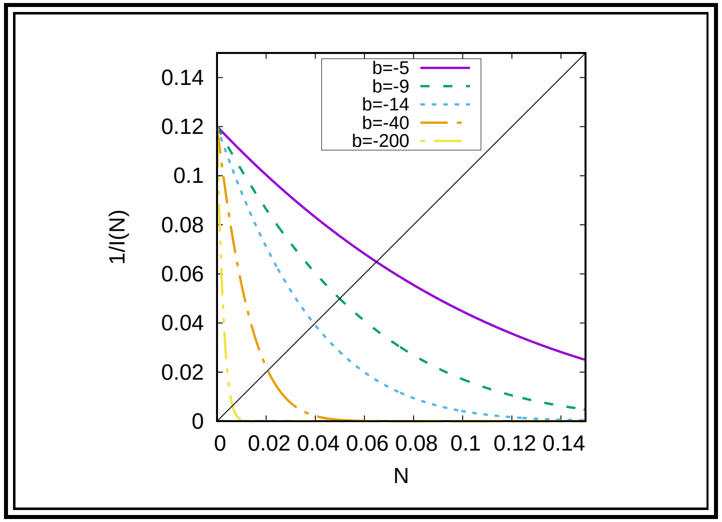
C-Cañizo-RamosLora,Phys. Rev. E 110 (2024)

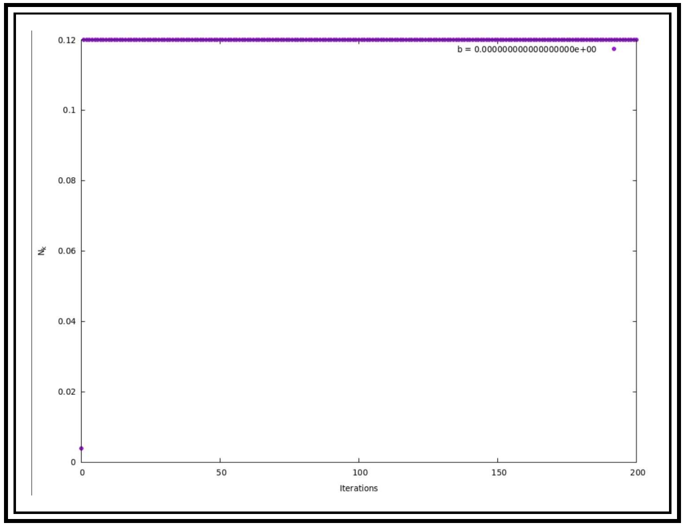
Pseudo-equilibria sequences

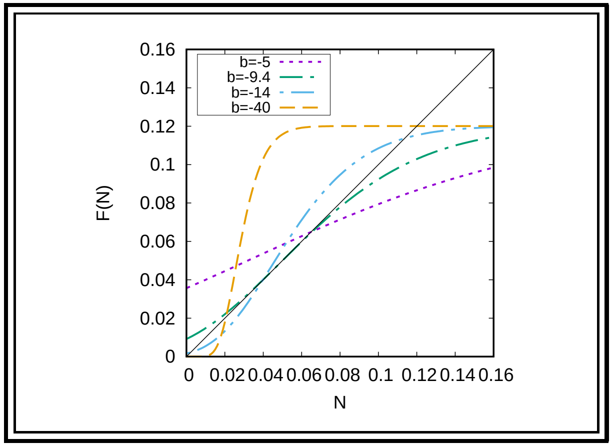
$b < 0$: Monotony of $\left\{N_{k,\infty}\right\}_{k\geq 0}$

There exists a value of the connectivity parameter b, $b^* < 0$, such that:

- If $b^* < b \leq 0$ the sequence $\left\{N_{k,\infty}\right\}_{k\geq 0}$ tends to the unique solution of $NI(N) = 1$
- If $b < b^*$, there exist two values N^-, N^+, $0 \leq N^- < N^+$, such that the sequence $\left\{N_{k,\infty}\right\}_{k\geq 0}$ tends to the 2-cycle $\{N^-, N^+\}$







The behaviour of $\{p_{k,\infty}(v)\}_{k\geq 0}$ is in **agreement with results of Ikeda-Roux-Salort-Smets, 2022**

$F = f \circ f$, $f(N) = 1/I(N)$

Pseudo equilibria and solutions to NNLIF

For **large delay**, the NNLIF equation evolves as the pseudo equilibrium sequence

