EXPLORING FITZHUGH-NAGUMO MODEL PHENOMENA WITH DRIVING INPUT SIGNAL AND NOISE

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SUMMARY

❖Introduction
❖A little history of FitzHugh-Nagumo model
❖Phase plane analysis
❖Explanation of some general Phenomena
❖Role of noise
❖White noise in a FHN model with periodic input
❖RA and NES results
❖Conclusions

INTRODUCTION

- Neurons receive input as a signal and send as output to other neurons which causes transmission of informations.

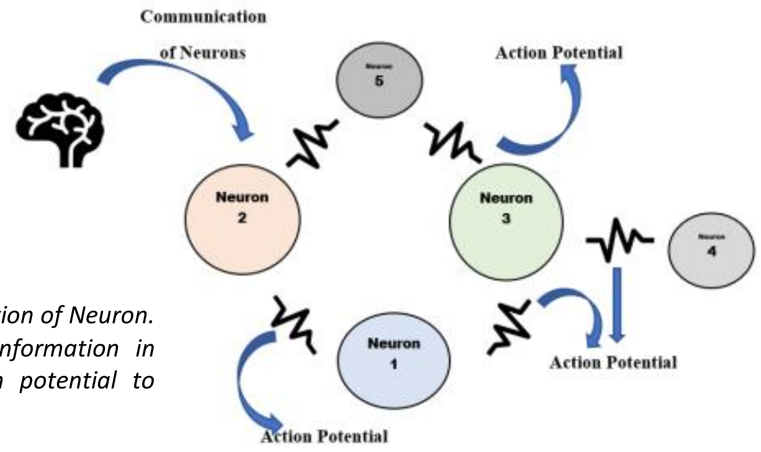

Fig 2*.* *Communication of Neuron. Neuron pass the information in the form of action potential to another neuron.*

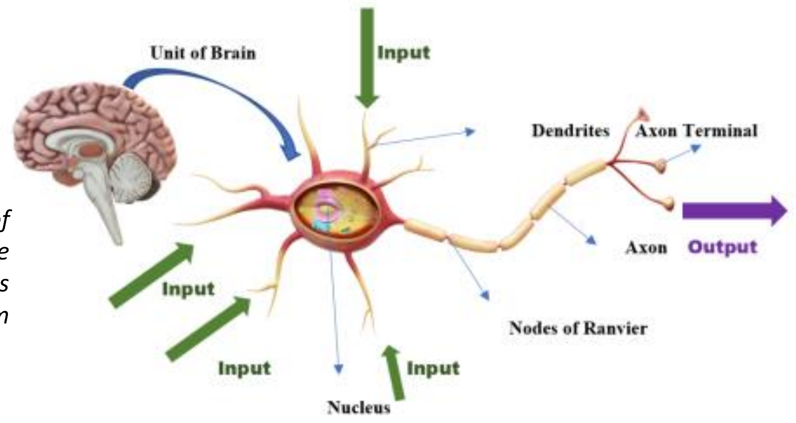

Fig 1*.* *Structure of Neuron. Signals are received by dendrites and passed in the form of output by axon.*

- The understanding of the activity of neurons in the brain has been modeled as nonlinear systems using mathematical modeling for decades.
- A simplified model, that mimics the properties of more complex and sophisticated models, is chosen.

Figures from: *Impact of external applied currents in BVP model Avinita Gautam, and Anupam Priyadarshi.*

A LITTLE HISTORY OF FITZHUGH-NAGUMO MODEL

1928, Van der Pol model.

The **van der Pol oscillator** is an oscillator with nonlinear damping governed by the second-order differential equation:

$$\ddot{x} - \varepsilon\left(1 - x^2\right)\dot{x} + x = 0$$

where x is the dynamical variable and ε > o the strength of dumping.

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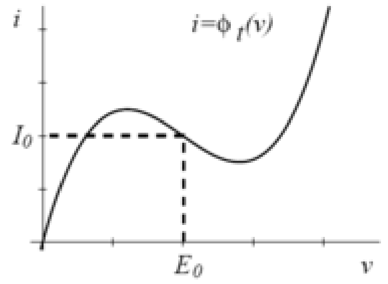
The equivalent circuit is a modified RLC loop, with the passive resistor replaced by an active element.

- $|x| \gg 1$ both the restoring and damping forces are large, so that |x(t)| should decrease with time. The system behaves like a strongly damped oscillator, and it disperses energy.
- $|x| \ll 1$, the damping force becomes negative: the energy of the system grows.

This is already a hint that there could be a **limit cycle** in the phase space.



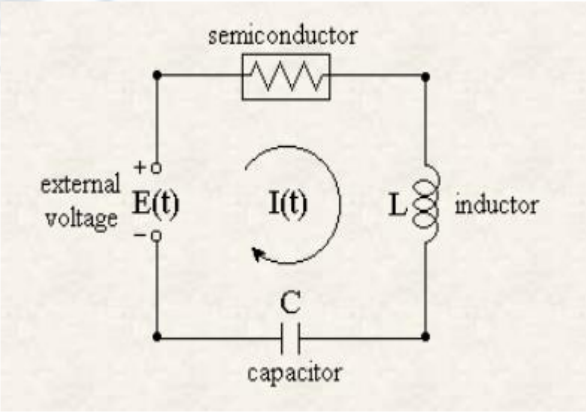


Fig: https://services.math.duke.edu/education/ccp/materials/diffeq/vander/vand1.html

A LITTLE HISTORY OF FITZHUGH-NAGUMO MODEL

1963 Nobel Prize in Medicine.

1952, Hodgkin-Huxley model.

- Semirealistic 4-dimensional model for the dynamics of the membrane potential, considering Na+, K+, and a leak current.
- Dynamics of ion channels highly nonlinear ⇒ difficult (expecially at that time) to resolve
- Highly nonlinear equation => linearization is not a good approximation

Membrane potential: $$I = C_m \frac{\mathrm{d}V_m}{\mathrm{d}t} + \bar{g}_{\mathrm{K}} n^4 (V_m - V_K) + \bar{g}_{\mathrm{Na}} m^3 h (V_m - V_{Na}) + \bar{g}_l (V_m - V_l),$$

potassium I_K , *slow*: $$\frac{dn}{dt} = \alpha_n(V_m)(1-n) - \beta_n(V_m)n$$

sodium I_{NA} , *fast*: $$\frac{dm}{dt} = \alpha_m(V_m)(1-m) - \beta_m(V_m)m$$

sodium I_{NA}, *slow*: $$\frac{dh}{dt} = \alpha_h(V_m)(1-h) - \beta_h(V_m)h$$

A LITTLE HISTORY OF FITZHUGH-NAGUMO MODEL

Dynamics of gating variables m, h, n.

- General form:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = -\frac{1}{\tau(V)}[x - x_s(V)]$$

Solution for constant V :

$$x(t) = (x_0 - x_s)\exp(-t/\tau) + x_s$$

⇒ exponential relaxation to steady state value x_s.

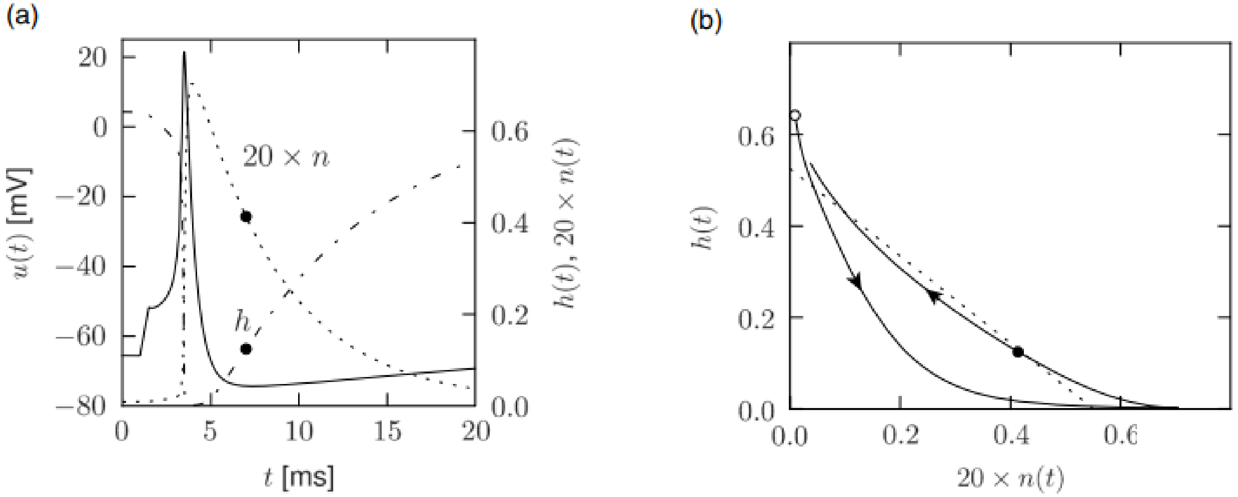


Fig. 4.5 Similarity of gating variables h and n. (a). After stimulation of the Hodgkin–Huxley model by a short current pulse, the membrane potential (solid line) exhibits an action potential. The time course of the variables n (dashed line) mirrors that of the variable h (dot-dashed). (b). During and after the action potential, the trajectory of the variables $n(t)$ and $h(t)$ (solid line) stays very close to the straight line $h = b - an$ (dashed) with slope a and offset b. The point $(n_0(u_{\text{rest}}), h_0(u_{\text{rest}}))$ is indicated with a circle.

