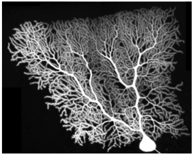
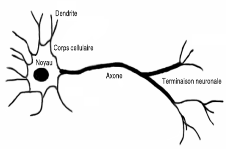
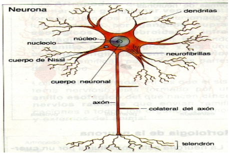
Fom voltage-conductance kinetic models

to integrate&fire equation for neural assemblies

Benoît Perthame







FRAMEWORK

General picture of 'statistical physics'

MACROSCOPIC/FLUID

$$\begin{cases} \frac{\partial}{\partial t} n + \mathrm{div}(nu) = 0 \\ \frac{\partial}{\partial t} nu + \mathrm{div}(nu \times u) + \nabla p = nF(x), \end{cases}$$

KINETIC/DILUTE GAS $\kappa \to 0$

$$\underbrace{\frac{\partial}{\partial t} f(x,\xi,t) + \xi.\nabla_x f}_{\text{Transport with velocity } \xi} + \underbrace{\mathrm{div}_v(F(x,v)f)}_{\text{Forces}} = \underbrace{\Delta_v f}_{\text{Fluctuations}}$$

PARTICLE SCALE $N \to \infty$

$$\begin{cases} \frac{d}{dt} X_i(t) = V_i(t), \qquad 1 \leq i \leq N, \\ \frac{d}{dt} V_i(t) = F\big(X(t), V(t)\big) \end{cases}$$

OUTLINE OF THE LECTURE

I. Single neurones dynamics

II. The nonlinear Noisy Integrate and Fire model

III. The voltage-conductance kinetic system for I&F

IV. The fast conductance limit

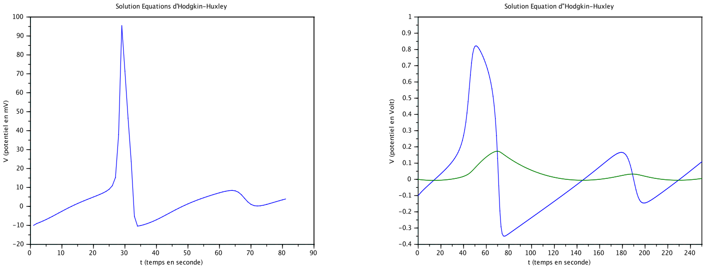
Single neurone dynamics

Standard models of **action potential**

Morris-Lecar
$$\begin{cases} \frac{dV(t)}{dt} = \sum_{i=1}^{I} g_i(t)(V_i - V(t)) + I(t), \\ \frac{dg_i(t)}{dt} = \frac{G_i\big(V(t)\big) - g_i(t)}{\tau_i}, \quad g_i(0) \geq 0, \quad i = 1, ..., I \end{cases}$$

FitzHugh-Nagumo
$$\begin{cases} \frac{dV(t)}{dt} = F\big(V(t)\big) - W(t) \\ \frac{dW(t)}{dt} = V(t) - \bar{V}, \end{cases}$$

Single neurone dynamics

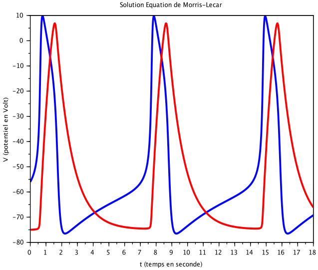


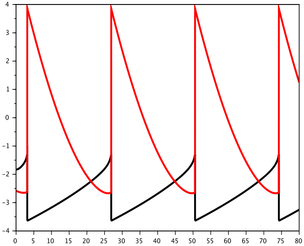
Solutions of Hodgkin-Huxley's model and of FitzHugh-Nagumo's model

- These models are accurate
- but very expensive/difficult to use for large assemblies of neurones.
- This motivates using Integrate-and-Fire models

Single neurone dynamics

- This motivates using Integrate-and-Fire models





Solutions of Morris-Lecar's model

Single neurone dynamics

The Leaky Integrate & Fire model

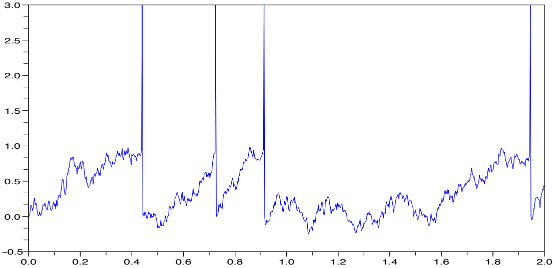
$$dV(t) = \big(-V(t) + I(t)\big)dt + \sigma dW(t), \qquad V(t) < V_{\mathrm{Firing}}$$

$$V(t_-) = V_{\mathrm{Firing}} \quad \Longrightarrow \quad V(t_+) = V_{\mathrm{Reset}}$$

$$0 < V_R < V_F$$

- $I(t)$ input current
- Noise or not
- Much simpler that Hodgkin-Huxley/FitzHugh-Nagumo models