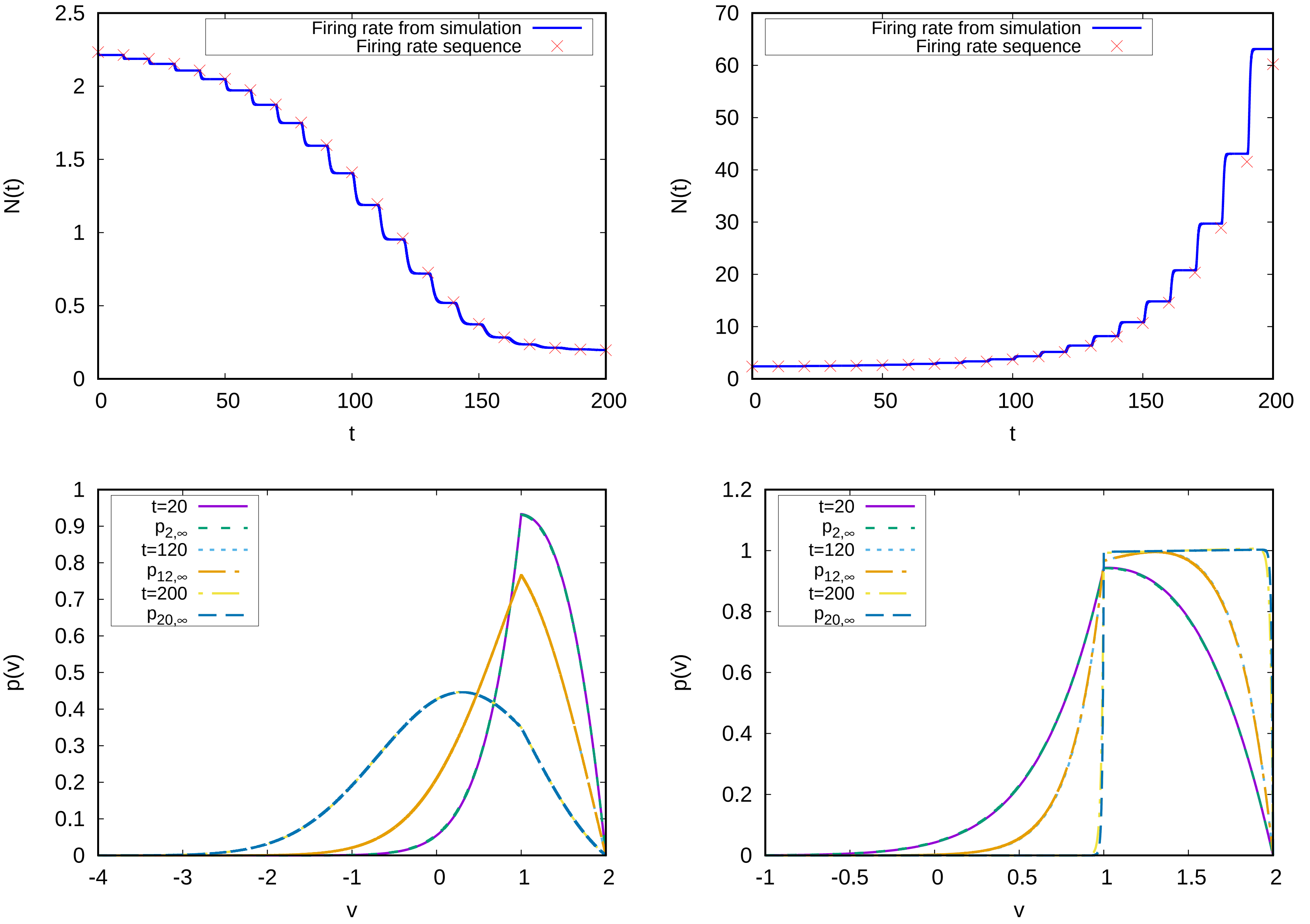
We observe numerically:

- $b > 0$:
  - A unique steady: system tends to it
  - Two steady states: system tends to the steady state with less firing rate or to a plateau distribution
  - Non steady states: system tends to a plateau distribution
- $b < 0$:
  - For $b* < b < 0$: system tends to the unique steady state
  - For $b < b* < 0$: system tends to a peridiodic solution (given by the solution initially with a pseudo equilibrium)

Some of these results can be proved analytically (see later slides)

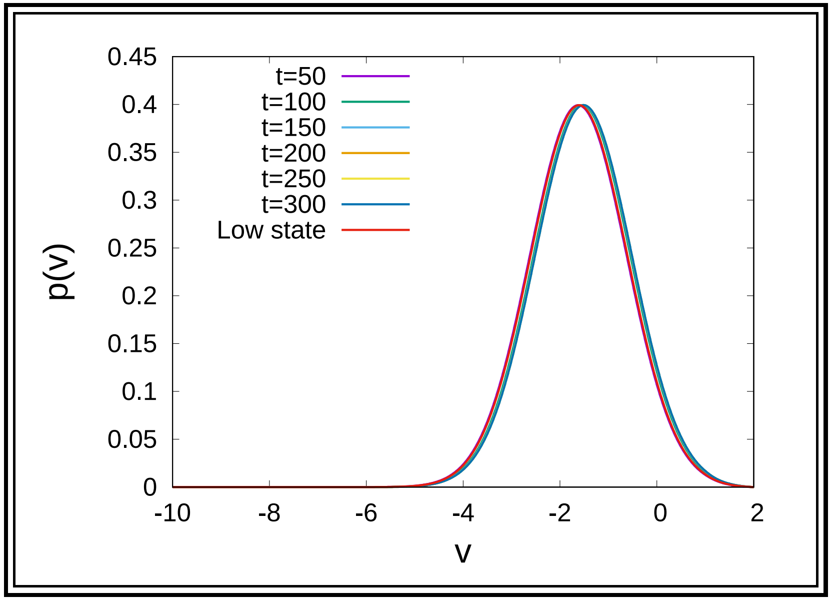
Pseudo equilibria and solutions to NNLIF