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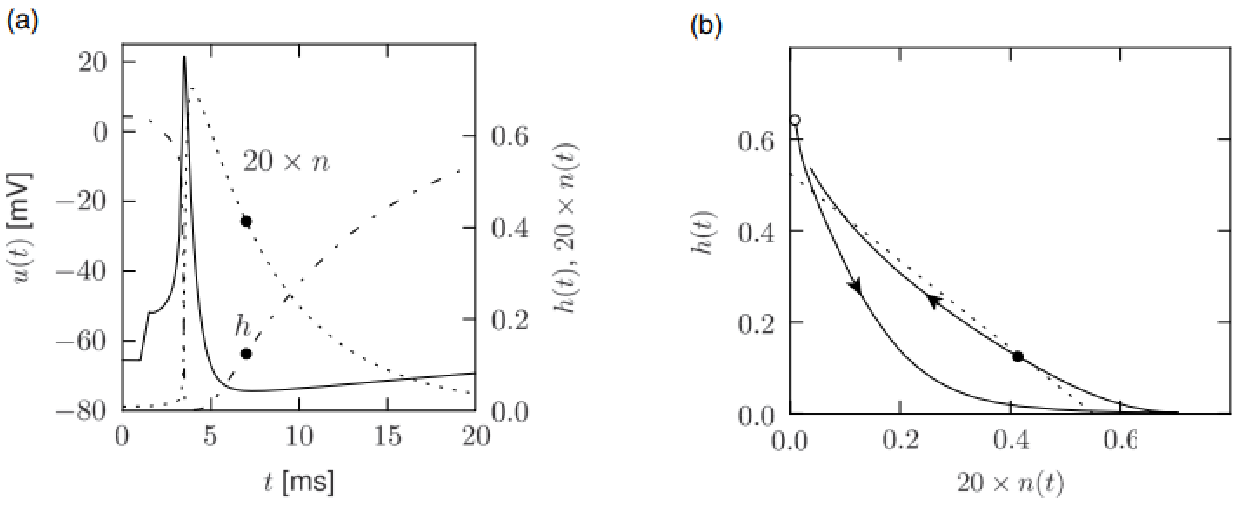
⇒ exponential relaxation to steady state value x_s.

small τ : *fast* relaxation ⇒ $x(t) \approx x_s(t)$

large τ : *slow* dynamics

- Approximate by steady state value: $m(t) \approx m_s(V)$
- Replace $h(t), n(t)$ by one effective current $w(t)$



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⇒ two equations for temporal evolution of $V(t)$ and $w(t)$

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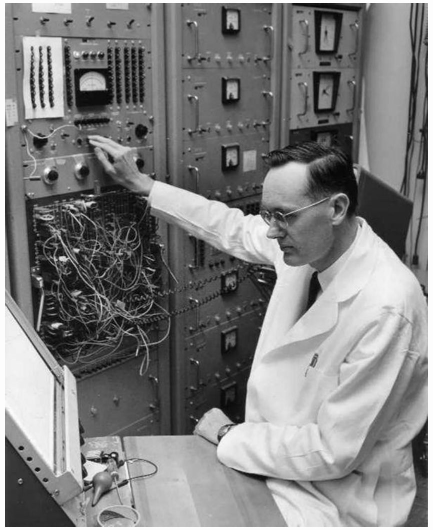


1961, FitzHugh model.

- FitzHugh derived 2-dimensional model for an excitable neuron:

$$\frac{\mathrm{d}v}{\mathrm{d}t} = v - \frac{v^3}{3} - w + I$$

$$\frac{\mathrm{d}w}{\mathrm{d}t} = \frac{1}{\tau}(v + a - bw)$$

- Typical values: $a = 0.7, b = 0.8, \tau = 13$

$$\Rightarrow \frac{\dot{v}}{\dot{w}} \sim 10 \Rightarrow w\ slow\ , v\ fast.$$

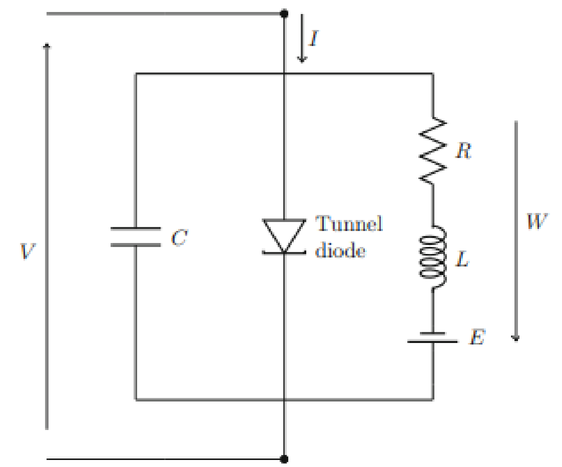
- Mathematically it derived from VdP eq. (1) and *the Lienard transformation*

$$w = -\dot{v} + v + \frac{v^3}{3}$$

The motivation for the FHN model was to isolate conceptually the essential mathematical properties of excitation and propagation from the electrochemical properties of sodium and potassium ion flow.

A LITTLE HISTORY OF FITZHUGH-NAGUMO MODEL

1962, J. Nagumo's circuit model.



- Using an electric circuit that included a tunnel diode, Nagumo et al. qualitatively modeled an axonal behaviors.
- The circuit consists of a capacitor (representing membrane capacitance) and a tunnel diode (representing the nonlinear dynamics of the fast membrane current) in parallel with a resistor (representing channel resistance), an inductor, and a battery (these last three components being in series).

Thus FitzHugh's equations and Nagumo's circuit model are equivalent.

PHASE PLANE ANALYSIS

Two-dimensional flow field:

$$\vec{F}(v,w) = \frac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix} v \\ w \end{pmatrix} = \begin{pmatrix} v - \frac{v^3}{3} - w + I \\ \frac{1}{\tau}(v + a - bw) \end{pmatrix}$$

(numerical) solution: $\begin{pmatrix} v(t) \\ w(t) \end{pmatrix} \Rightarrow$ trajectory in 2-D plane

Characteristics:

- trajectories cannot cross (uniqueness of solutions)
- **nullclines** define lines in the 2-D plane:

$$\dot{v} = 0 \Rightarrow w = v - \frac{v^3}{3} + I \qquad \textit{fast V-Nullcline}$$

$$\dot{w} = 0 \Rightarrow w = (v + a)/b \qquad \textit{slow W-Nullcline}$$

- crossings of the nullclines correspond to fixed points (stable for I = 0)

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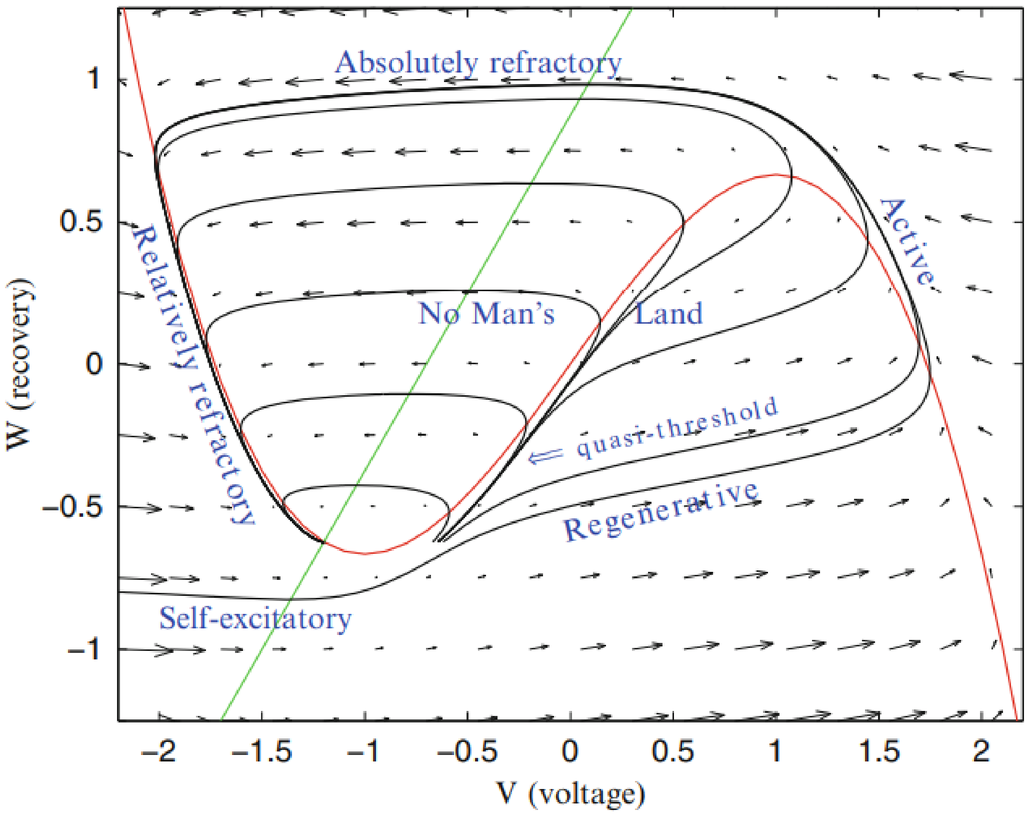

Fig. Phase plane map associating FHN system behavior with initial conditions .

PHASE PLANE ANALYSIS

- The fixed point of the FHN system is located at the intersection of the nullclines. (Under conditions $1 - 2b/3 < a < 1, 0 < b < 1, and\ b > \varepsilon^2$, there is exactly one fixed point.)
- The fixed point is stable for low values of applied current. As I increases, the V-nullcline shifts upward, and the location of the equilibrium shifts toward the middle branch.
- As the fixed point reaches the left knee of the V-nullcline, it undergoes a Hopf bifurcation, and a limit cycle is born. Thus, for sufficiently large values of I, the FHN system simulates tonic spiking, as shown in Fig. 2b.