Single neurone dynamics



Solution to the LIF model

- N. Brunel and V. Hakim, R. Brette, W. Gerstner and W. Kistler, Omurtag, Knight and Sirovich, Cai and Tao...
- Fit to measurements
- Use more realistic dynamics in place of $-\mathbf{v}$

Single neurone dynamics

FIGURE 4 | Fitting spiking models to electrophysiological recordings. (A) The response of a cortical pyramidal cell to a fluctuating current (from the INCF competition) is fitted to various models: MAT (Kobayashi et al., 2009), adaptive integrate-and-fire, and Izhikevich (2003). Performance on the training data is indicated on the right as the gamma factor (close to the proportion of predicted spikes), relative to the intrinsic gamma factor of the neuron (i.e., proportion of common spikes between two trials). Note that the voltage units for the models are irrelevant (only spike trains are fitted). **(B)** The response of an anteroventral cochlear nucleus neuron (brain slice made from a P12 mouse, see Methods in Magnusson et al., 2008) to the same fluctuating current is fitted to an adaptive exponential integrate-and-fire (Brette and Gerstner, 2005; note that the responses do not correspond to the same portion of the current as in **(A)**). The cell was electrophysiologically characterized as a stellate cell (Fujino and Oertel, 2001). The performance was $\Gamma = 0.39$ in this case (trial-to-trial variability was not available for this recording).

From C. Rossant et al, Frontiers in Neuroscience (2011)

Leaky Integrate and Fire (linear)

The probability $n(v,t)$ to find a neuron at the potential v solves the Fokker-Planck Eq. on the half line

$$
\begin{cases}
\frac{\partial n(v,t)}{\partial t} + \frac{\partial}{\partial v} \overbrace{\left[\left(-v + I(t)\right) n(v,t)\right]}^{\text{leak+external currents}} - a \overbrace{\frac{\partial^2 n(v,t)}{\partial v^2}}^{\text{Noise}} = \overbrace{N(t)\,\delta(v = V_R)}^{\text{neurons reset}}, \\
\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad v \leq V_F, \\
n(V_F, t) = 0, \qquad n(-\infty, t) = 0, \\
N(t) := -a \frac{\partial n(V_F,t)}{\partial v} \geq 0, \qquad \text{(flux of neurons firing at } V_F\text{)}
\end{cases}
$$

Leaky Integrate and Fire (linear)

The probability $n(v,t)$ to find a neuron at the potential v solves the Fokker-Planck Eq. on the half line

$$\begin{cases} \frac{\partial n(v,t)}{\partial t} + \frac{\partial}{\partial v}\overbrace{\big[\big(-v+I(t)\big)n(v,t)\big]}^{\text{leak+external currents}} - a\overbrace{\frac{\partial^2 n(v,t)}{\partial v^2}}^{\text{Noise}} = \overbrace{N(t)\,\delta(v=V_R)}^{\text{neurons reset}}, \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad v \leq V_F, \\ n(V_F,t)=0, \qquad n(-\infty,t)=0, \\ N(t) := -a\frac{\partial n(V_F,t)}{\partial v} \geq 0, \qquad \text{(flux of neurons firing at } V_F) \end{cases}$$

$N(t)$ is also a Lagrange multiplier for the constraint

$$\int_{-\infty}^{V_F} n(v,t)dv = 1.$$

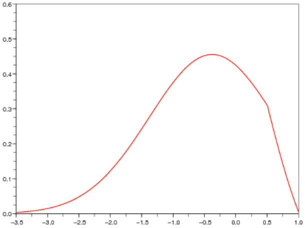
Leaky Integrate and Fire (linear)

$$\begin{cases} \frac{\partial n(v,t)}{\partial t} + \frac{\partial}{\partial v}\left[\big(-v + I(t)\big)n(v,t)\right] - a\frac{\partial^2 n(v,t)}{\partial v^2} = N(t)\,\delta(v = V_R), \\ \hfill v \le V_F \\ n(V_F,t) = 0, \qquad n(-\infty,t) = 0 \\ N(t) := -a\frac{\partial n(V_F,t)}{\partial v} \ge 0, \qquad \text{(flux of firing neurons at } V_F) \end{cases}$$