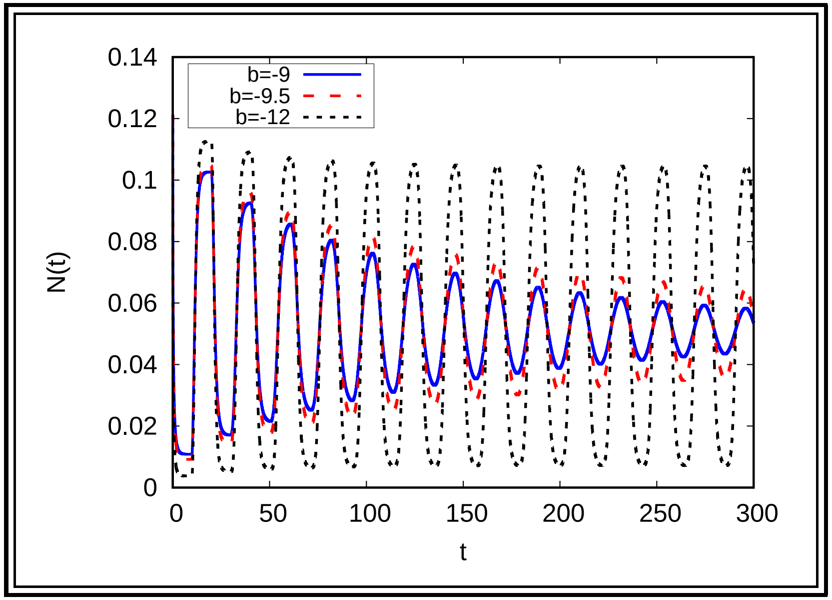
delay=10 b=1.5



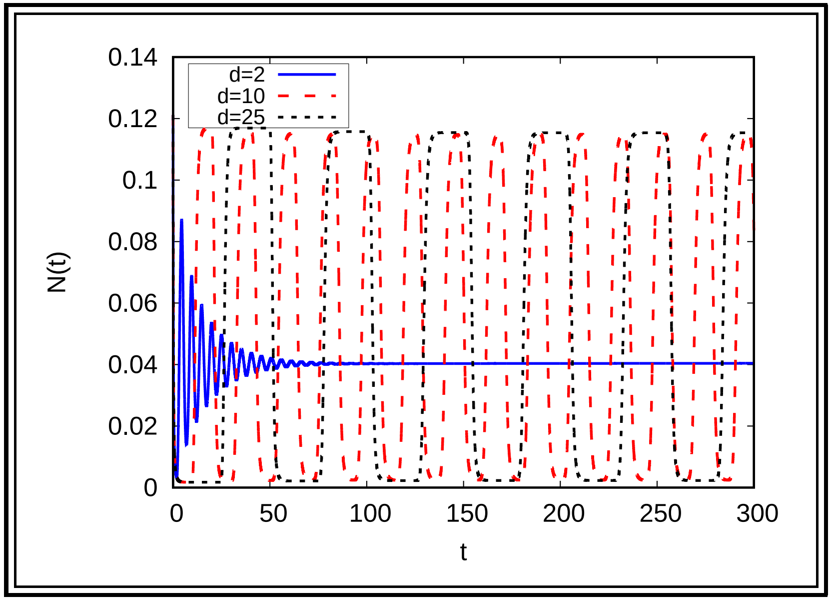
Pseudo equilibria and solutions to NNLIF