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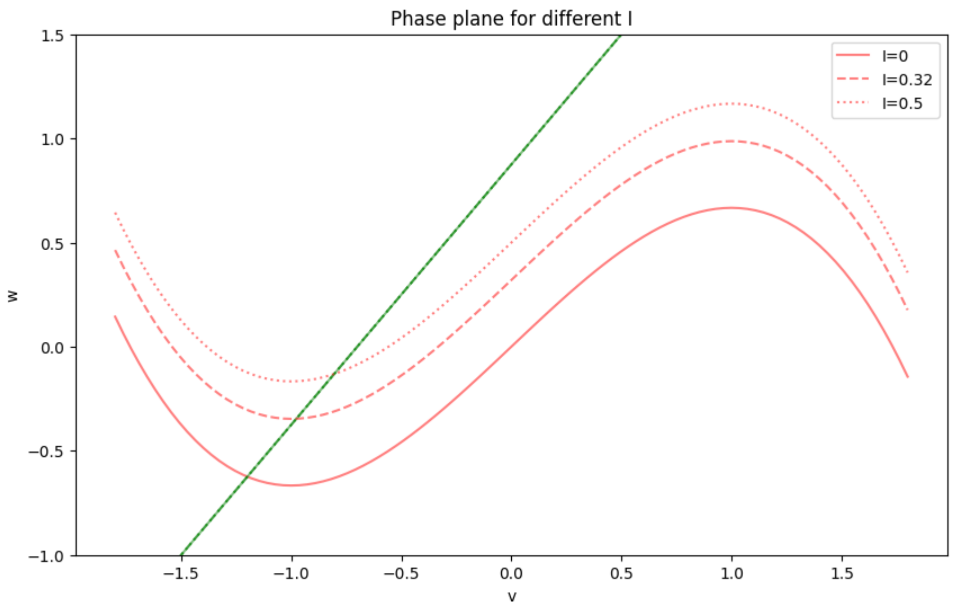

Fig. The intersection of the v-nullcline and the w-nullcline gives the single **critical point** of the system. An increase in the external current stimulus I shifts the v-nullcline up and changes the position of the critical point.
Parameter used: "a":.7, "b":.8, "eps":0.077.

SMALL EXTERNAL STIMULUS CURRENTS $0 \le I_{ext} < 0.324$

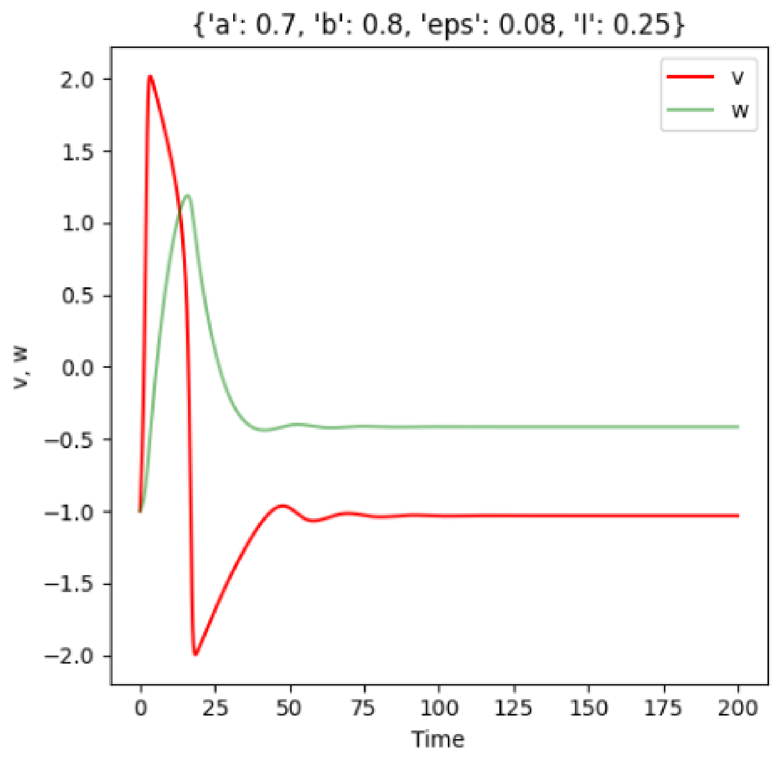

Fig. The time evolution of the two state variables. There are small oscillations which become quickly damped around critical point.

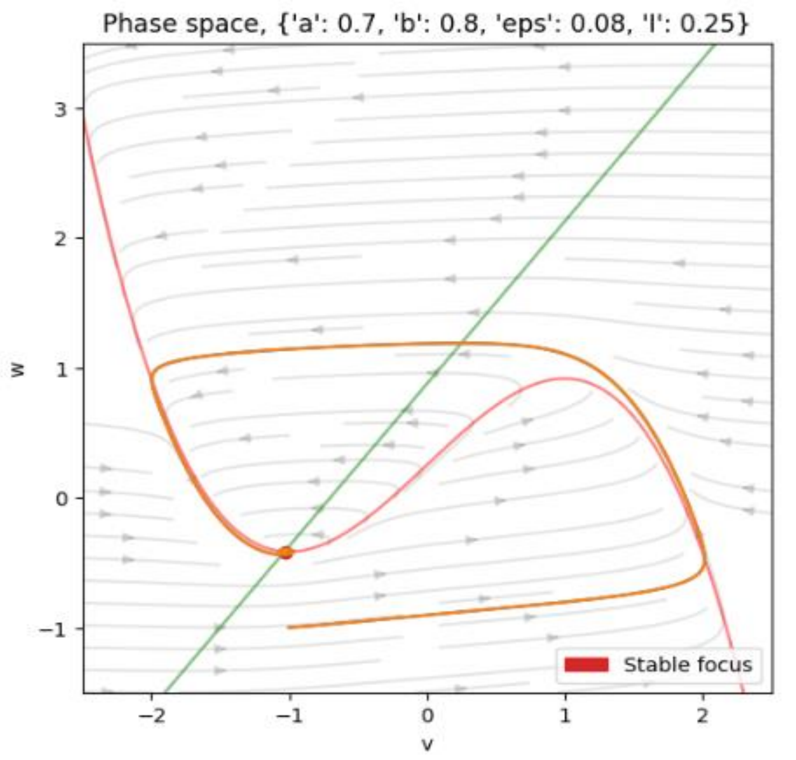

Fig. The phase space trajectory is attracted to the critical point.

- The state variables evolve to the critical point without exciting a spike in the potential v
- Fixed point remains stable ⇒ small damped oscillations
- Critical point is a stable focus

AT THE BIFURCATION $I\_ext = 0.324$

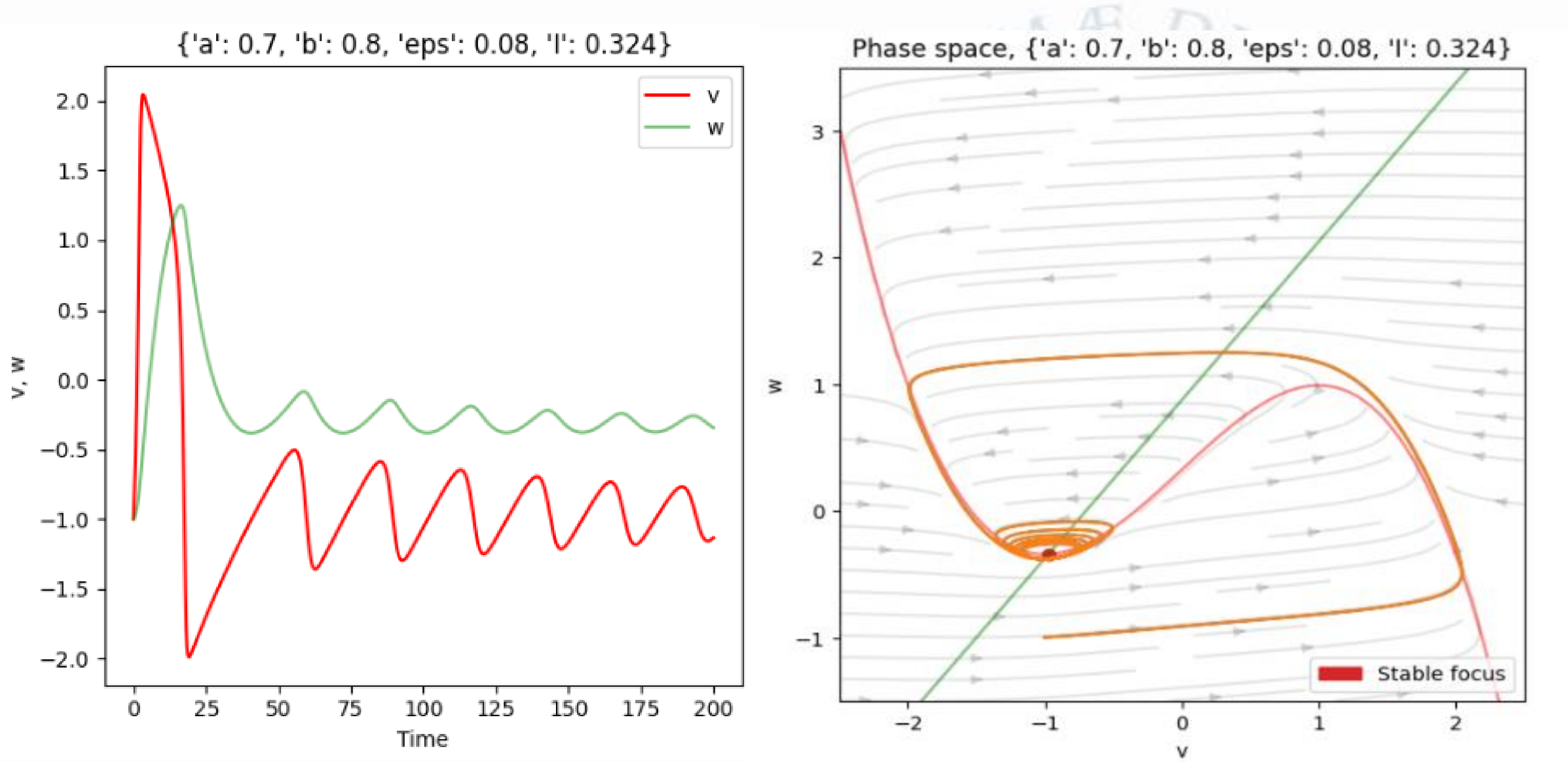

Fig. The critical point is at the boundary of regions 1 and 2. The trajectory oscillates around the critical point without an action potential being produced.

- For an external current stimulus $I\_ext = 0.324$, the critical point is at the boundary between regions 1 and 2. The trajectory oscillates around the critical point without an action potential being initiated.
- For weak current stimuli, there is a **stable** fixed equilibrium point.