Properties (Cáceres, Carrillo, BP) For $\equiv 0$, solutions satisfy

- $n \geq 0, \qquad \int_{-\infty}^{V_F} n(v,t)dv = 1,$
- $n(v,t) \underset{t\to\infty}{\longrightarrow} P(v)$ (unique steady state)
- The convergence rate is exponential

Conclusion Total desynchronization



Leaky Integrate and Fire (linear)

The proof uses

- the Relative Entropy. For $H(\cdot)$ convex,

$$\frac{d}{dt}\int_{-\infty}^{V_F} P(v)H\Big(\frac{n(v,t)}{P(v)}\Big)dv = -D_{\text{diff}} - D_{\text{jump}},$$

- Hardy/Poincaré inequality,

$$\int_{-\infty}^{V_F} P(v)|u(v)|^2 dv \le C \overbrace{\int_{-\infty}^{V_F} P(v)|\nabla u(v)|^2 dv}^{D_{\text{diff}}},$$

when
$$\int_{-\infty}^{V_F} P(v)u(v)dv = 0, \qquad P(V_F) = 0$$

See : Ledoux, Barthe and Roberto (2006)

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Noisy LIF networks

For networks, the current $I(t) = bN(t)$ is related to the network activity

$$\begin{cases} \frac{\partial n(v,t)}{\partial t} + \frac{\partial}{\partial v}\left[\left(-v + bN(t)\right) n(v,t)\right] - a\left(N(t)\right) \frac{\partial^2 n(v,t)}{\partial v^2} = N(t)\, \delta_{V_R}(v), \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad v \leq V_F, \\ n(V_F,t) = 0, \qquad n(-\infty, t) = 0, \\ N(t) := -a\left(N(t)\right) \frac{\partial}{\partial v} n(V_F, t) \geq 0, \qquad \text{flux of firing neurons at } V_F \end{cases}$$

Constitutive laws

- b = connectivity
- $b > 0$ excitatory neurones
- $b < 0$ inhibitory neurones
- $a(N) = a_0 + a_1 N$

Noisy LIF networks

$$
\begin{cases}
\frac{\partial n(v,t)}{\partial t} + \frac{\partial}{\partial v}\left[\left(-v + bN(t)\right) n(v,t)\right] - a\big(N(t)\big)\frac{\partial^2 n(v,t)}{\partial v^2} = N(t)\,\delta_{V_R}(v), \\
\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad v \le V_F, \\
n(V_F,t) = 0, \qquad n(-\infty,t) = 0, \\
N(t) := -a\big(N(t)\big)\frac{\partial}{\partial v} n(V_F,t) \ge 0, \quad \text{flux of firing neurons at } V_F.
\end{cases}
$$

Can be derived from a large system of N interacting neurons[1] : for $1 \le i \le N$

$$
\frac{d}{dt} V_i(t) = -V_i(t) + \frac{\beta}{N}\sum_{j=1}^{N}\sum_{k} \delta(t - t_j^k) + \sigma dW_i(t), \qquad V_i(t) < V_F,
$$

with t_j^k the spiking times : $V_j(t_j^k) = V_F$.

1.Delarue, Faugeras, Fournier, Inglis, Lochenbach, Rubenthaler, Talay, Tanre...

Noisy LIF networks (blow-up)

Theorem (J. Carrillo, BP, D. Salort, D. Smets) [Existence]
Solutions exist in the cases

- $b \leq 0$ and they are globally bounded
- $|b|$ is small and initial data close to the steady state and converge to the steady state

Open question : Do solutions converge to the steady state when $b < 0$?