delay=25 b=-14





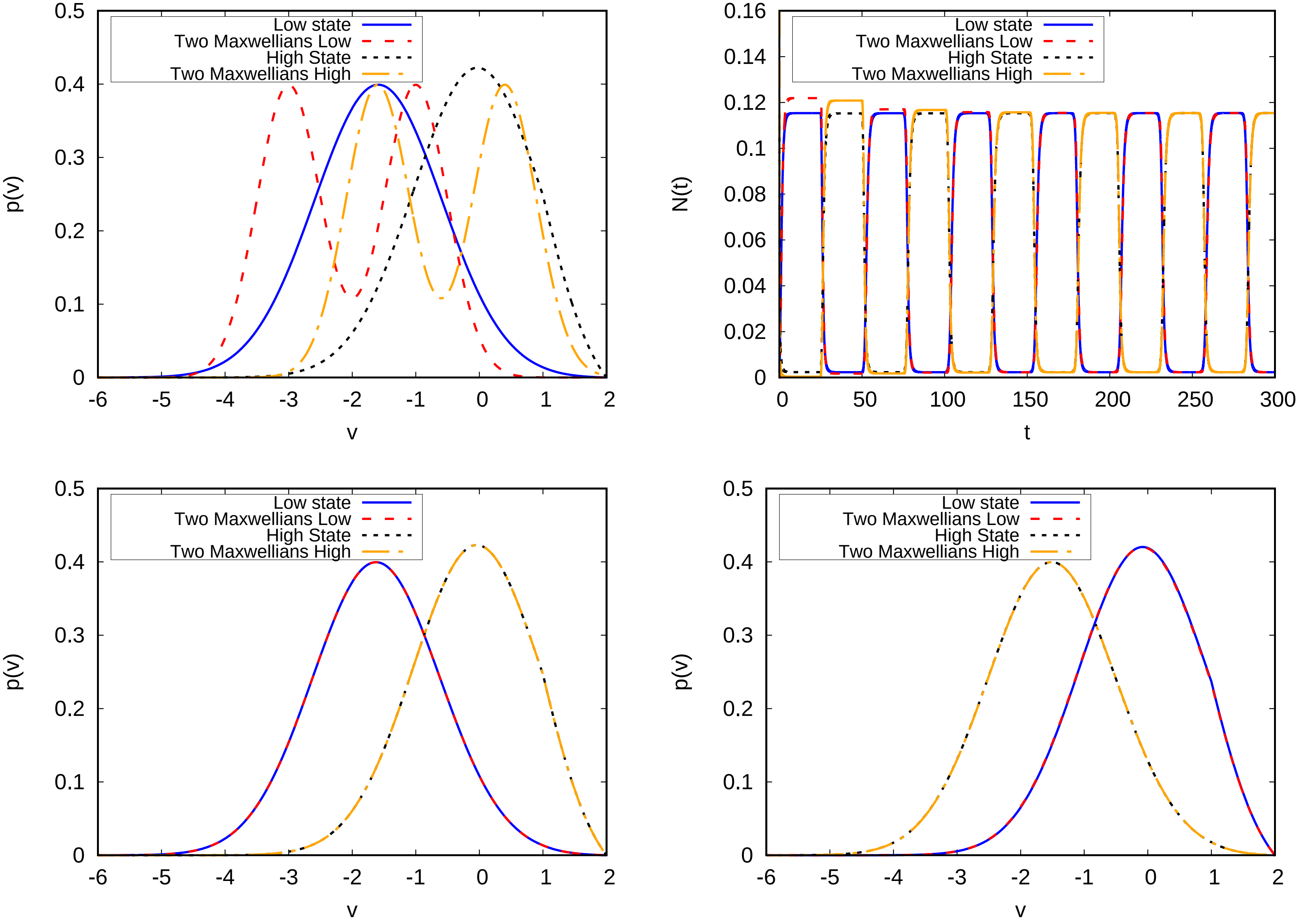
delay=10



$b = -14$

Pseudo equilibria and solutions to NNLIF

delay=25 b=-14



Convergence to a steady state

- Entropy method (quasi-linear case)
- New strategy without restrictions on the connectivity parameter

How to overcame |b| small?

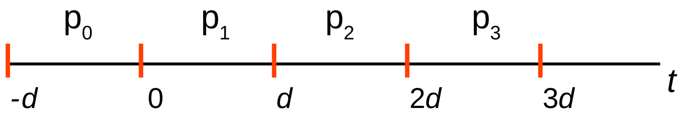
Different techniques

(C-Cañizo-RamosLora, 2024, 2025)

- Systems with **large delay**.

  Under technical assumptions:

  If $\{N_{k,\infty}\} \to N_\infty$, thus $||p(.,t) - p_\infty(.)||_X \leq Qe^{-\mu t}||p_0 - p_\infty||_X$ for all $t \geq 0$, $(Q, \mu > 0)$



Nonlinear system tends through the pseudo-equilibria sequence to the limit of the pseudo-equilibria sequence, which is p_∞

Only works for weakly connected networks (small $|b|$)

Technical difficulties!

Numerical simulations show that this is also true for large b: Global behaviour

C-Cañizo-RamosLora,Phys. Rev. E 110 (2024)

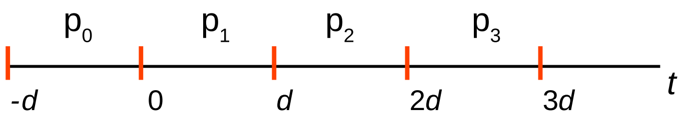
Different techniques

(C-Cañizo-RamosLora, 2024, 2025)

- Systems with **large delay**.

  Under technical assumptions:

  If $\{N_{k,\infty}\} \to N_\infty$, thus $\|p(.,t) - p_\infty(.)\|_X \le Qe^{-\mu t}\|p_0 - p_\infty\|_X$ for all $t \ge 0$, $(Q, \mu > 0)$

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  Only works for weakly connected networks (small $|b|$)

  Technical difficulties!

  Numerical simulations show that this is also true for large b: Global behaviour

  C-Cañizo-RamosLora,Phys. Rev. E 110 (2024)