INTERMEDIATE EXTERNAL STIMULUS CURRENTS $0.325 \leq I_{ext} \leq 1.42$

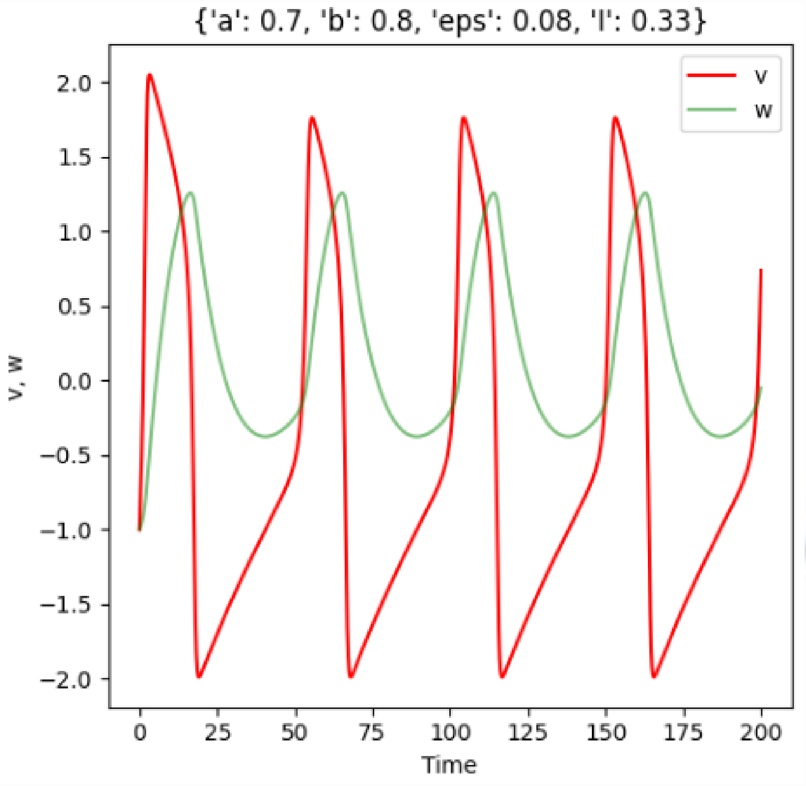

Fig. A series of action potentials are produced. The fixed equilibrium point is unstable and leads to tonic firing of the neuron.

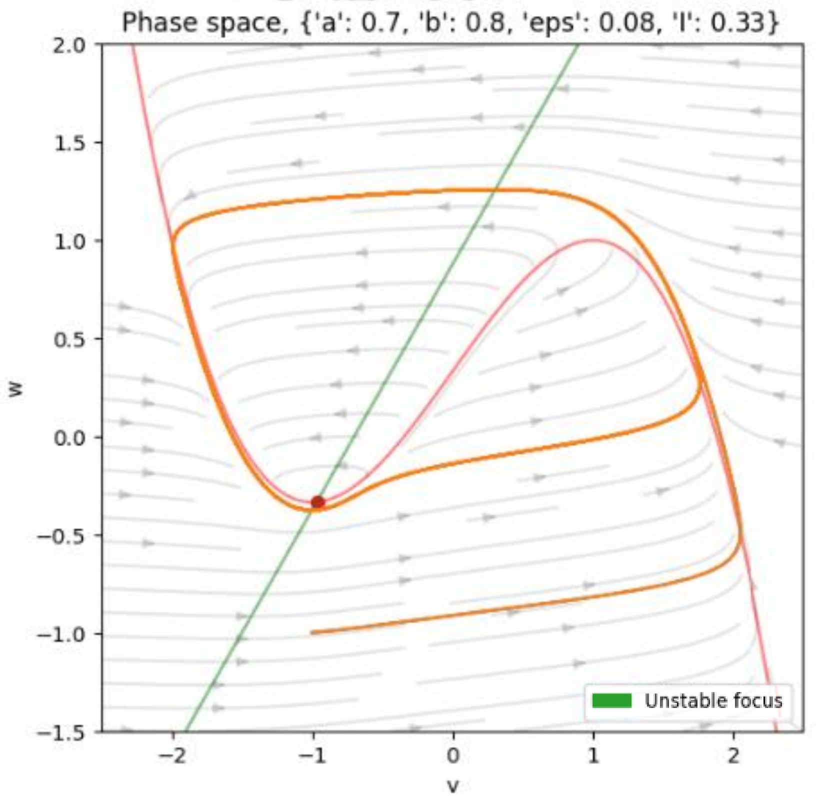

Fig. The trajectory forms closed loops around the critical point which results in the repetitive spiking of the neuron. It sweeps out a closed orbit and never hits the critical point and therefore keeps repeating itself.

- The critical point is in region 2 and is an unstable equilibrium point.
- The neuron spikes repetitively, that is, the model exhibits periodic (**tonic spiking**) activity.

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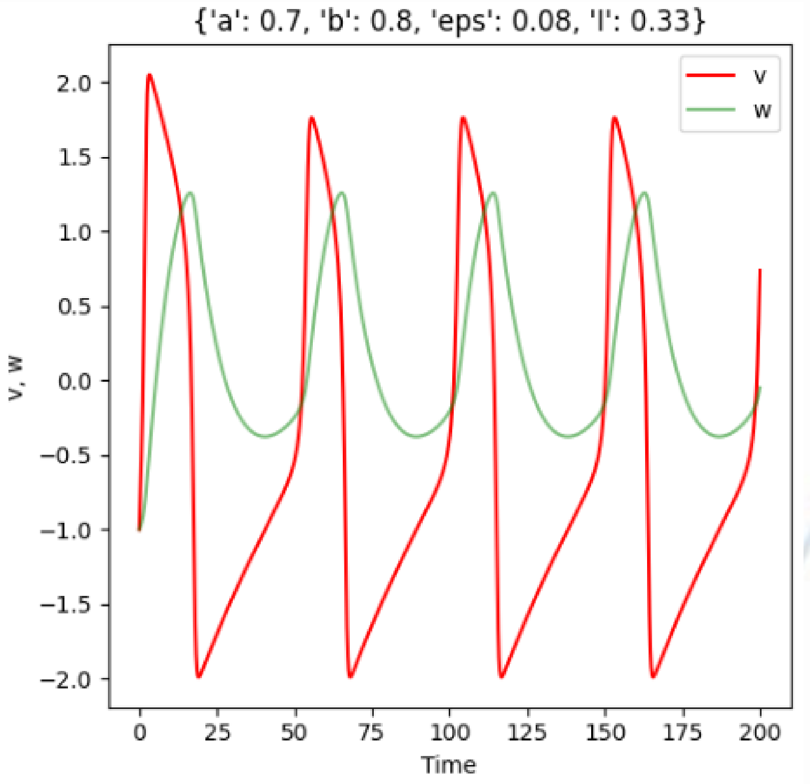

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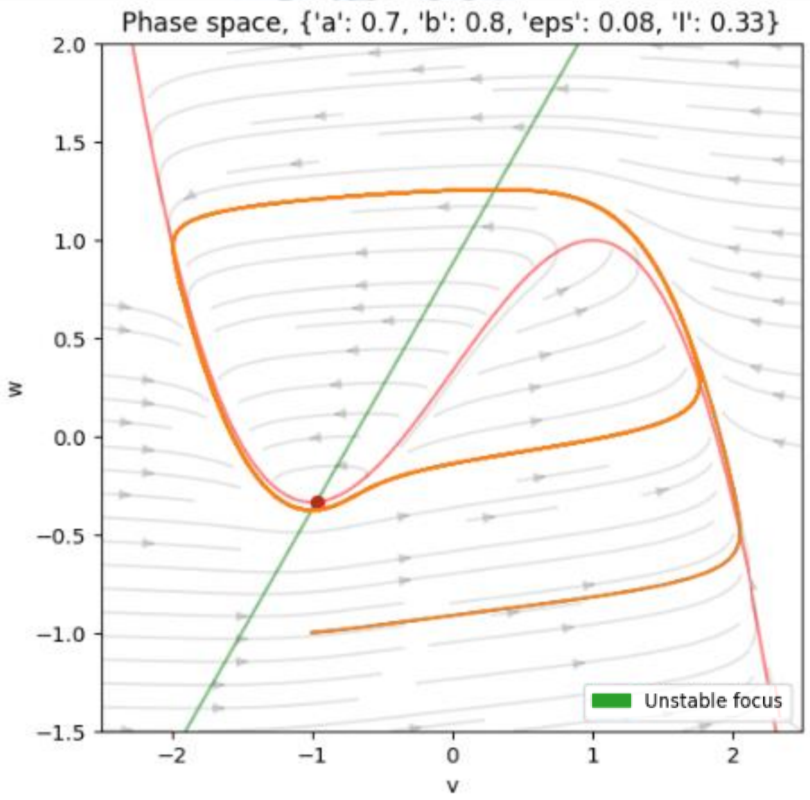

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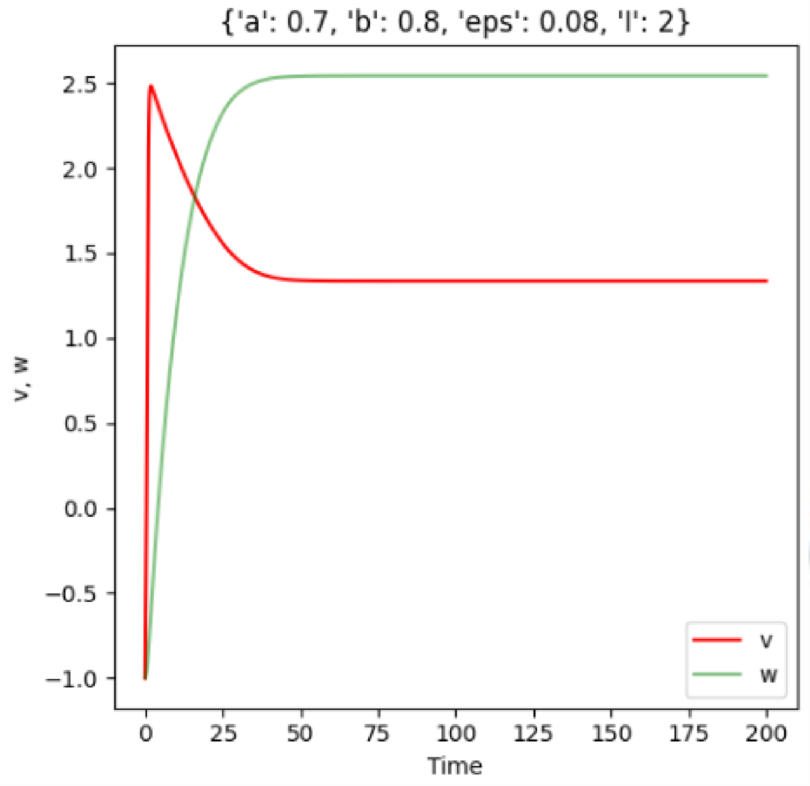
- The critical point is in region 2 and is an unstable equilibrium point.
- The neuron spikes repetitively, that is, the model exhibits periodic (**tonic spiking**) activity.
- After a spike, the neuron returns to its resting state during the **refractory period** where the system is indifferent to any external stimuli.
- Here we have an **Hopf bifurcation**.