Theorem (M. Cáceres, J. Carrillo, BP) [excitatory, blow-up]
Assume $a \geq a_0 > 0$ and $b > 0$. Then the solution blows-up in finite time **if the initial data is concentrated enough around** $v = V_F$ (depending on b)

Surprisingly : Noise does not help

Noisy LIF networks (blow-up)

Proof. For $\mu = 2\max(\frac{1}{b}, \frac{V_F}{a_0})$, define

$$\phi(v) = e^{\mu v}, \qquad M_\mu(t) := \int_{-\infty}^{V_F} \phi(v) n(v,t).$$

For smooth solutions, we prove that $M_\mu(t)$ becomes larger than $e^{\mu V_F}$

$$\frac{dM_\mu}{dt} = \mu \int_{-\infty}^{V_F} (bN(t) - v + \mu a)\phi(v)p(v,t) - N(t)\phi(V_F) + N(t)\phi(V_R)$$

$$\geq N(t) \underbrace{\left[b\mu M_\mu(t) - \phi(V_F)\right]} + \underbrace{\mu\left[\mu a_0 - V_F\right]}_{\geq \mu V_F > 0} M_\mu(t)$$

> 0 is needed only initially

OK for b large enough or $M_\mu(0)$ large enough

To go further : the difficulty : no relation between M_μ and N

Noisy LIF networks (blow-up)

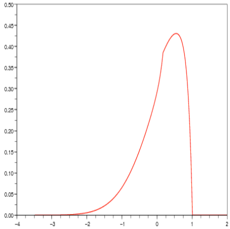
Possible interpretation

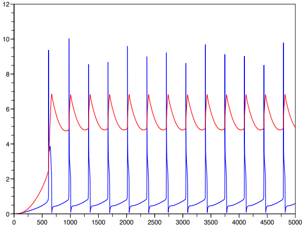
- $N(t) \to \rho\delta(t - t_{\mathrm{BU}})$ and $t_{\mathrm{BU}} > 0$,
- partial synchronization

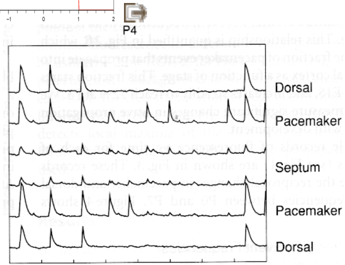
Simplified models : Kuramoto. See Carillo-Ha-Kang, Ha et al, Dumont-Henry, Giacomin...

Huygens

Spontaneous activity (regularized)







Left : Excitatory integrate and fire model with refractory state and random firing threshold

Right : Conhaim et al (2011) J. of physiology 589(10) 2529-2541.

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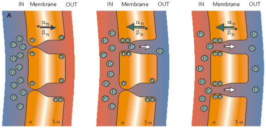
Voltage-conductance I&F



From J. Malmivuo and R. Plonsey, Principles and Appl. of bioelectric and biomagnetic fields, OUP 1995

For ion channels or synaptic conductances : models *à la* Hodgkin-Huxley

$$\frac{\partial}{\partial t} p(v,g,t) + \frac{\partial}{\partial v}\left[(g_L(V_L - v) + g(V_E - v))p(v,g,t)\right] + \frac{\partial}{\partial g}\left[\frac{G(v,t) - g}{\sigma_E} p(v,g,t)\right] - \frac{a}{\sigma_E}\frac{\partial^2}{\partial g^2} p(v,g,t) = 0,$$

$$v \in (V_L, V_F), \; g \geq 0, \qquad V_L < V_F < V_E$$

Boundary conditions :

- No flux condition at $g = 0$
- For $g < g_F$, $g_L(V_L - V_F) + g(V_E - V_F) < 0$, we impose 0 flux at V_L and V_F ;
- For $g > g_F$, outgoing flux at $V_F := N(g,t)$ at $V_F < V_E$ enters at $v = V_L$
- $G(v,t)$ depends on $\int_0^\infty N(g,t)dg$

D. Cai, Shelley, McLaughlin, Rangan, L. Tao, Kovacic, Ly, Trnachina...

Mathematical interest : degenerate parabolic

Voltage-conductance I&F

Similar to the Kinetic Fokker-Planck model of interacting particles

$$\frac{\partial}{\partial t} p(x, v, , t) + v.\nabla_x p - \mathrm{div}_v(vp) - \Delta_v p = 0$$

Enormous litterature on regularizing effects, time decay

Bouchut, Desvillettes

Villani, Hérau

Dolbeault, Mouhot, Schmeiser, Herda

Voltage-conductance I&F

$$\frac{\partial}{\partial t}p(v,g,t)+\frac{\partial}{\partial v}\left[\left(g_L(V_L-v)+g(V_E-v)\right)p(v,g,t)\right]$$
$$+\frac{\partial}{\partial g}\left[\frac{G(v,t)-g}{\sigma_E}p(v,g,t)\right]-\frac{a}{\sigma_E}\frac{\partial^2}{\partial g^2}p(v,g,t)=0,$$

$$v\in(V_L,V_F),\ g\geq 0,\qquad V_L<V_F<V_E$$

Theorem (D. Salort, BP+ Zhennan Zhou, XuAn Dou)