- Local stability through linearization

  Works for general connectivity strength with and without delay

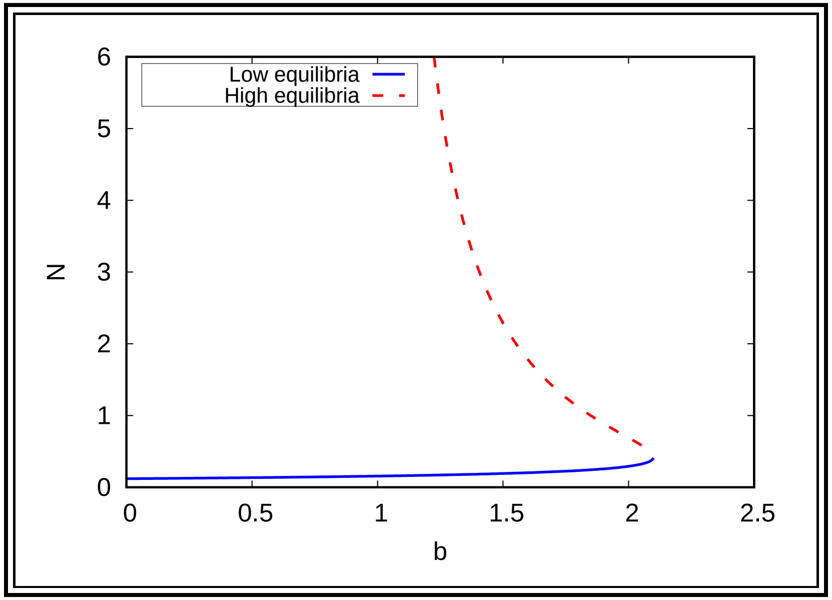
  Stability/unstability map in terms of b and d (at least numerically)

  Even without any delay some connections with firing rate sequences!!

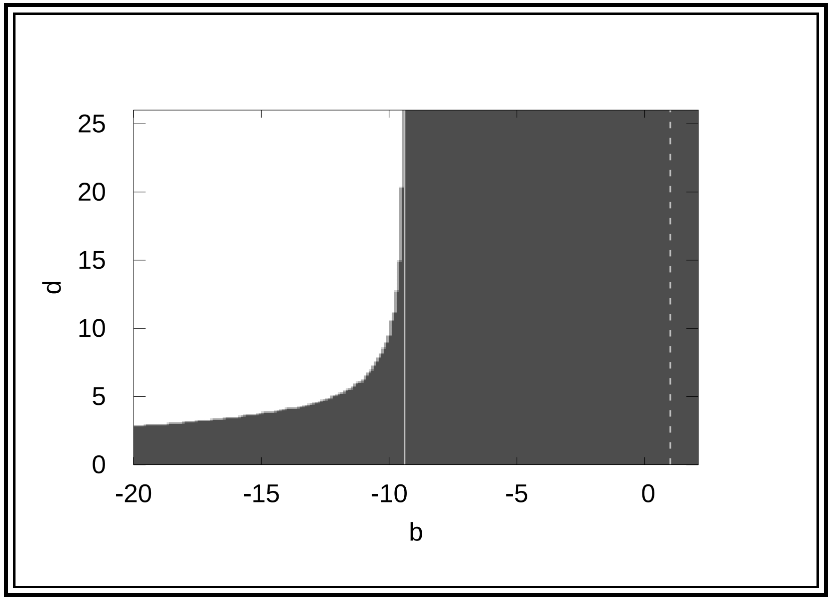
  C-Cañizo-RamosLora,Commun. Math. Phys. Vol 406, (2025)

Different techniques

(C-Cañizo-RamosLora, 2025)



Value of the stationary firing rate ($b > 0$) (for $b < 0$ there is only one equilibrium)



Stability map of the linearized equation, stability (dark) or instability (white)

Summary about the simplest NNLIF

- The **sign** of the connectivity parameter b describes if the network is
  - average-excitatory (b>0)
  - average-inhibitory (b<0)
- **Existence of solutions**
  - Inhibitory case: Global existence
  - Excitatory case: Local existence
    - **Blow-up** phenomena
    - If **delay** transmission is included there is **global existence**
- **Stationary solutions**
  - Inhibitory case: A unique steady states
  - Excitatory case:
    - b small a unique steady states
    - b large non steady states
    - Intermediate values of b: at least one or at least two

Summary about the simplest NNLIF

Pseudo equilibria

- Large-delay NNLIF models can be approximated by a discrete sequence of pseudo equilibrium sequence
- Quick simulations give accurate information about the NNLIF system
- Periodic solutions appear for strongly inhibitory systems with large delay
- For excitatory systems with large delay bistability phenomenon appears between the steady state with less firing rate and a plateau distribution

Summary about the simplest NNLIF

Two different methods to prove convergence to equilibrium

- Entropy dissipation method:
  - $|b|$ small is required to control the term without sign
- Strong norm + spectral gap for linear equations
  - New strategy
  - Applied without restriction on b
  - Surprising link with pseudo equilibria
  - Open question Does it work for plateau distributions and periodic solutions (inhibitory case)?
  - It works for other models

Open question How to prove the convergence to periodic solutions? see works of Roux-Salort and collaborators

Extensions of NNLIF

- Refractory state
- Randomness on the discharge potential
- Network consisting of excitatory and inhibitory neurons, as different populations
- Network consisting of excitatory and inhibitory neurons with delay and refractory states
- Nonlinear Fokker-Planck including conductance

Course summary

- A few mathematical models which describe the activity of neural networks by means of the membrane potential
  - ODE models:
    - Hodgkin-Huxley model
    - Morris-Lecar model
    - FitzHugh-Nagumo model
    - Integrate-and-fire model