LARGE STIMULUS CURRENTS $I_{ext} > 1.42$



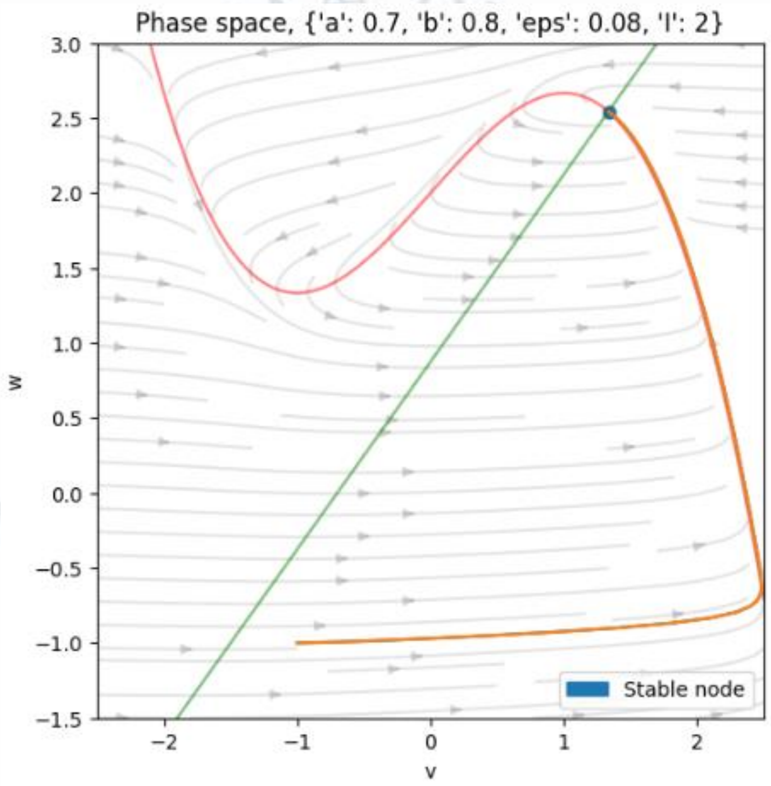
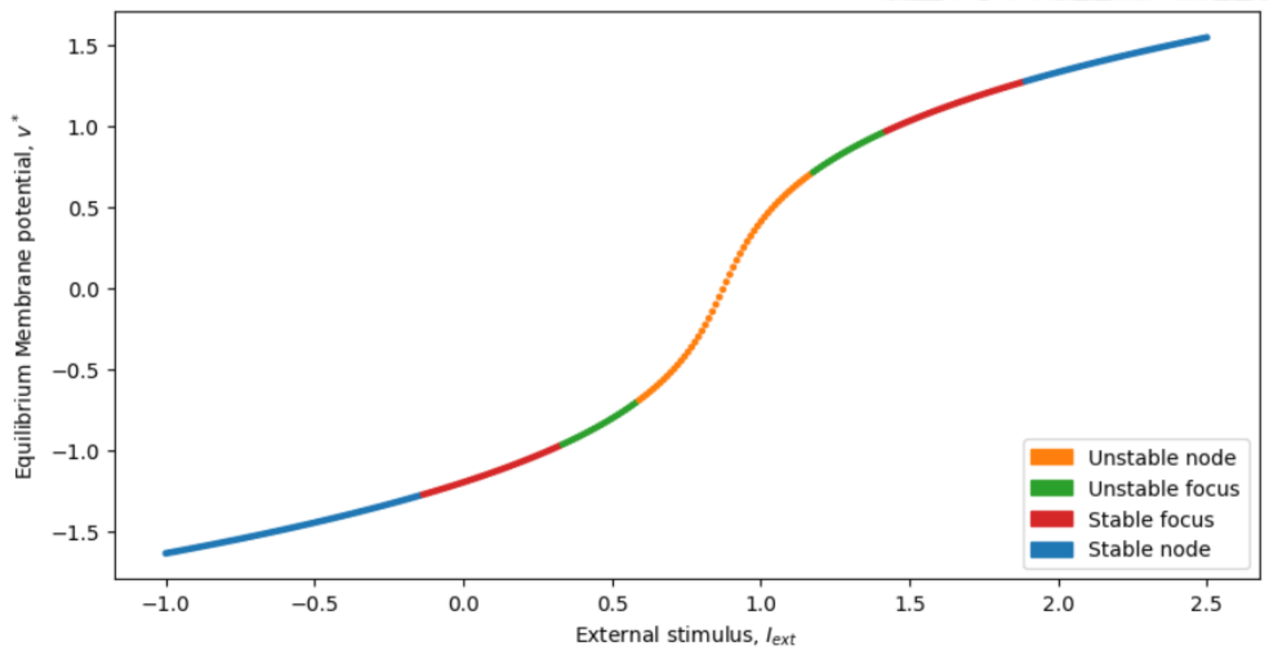


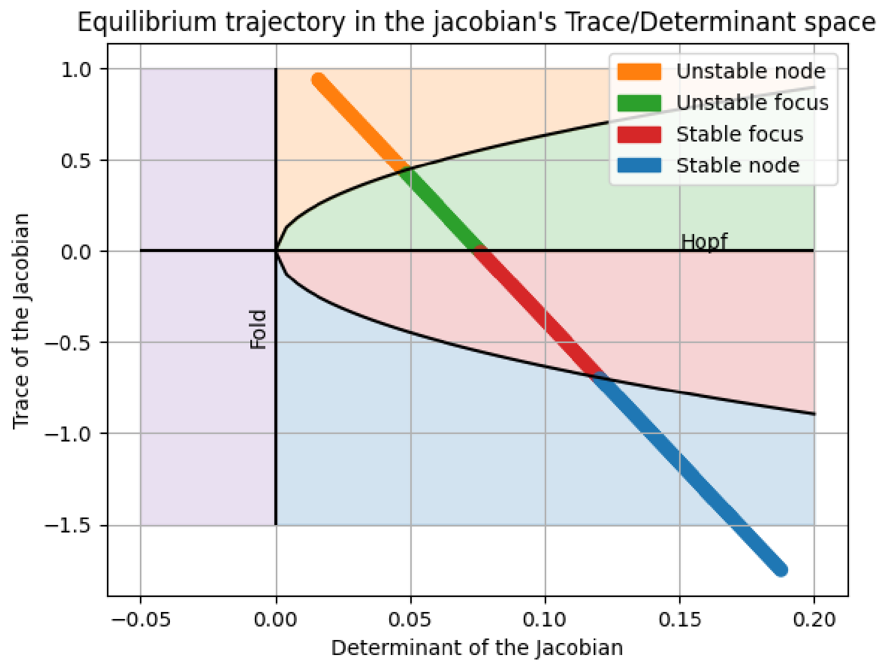
Fig. The critical point is in region 3. The trajectory is attracted to the critical point. No action potentials are generated.

- At the start $(\frac{dv}{dt} > 0, \frac{dw}{dt} > 0)$ v evolves faster than w, that is, v increases rapidly while w remains virtually unchanged (near-horizontal part of the v-w trajectory).
- As the trajectory approaches the v-nullcline, the rate of change of v slows down and w becomes more prominent.
- Since $\frac{dw}{dt}$ is still positive, w must increase, and the trajectory moves upwards. The fixed point then attracts this curve and the evolution ends at the fixed point.

BIFURCATION DIAGRAM ON THE EXTERNAL STIMULUS I

- Using standard techniques for studying the stability of fixed points, and creating an array of Input current, the following diagram of bifurcation were obtained:





EXCITATION BLOCK PHENOMENON

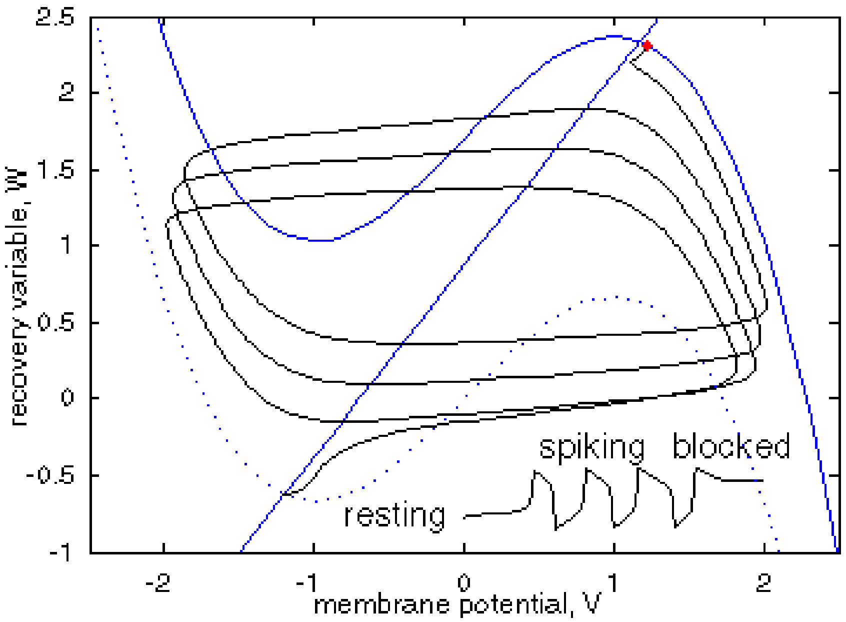


Fig. Figure adapted from http://www.scholarpedia.org/article/FitzHugh-Nagumo_equation#fig:Nagumo_Circuit.gif

- The precise mathematical mechanism involves appearance and disappearance of a **limit cycle attractor**.