- Stationary solutions belong to L^∞
- Evolution solutions are globally bounded in L^p (no blow-up)

Open questions : Long time asymptotic (nonlinear), regularity up to boundary

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Asymptotic of Voltage-conductance

$$\frac{\partial}{\partial t}p(v,g,t) + \frac{\partial}{\partial v}\left[\left(g_L(V_L - v) + g(V_E - v)\right)p(v,g,t)\right]$$
$$+\frac{\partial}{\partial g}\left[\frac{G(v,t)-g}{\sigma_E}p(v,g,t)\right] - \frac{a}{\sigma_E}\frac{\partial^2}{\partial g^2}p(v,g,t) = 0,$$

See D. Cai, Shelley, McLaughlin, Rangan..., σ_E is small

Section based on :

Kim, Jeongho ; PB ; Salort, D. Fast voltage dynamics of voltage-conductance models for neural networks. Bull. Braz. Math. Soc. 52 (2021), no. 1.

PB, Salort, D. Derivation of a voltage density equation from a voltage-conductance kinetic model for networks of integrate-and-fire neurons. Commun. Math. Sci. 17 (2019).

Asymptotic of Voltage-conductance

$$\frac{\partial}{\partial t}p(v,g,t)+\frac{\partial}{\partial v}\left[\left(g_L(V_L-v)+g(V_E-v)\right)p(v,g,t)\right]$$
$$+\frac{\partial}{\partial g}\left[\frac{G(v,t)-g}{\sigma_E}p(v,g,t)\right]-\frac{a}{\sigma_E}\frac{\partial^2}{\partial g^2}p(v,g,t)=0,$$

For σ_E small, formally,

$$\frac{\partial}{\partial g}\left[G(v,t)-g\,p(v,g,t)\right]-a\frac{\partial^2}{\partial g^2}p(v,g,t)=0 \quad + \quad \text{no flux at } g=0$$

$$p(v,g,t)=n(v,t)\mathcal{P}(v,g,t)$$

and

$$\frac{\partial}{\partial t}n(v,t)+\frac{\partial}{\partial v}\left[\mathcal{G}(v,t)\left(\mathcal{V}(v,t)-v\right)n\right]=0$$

Asymptotic of Voltage-conductance

$$\frac{\partial}{\partial t} p(v,g,t) + \frac{\partial}{\partial v}\left[\left(g_L(V_L - v) + g(V_E - v)\right)p(v,g,t)\right]$$
$$+\frac{\partial}{\partial g}\left[\frac{G(v,t)-g}{\sigma_E} p(v,g,t)\right] - \frac{a}{\sigma_E}\frac{\partial^2}{\partial g^2} p(v,g,t) = 0,$$

For σ_E small, formally,

$$\frac{\partial}{\partial g}\left[G(v,t) - g\,p(v,g,t)\right] - a\frac{\partial^2}{\partial g^2} p(v,g,t) = 0 \quad + \quad \text{no flux at } g = 0$$

$$p(v,g,t) = n(v,t)\mathcal{P}(v,g,t)$$

and

$$\frac{\partial}{\partial t} n(v,t) + \frac{\partial}{\partial v}\left[\mathcal{G}(v,t)\big(\mathcal{V}(v,t) - v\big)n\right] = 0$$

$$\mathcal{G}(v,t) := g_L + \int_0^\infty g\mathcal{P}(v,g,t)dg$$

$$\mathcal{G}(v,t)\mathcal{V}(v,t) := g_L V_L + V_E \int_0^\infty g\mathcal{P}(v,g,t)dg$$

To prove this is open

Asymptotic of Voltage-conductance

Simpler formalism, more amenable to analysis

$$\frac{\partial}{\partial t} p_\varepsilon + \frac{\partial}{\partial v} \left[\left(g_L(V_L - v) + g(V_E - v) \right) p_\varepsilon \right] + \frac{1}{\varepsilon} \frac{\partial}{\partial g} \left[\left(G_{eq}(v, b\mathcal{N}_\varepsilon(t)) - g \right) p_\varepsilon \right]$$
$$- \frac{a}{\varepsilon} \frac{\partial^2}{\partial g^2} p_\varepsilon + \underbrace{\phi_F(v) p_\varepsilon}_{\text{Firing}} = 0, \qquad V_L < v < V_E$$