Course summary

- A few mathematical models which describe the activity of neural networks by means of the membrane potential
  - ◇ ODE models
  - ◇ PDE models:
    - ○ Nonlinear Noisy Leaky Integrate and Fire (NNLIF): $\rho(t,v)$, $\rho_E(t,v)$, $\rho_I(t,v)$, $R_E(t)$, $R_I(t)$
    - ○ Nonlinear Fokker-Planck including conductance: $\rho(t,v,g)$
    - ○ Age-structured partial differential equations $\rho(t,s)$

$$\begin{cases} \partial_t \rho(t,a) + \partial_a \rho(t,a) + S(a,X(t))\rho(t,a) = 0 & \\ \rho(t,a=0) = N(t) := \int_0^\infty S(a,X(t))\rho(t,a)\,da & t > 0, \\ \rho(t=0,a) = \rho^0(a) & a > 0, \end{cases}$$

    - ○ Different past network activity:
      - · $X(t) = JN(t)$
      - · $X(t) = JN(t-d)$
      - · $X(t) = J\int_0^\infty \alpha(s)N(t-s)\,ds$ with $\int_0^\infty \alpha(s)\,ds = 1$ and $\alpha(\cdot) \geq 0$
    - ○ $J \geq 0$ is the strength of interconnections

Course summary

- A few mathematical models which describe the activity of neural networks by means of the membrane potential
  - ODE models
  - PDE models

- Results related with neurophysiological phenomena

- **Math issues**:
  - Steady states
  - Local/global existence - Blow-up phenomenon
  - Long time behaviour

Thank you very much for your attention

(and for using your neurons for it!)

We keep in touch (caceres@ugr.es)

Blow-up: Proof

We choose $\phi(v) = e^{\mu v}$ with $\mu > \max(\frac{V_F}{a_m}, \frac{1}{b})$, then a weak solution satisfies

Blow-up: Proof

We choose $\phi(v) = e^{\mu v}$ with $\mu > \max(\frac{V_F}{a_m}, \frac{1}{b})$, then a weak solution satisfies

$$\frac{d}{dt}\int_{-\infty}^{V_F} \phi(v)p(v,t)\,dv \geq \mu \int_{-\infty}^{V_F} (bN(t) - v)\phi(v)p(v,t)\,dv$$

$$+\mu^2 a_m \int_{-\infty}^{V_F} \phi(v)p(v,t)\,dv + N(t)\Big(\phi(V_R) - \phi(V_F)\Big)$$

Blow-up: Proof

We choose $\phi(v) = e^{\mu v}$ with $\mu > \max(\frac{V_F}{a_m}, \frac{1}{b})$, then a weak solution satisfies

$$\frac{d}{dt}\int_{-\infty}^{V_F} \phi(v)p(v,t)\,dv \geq \mu[bN(t) + \underbrace{\mu a_m - V_F}_{>0}] \int_{-\infty}^{V_F} \phi(v)p(v,t)\,dv$$

$$-N(t)\phi(V_F)$$

Blow-up: Proof

We choose $\phi(v) = e^{\mu v}$ with $\mu > \max(\frac{V_F}{a_m}, \frac{1}{b})$, then a weak solution satisfies

$$\frac{d}{dt}\underbrace{\int_{-\infty}^{V_F} \phi(v)p(v,t)\,dv}_{M_\mu(t)} \geq \mu[bN(t) + \underbrace{\mu a_m - V_F}_{>0}]\underbrace{\int_{-\infty}^{V_F} \phi(v)p(v,t)\,dv}_{M_\mu(t)}$$

$$-N(t)\phi(V_F)$$

Blow-up: Proof

We choose $\phi(v) = e^{\mu v}$ with $\mu > \max(\frac{V_F}{a_m}, \frac{1}{b})$, then a weak solution satisfies

$$\frac{d}{dt}M_\mu(t) \geq \mu[bN(t) + \mu a_m - V_F]\,M_\mu(t)$$

$$-N(t)\phi(V_F)$$

Blow-up: Proof

We choose $\phi(v) = e^{\mu v}$ with $\mu > \max(\frac{V_F}{a_m}, \frac{1}{b})$, then a weak solution satisfies

$$\frac{d}{dt} M_\mu(t) \geq \mu \left[bN(t) + \mu a_m - V_F \right] M_\mu(t)$$

$$-N(t)\phi(V_F)$$

and by Gronwall's lemma:

$$M_\mu(t) \geq e^{\mu \int_0^t (bN(s)+\mu a_m - V_F)\, ds} \left(M_\mu(0) - \phi(V_F) \int_0^t N(s) e^{-\mu \int_0^s (bN(z)+\mu a_m - V_F)\, dz}\, ds \right)$$

Blow-up: Proof

We choose $\phi(v) = e^{\mu v}$ with $\mu > \max(\frac{V_F}{a_m}, \frac{1}{b})$, then a weak solution satisfies

$$\frac{d}{dt} M_\mu(t) \geq \mu[bN(t) + \mu a_m - V_F]\, M_\mu(t)$$

$$-N(t)\phi(V_F)$$

and by Gronwall's lemma:

$$M_\mu(t) \geq e^{\mu \int_0^t (bN(s)+\mu a_m - V_F)\, ds} \left(M_\mu(0) - \frac{\phi(V_F)}{\mu b} \right)$$

Blow-up: Proof

We choose $\phi(v) = e^{\mu v}$ with $\mu > \max(\frac{V_F}{a_m}, \frac{1}{b})$, then a weak solution satisfies