- The FitzHugh-Nagumo model explains the **excitation block phenomenon**, i.e., the cessation of repetitive spiking as the amplitude of the stimulus current increases.
- Increasing the stimulus further shifts the equilibrium to the right (stable) branch of the N-shaped nullcline, and the oscillations are blocked (by excitation!).

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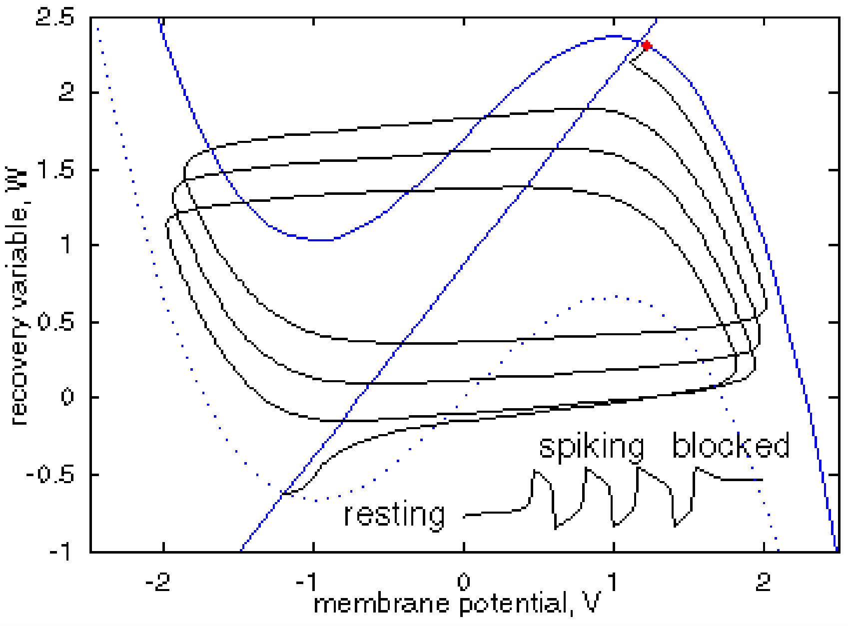

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- Increasing the stimulus further shifts the equilibrium to the right (stable) branch of the N-shaped nullcline, and the oscillations are blocked (by excitation!).
- Numerical simulation of the membrane potential v:

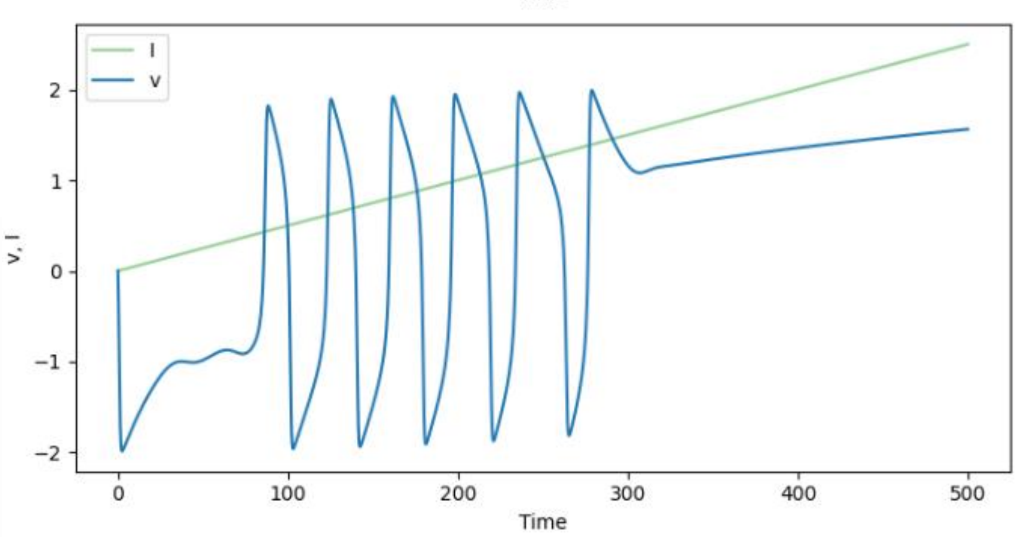
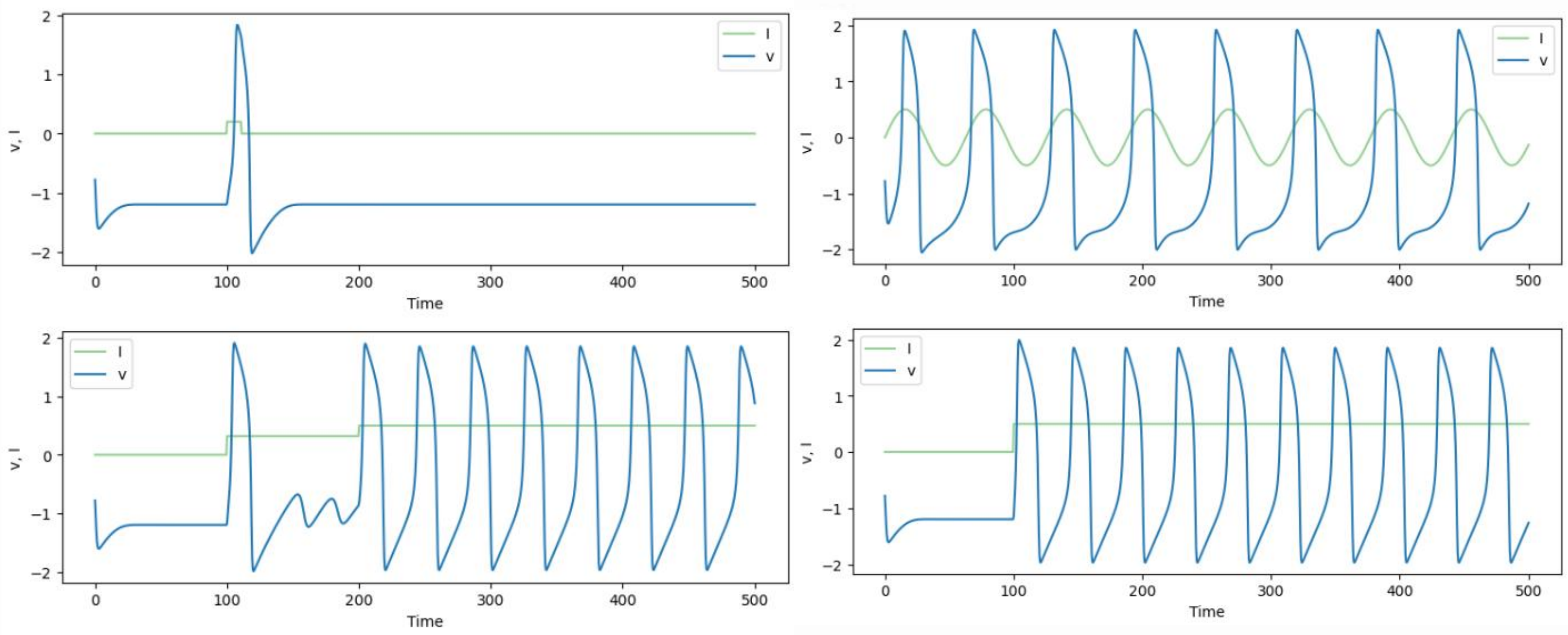


Fig. Parameter used for numerical simulation of the potential:
"a":.7,
"b":.8,
"eps":0.077

TIME DEPENDENT INPUT CURRENT $I(t)$



Figs. Evolution of potential membrane with a time dependent current as input. **A** represents a step function with amplitude 0.1. **B** represents another step function with amplitudes 0.1 and 0.5 **C** A sinusoidal input with amplitude 0.5 and freq 0.1 **D** step function with amplitude 0.5 (tonic spiring)

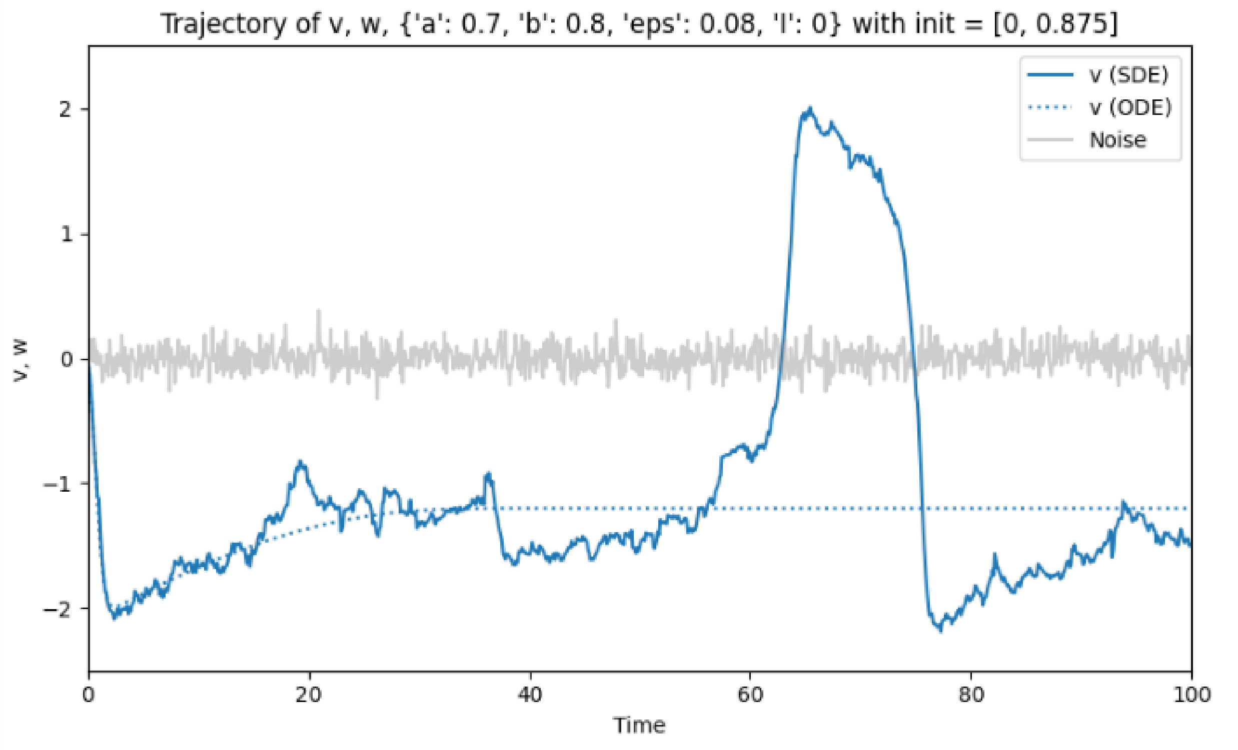
ROLE OF NOISE

- In vivo recordings of neuronal activity are characterized by a high degree of irregularity
- Noise is therefore often added explicitly to neuronal dynamics to mimic the unpredictability of neuronal recordings
- **Intrinsic** noise sources: thermal noise, noise from the finite number of ion channels in a patch of neuronal membrane; **extrinsic** noise: synaptic 'bombardment' noise from the network, Noise-connectivity etc.
- It has also constructive roles: Coherence Resonance **CR** and Stochastic Resonance **SR…**