Network activity

- $N_\varepsilon(t, g) := \int_{V_R}^{V_E} \phi_F(v) p_\varepsilon(v, g, t) dv$
- $\mathcal{N}_\varepsilon(t) := \int_0^\infty N_\varepsilon(t, g) dg$

Boundary condition at V_R

- $\left(g_L(V_L - V_R) + g(V_E - V_R) \right) p_\varepsilon = N_\varepsilon(t, g)$

Asymptotic of Voltage-conductance

Theorem (Uniform bounds) The bounds hold

$$\sup_{0 \le t \le T} \sup_{g \ge 0} N_\varepsilon(t, g) \le C(T)$$

$$\sup_{0 \le t \le T} \sup_{V_R \le v \le V_E} \sup_{g \ge 0} p_\varepsilon(t, v, g) \le C(T)$$

$$\sup_{0 \le t \le T} \sup_{V_R \le v \le V_E} n(t, v) \le C(T) \| n^0 \|_{L^\infty}$$

Asymptotic of Voltage-conductance

Theorem (Asymptotic of the non-linear model) The bounds hold

$$\sup_{0\le t\le T}\ \sup_{g\ge 0}\ N_\varepsilon(t,g) \le C(T)$$

$$\sup_{0\le t\le T}\ \sup_{V_R\le v\le V_E}\ \sup_{g\ge 0}\ p_\varepsilon(t,v,g) \le C(T)$$

$$\sup_{0\le t\le T}\ \sup_{V_R\le v\le V_E}\ n(t,v) \le C(T)\|n^0\|_{L^\infty}$$

and the voltage-conductance equation converges to the "macroscopic" equation

$$\frac{\partial}{\partial t}n(v,t) + \frac{\partial}{\partial v}\left[\mathcal{G}(v,t)\big(\mathcal{V}(v,\mathcal{N}(t)) - v\big)n\right] + \phi_F(v)n(v,t) = 0$$

with

$$\mathcal{G}(v,t) = \mathcal{G}(v,\mathcal{N}(t))$$

$$\mathcal{V}(v,t) = \mathcal{V}(v,\mathcal{N}(t))$$

$$\mathcal{N}(t) := \int_{V_R}^{V_E} \phi_F(v)n(v,t)dv$$

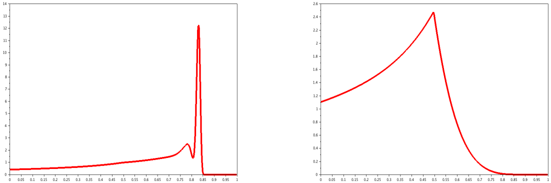
$$\mathcal{G}(V_R,t)\big(\mathcal{V}(v - V_R,\mathcal{N}(t)) - V_R\big) = \mathcal{N}(t)$$

Asymptotic of Voltage-conductance

$$\frac{\partial}{\partial t} n(v,t) + \frac{\partial}{\partial v}\left[\mathcal{G}(v,t)\big(\mathcal{V}(v,t) - v\big) n\right] + \phi_F(v) n(v,t) = 0$$

Theorem (qualitative behaviour) Depending on the connectivity, the dynamics can

- be globally attractive to a single steady state



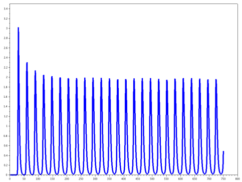
Examples of steady states, depending on $\phi_F(v)$

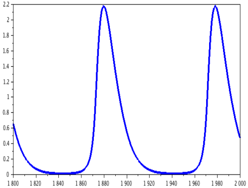
Asymptotic of Voltage-conductance

$$\frac{\partial}{\partial t} n(v,t) + \frac{\partial}{\partial v}\left[\mathcal{G}(v,t)\big(\mathcal{V}(v,t) - v\big) n\right] + \phi_F(v) n(v,t) = 0$$

Theorem (qualitative behaviour) Depending on the connectivity, the dynamics can

- be globally attractive to a single steady state
- have several steady states which can be unstable





CONCLUSION

- Several highly nonlinear PDEs are used in the neuroscience
- Many problems in multiscale analysis
- Open mathematical problems
  - synchronization
  - or stable steady state (connectivity)
  - regularity vs singularities

CONCLUSION

THANKS TO MY COLLABORATORS

M. J. Carceres J. A. Carrillo D. Smets

Zhennan Zhou XuAn Dou

D. Salort Jeongho Kim

THANK YOU