$M_\mu(t) \geq K e^{\mu(\mu a_m - V_F)t}$ with $\mu(\mu a_m - V_F) > 0$
and $K > 0$ is we assume the initial data such that
$K := \left(M_\mu(0) - \frac{\phi(V_F)}{\mu b}\right) > 0$

But since $p(v,t)$ is a probability density,
$\int_{-\infty}^{V_F} p(v,t)\, dv = \int_{-\infty}^{V_F} p^0(v)\, dv = 1$, and $\mu > 0$ then

$$M_\mu(t) = \int_{-\infty}^{V_F} \phi(v) p(v,t)\, dv \leq e^{\mu V_F},$$

leading to a contradiction

(return)

Notion of solution

A pair of nonnegative functions (p, N) with $p \in L^{\infty}\left(\mathbb{R}^{+}; L^{1}_{+}(-\infty, V_F)\right)$, $N \in L^{1}_{\mathrm{loc},+}(\mathbb{R}^{+})$ is a weak solution if for any test function $\phi(v,t) \in C^{\infty}((-\infty, V_F] \times [0,T])$ such that $\frac{\partial^2 \phi}{\partial v^2}$, $v\frac{\partial \phi}{\partial v} \in L^{\infty}((-\infty, V_F) \times (0,T))$, we have

$$\int_0^T \int_{-\infty}^{V_F} p(v,t)\left[-\frac{\partial \phi}{\partial t} - \frac{\partial \phi}{\partial v} h(v,N) - a\frac{\partial^2 \phi}{\partial v^2}\right] dv\, dt =$$

$$\int_0^T N(t)[\phi(V_R,t) - \phi(V_F,t)]\, dt +$$

$$\int_{-\infty}^{V_F} p^0(v)\phi(0,v)\, dv - \int_{-\infty}^{V_F} p(v,T)\phi(T,v)\, dv.$$

(return)

Notion of solution

- By choosing test functions: $\psi(t)\phi(v)$ where
  $\phi(v) \in C^\infty((-\infty, V_F]),\ v\frac{\partial \phi}{\partial v}, \frac{\partial^2 \phi}{\partial v^2} \in L^\infty((-\infty, V_F)),$

  $$\frac{d}{dt}\int_{-\infty}^{V_F} \phi(v)p(v,t)dv = \int_{-\infty}^{V_F} \left[\frac{\partial \phi}{\partial v}h(v,N) + a\frac{\partial^2 \phi}{\partial v^2}\right] p(v,t)dv$$

  $$+N(t)[\phi(V_R) - \phi(V_F)]$$

  holds in the distributional sense

- $\phi \equiv 1 \Longrightarrow \int_{-\infty}^{V_F} p(v,t)\, dv = \int_{-\infty}^{V_F} p^0(v)\, dv = 1$

(return)

Rewriting as a Stefan like problem

(Rescale the variables, in order to have $a = 1$ and $V_F = 0$)

First change of variables: (Classical change to transform the linear Fokker-Planck into a heat equation, see *Carrillo-Toscani, Ind. Univ. Math. Jour. (2000)*)

$$y = e^t v, \quad \tau = \frac{1}{2}(e^{2t} - 1)$$

Define

$$w(y,\tau) = \alpha(\tau) p(y\alpha(\tau), -\log(\alpha(\tau)))$$

and $\underbrace{M(\tau) = N(t)\alpha^2(\tau)}_{\text{firing rate in new variables}}$ where $\alpha(\tau) = (\sqrt{2\tau + 1})^{-1}$

Second change of variables:

$$x = y - \int_0^\tau \mu(t-d)\alpha(s)\, ds \quad \mu(t) := b_0 + bN(t)$$

Define $u(x,\tau) = w\left(x + \int_0^\tau \mu(t-d)\alpha(s)\, ds, \tau\right)$

Carrillo-González-Gualdani-Schonbek, Comm. in PDEs, Vol. 38(3), 385-409, (2013) for $d = 0$

Rewriting as a Stefan like problem

Thus we obtain for $\tau > 0$, $x < s(\tau)$:

$$\begin{cases} u_t(x,\tau) = u_{xx}(x,\tau) + M(t)\delta(x - s_1(\tau)), \\ s_1(\tau) = s(\tau) + \frac{V_R}{\alpha(\tau)}, \\ s(\tau) = -b_0(\sqrt{2\tau+1} - 1) - \boldsymbol{b \int_0^\tau N(t-d)\alpha(s)ds}, \\ M(\tau) = -u_x(s(\tau),\tau), \\ N(t) = N(0), & t \in (-d, 0], \\ u(-\infty,\tau) = u(s(\tau),\tau) = 0, \\ u(x,0) = u_0(x), & x < 0, \end{cases}$$

where $d > 0$ and $\alpha(\tau) = \frac{1}{\sqrt{2\tau+1}}$

Rewriting as a Stefan like problem

Handling the delay we obtain the equivalent system

$$\begin{cases} u_t(x,t) = u_{xx}(x,t) + M(t)\delta(x - s_1(t)), \\ s_1(t) = s(t) + \frac{V_R}{\alpha(t)}, \\ s(t) = -b_0(\sqrt{2t+1} - 1) - \frac{b}{\sqrt{1-\hat{d}}} \int_{-\frac{1}{2}\hat{d}}^{(1-\hat{d})t - \frac{1}{2}\hat{d}} M(s)\alpha^{-1}(s)ds, \\ M(t) = -u_x(s(t),t), \\ M(t) = M(0), & t \in (-\hat{d}, 0], \\ u(-\infty, t) = u(s(t),t) = 0, \\ u(x,0) = u_0(x), & x < 0, \end{cases}$$

where $\hat{d} = (1 - e^{-2d}) \in [0,1)$ and $\alpha(t) = \frac{1}{\sqrt{2t+1}}$.