- Many papers analyzed the influence of noise on FHN model in the absence of any periodic forcing (coherence resonance) or in a subthreshold regime (stochastic resonance, etc.)
- One is therefore led to interpret the role of the noise as a compromise—it enhances weak signal encoding at the expense of a reduction in the information encoded about suprathreshold signals.

ADDING NOISE TO THE SYSTEM WITH NO CURRENT: NOISE-INDUCED SPIKING

- Adding noise to the system with no current leads to to a phenomenoun called Noise Induced Spiking



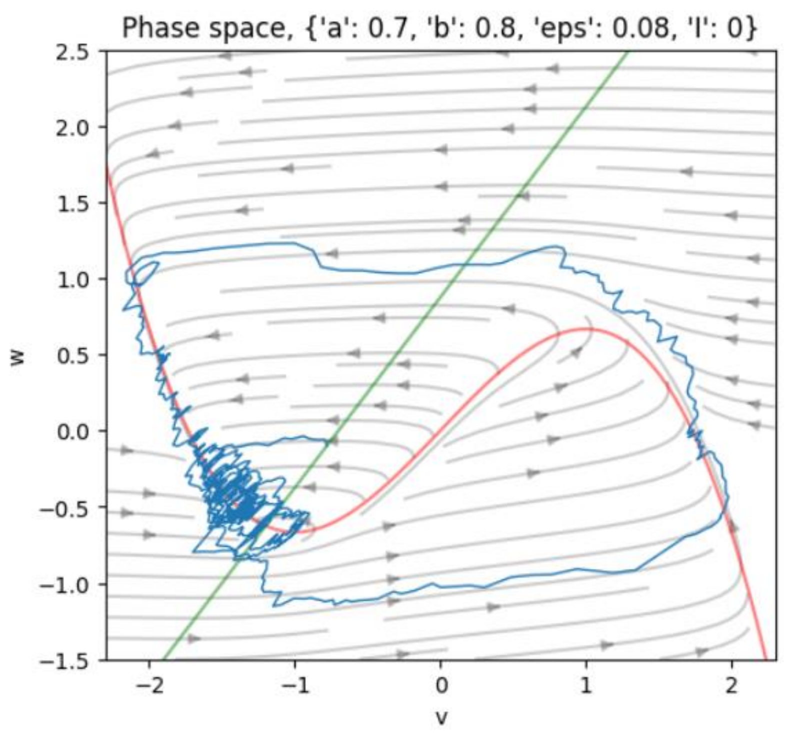
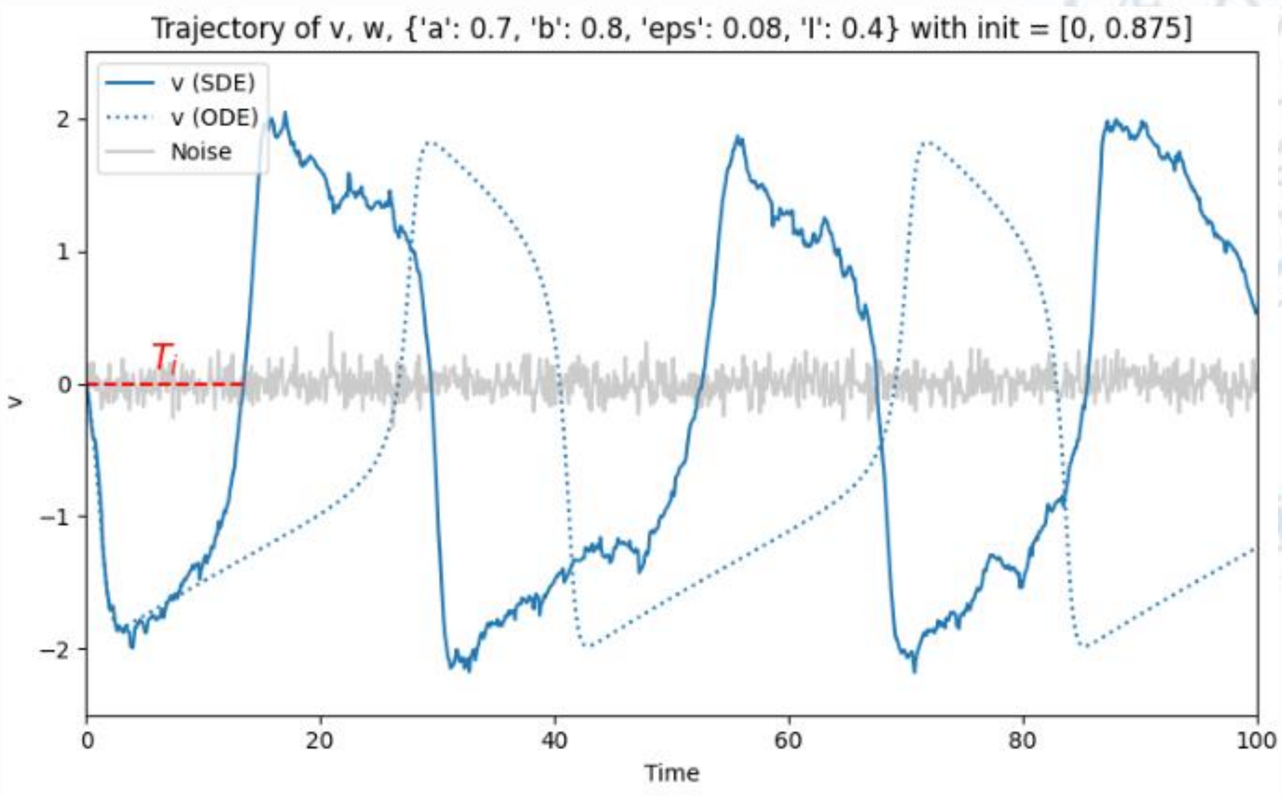
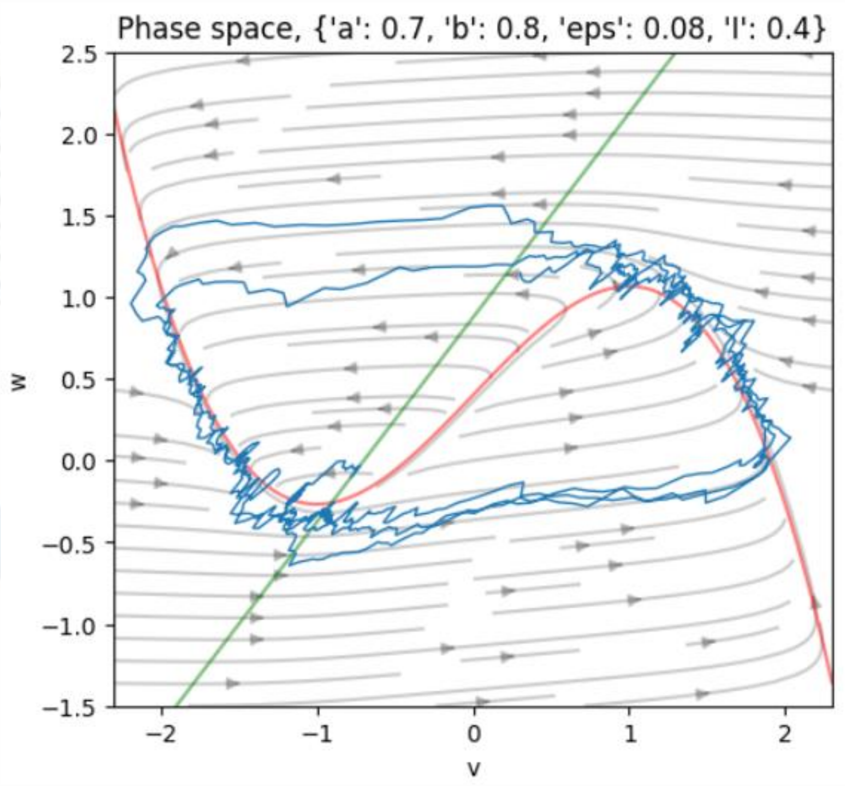


Fig. Presence of noise allows the membrane variable $v(t)$ to cross the threshold and produce spikes despite the model being below the threshold when only the deterministic component is considered. For numerical simulations it has been used the ***Euler-Maruyama method***, see Appendix A.

ADDING NOISE TO THE SYSTEM WITH CONSTANT CURRENT





ADDING WHITE NOISE AND PERIODIC SIGNAL INPUT

- Let's now consider the FHN model driven by periodic input:

$$\begin{aligned}\dot{x} &= x - \frac{x^3}{3} - y + A\sin(\omega t + \varphi_0) + \zeta_x \\ \dot{y} &= \varepsilon(x + I) + \zeta_y,\end{aligned}$$

Where $\zeta_i(t)\ (i = x, y)$ is an independent Gaussian white noises with zero mean and correlation function :

$$\langle \xi(t)\xi(t+\tau)\rangle = D\delta(\tau)$$

CHOOSING PARAMETERS – SUPRATHRESHOLD REGIME

- In the absence of external driving force there is only one stationary state given by $x_0 = -I, y_0 = -I + \frac{I^3}{3}$
- If $(|I| < 1)$ then (x_0, y_0) is unstable with stable periodic solution;
  If $(|I| > 1)$ then (x_0, y_0) is stable with all the trajectories converging at this point (attractor)
- Here we set $I = 1.1$.