(return)

Integral formulation

$$M(t) = -2\int_{-\infty}^{0} G(s(t), t, \xi, 0)u_0'(\xi)d\xi$$

$$+2\int_0^t M(\tau)G_x(s(t), t, s(\tau), \tau)d\tau - 2\int_0^t M(\tau)G_x(s(t), t, s_1(\tau), \tau)d\tau,$$

where G is the Green's function for the heat equation on the real line $G(x, t, \xi, \tau) = \frac{1}{\sqrt{4\pi(t-\tau)}}e^{-\frac{|x-\xi|^2}{4(t-\tau)}}$ and satisfies the **Green identity**

$$\frac{\partial}{\partial\xi}\left(G\frac{\partial u}{\partial\xi} - u\frac{\partial G}{\partial\xi}\right) - \frac{\partial}{\partial\tau}(Gu) = 0$$

(return)

Local existence

With a fixed point argument and the integral formulation of M:

Theorem (C-Roux-Salort-Schneider) [Local existence]
Let $u_0(x)$ be a non-negative function in $C^0((-\infty,0]) \cap C^1((-\infty,V_R)\cup(V_R,0]) \cap L^1((-\infty,0))$ such that $u_0(0)=0$.
Suppose u_0, $(u_0)_x$ decay to zero as $x \to -\infty$ and that the left and right derivatives at V_R are finite.
Then there exists a time $T>0$ such that $M(t)$ defined by the integral formulation exists for $t \in [0,T]$ and is unique in $C^0([0,T])$.
The existence time T satisfies

$$T \le \left(\sup_{x\in(-\infty,V_R)\cup(V_R,0]} |u_0'(x)| \right)^{-1}.$$

Local existence

And as a **corollary**
There exists a unique solution of the Stefan like problem for $t \in [0,T]$

Proof. Once M is known the equation for u decouples, and u can be calculated via the Duhamel's formula

$$\begin{aligned} u(x,t) &= \int_{-\infty}^{V_R} G(x,t,\xi,0)u_0(\xi)\,d\xi + \int_{V_R}^{0} G(x,t,\xi,0)u_0(\xi)\,d\xi \\ &\quad - \int_0^t M(\tau)G(x,t,s(\tau)\tau)\,d\tau + \int_0^t M(\tau)G(x,t,s_1(\tau)\tau)\,d\tau. \end{aligned}$$

Finally, the local existence theorem is translated into the NNLIF equation, since ρ and N are recovered **undoing the changes of variables**

(return)

Super solution

Let $T \in \mathbb{R}_+$, $d \geq 0$ $(\bar{\rho},\bar{N})$ is said to be a (classical) super solution to the delayed NNLIF model on $(-\infty, V_F] \times [0, T]$ if for all $t \in [0, T]$ we have $\bar{\rho}(V_F, t) = 0$ and

$$\partial_t \bar{\rho} + \partial_v[(-v + b\bar{N}(t-d))\bar{\rho}] - a\partial_{vv}\bar{\rho} \geq \delta_{v=V_R}\bar{N}(t),$$

$$\bar{N}(t) = -a\partial_v \bar{\rho}(V_F, t),$$

on $(-\infty, V_F] \times [0, T]$ in the distributional sense and on $((-\infty, V_F] \setminus V_R) \times [0, T]$ in the classical sense, with arbitrary values for $\bar{N}$ on $[-d, 0)$

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$$\bar N(t) = -a\partial_v \bar\rho(V_F,t),$$

on $(-\infty, V_F] \times [0,T]$ in the distributional sense and on $((-\infty, V_F] \setminus V_R) \times [0,T]$ in the classical sense, with arbitrary values for $\bar N$ on $[-d,0)$

We consider super solution $\bar\rho$ on $[0,d]$ of the form

$$\bar\rho(v,t) = e^{\xi t} f(v),$$

where ξ is large enough and f is a carefully selected function.

Super solution

Comparison principle

Let (p, N) *be a solution of the NNLIF model on* $(-\infty, V_F] \times [0, T]$ *for the initial condition* (p_0, N_0) *and* $(\bar{p}, \bar{N})$ *be a super-solution* $(-\infty, V_F] \times [0, T]$. *Assume that* $\forall\, v \in (-\infty, V_F]$, $\bar{p}(v, 0) \geq p_0(v)$ *and* $\forall t \in [-d, 0)$, $\bar{N}(t) = N_0(t)$. *Then*

$$\forall (v, t) \in (-\infty, V_F] \times [0, T],\ \bar{p}(v, t) \geq p(v, t) \quad \textit{and}\ \bar{N}(t) \geq N(t)$$

And we find a contradiction if we assume that the firing rate explodes in a finite time

(return)