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- Here we set $I = 1.1$.
- Parameter chosen: $\varepsilon = 0.05, A = 0.5$, so that frequency range where the signal of such amplitude is suprathreshold is $\omega \in (0.013 - 1.9)$.
- We are interested in the mean response time (**MRT**) of the neuron when external stimulus and white noise are present.
- External force is **suprathreshold** if the system, starting from the point (x0, y0), exhibits spikes *even in the deterministic dynamical regime*.

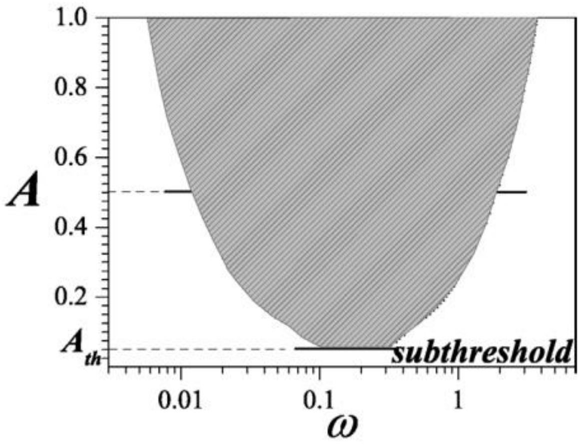


Fig. 1. The parameter plane (ω, A) for $D = 0$, $\varphi_0 = 0$. Suprathreshold signals are the signals with amplitudes and frequencies taken from the shaded region.

MEAN RESPONSE TIME MRT

- The mean response time (**MRT**) is obtained by averaging the first passage through the boundary x = 0 over the ensemble of N realizations: $\tau = \frac{1}{N}\sum_i T_i$, where T_i is the response time for ith realization.

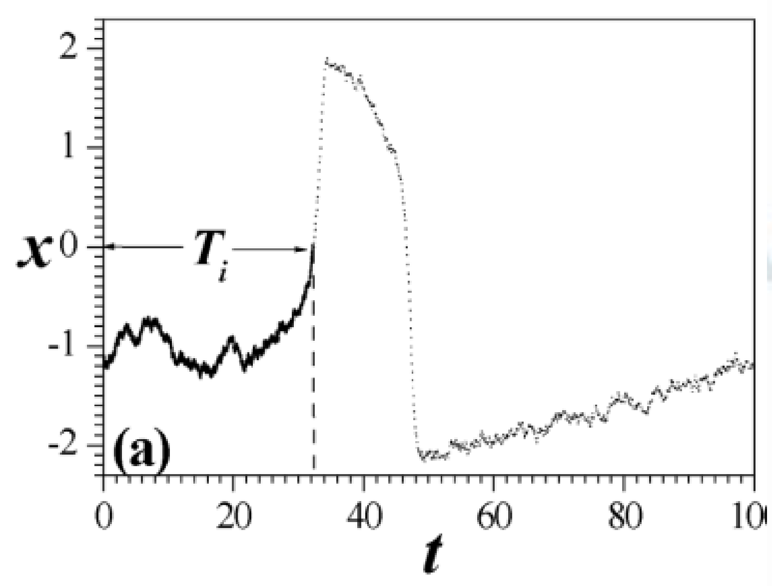


Fig. (1a) An example of a stochastic trajectory for case I. A = 0.5, ω = 0.01, D = 0.01. The estimation of the response time as a first passage time at the boundary x = 0.
(2a) The response time dependence versus frequency of periodic driving for the deterministic case, A = 0.5.

MEAN RESPONSE TIME MRT

- The mean response time (**MRT**) is obtained by averaging the first passage through the boundary x = 0 over the ensemble of N realizations: $\tau\ = \frac{1}{N}\sum_i T_i,$ where T_i is the response time for ith realization.
- In the absence of noise, within the range where signal is suprathreshold, this time has a nonmonotonic behavior as a function of driving frequency with a minimum at ω ~ 1.2

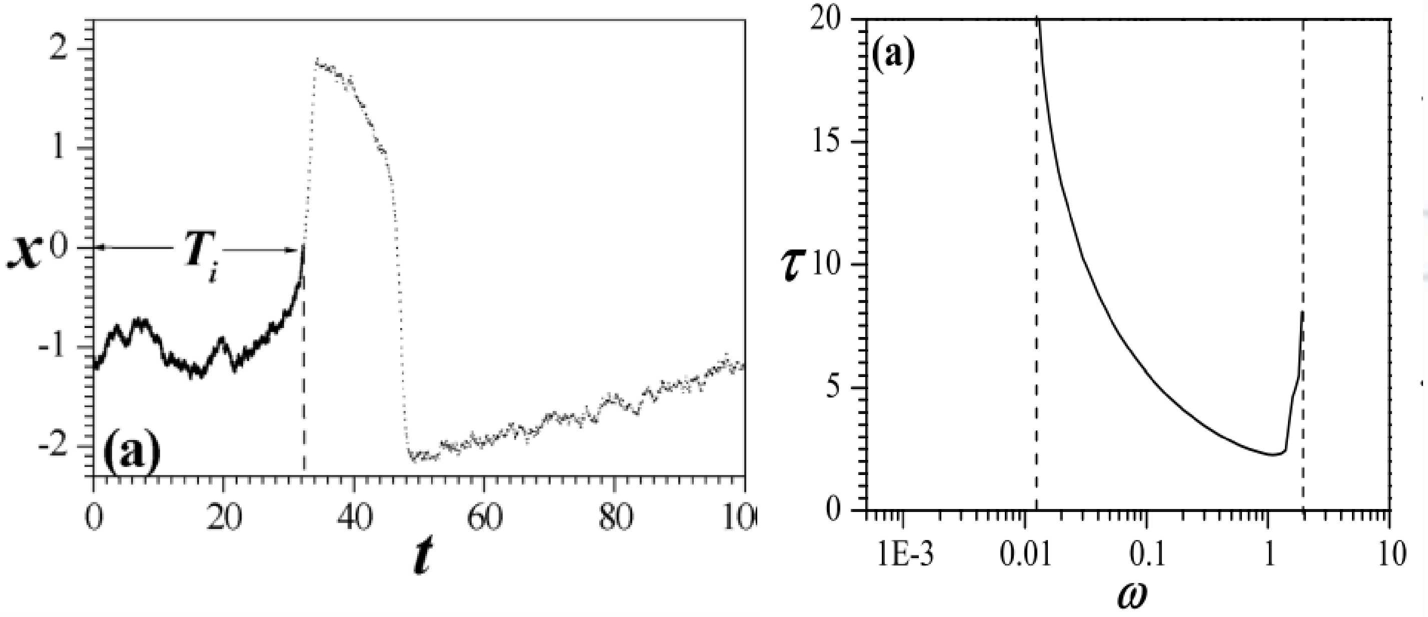
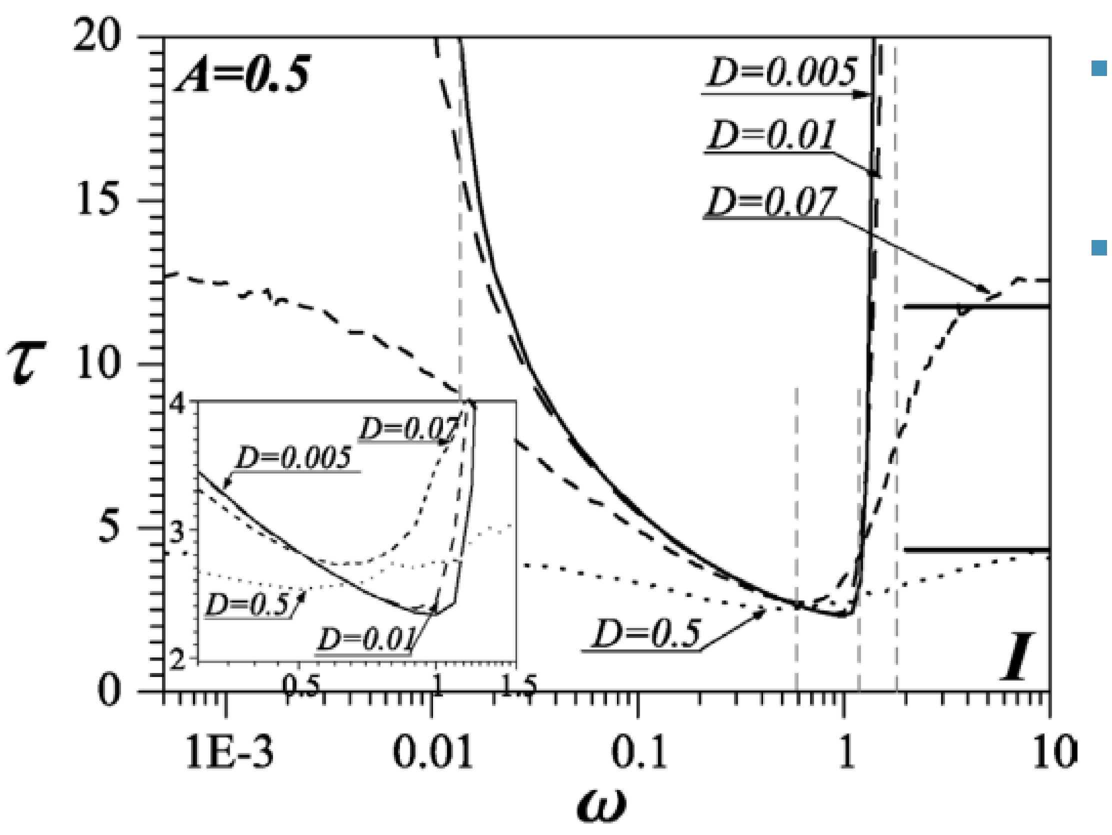


Fig. (1a) An example of a stochastic trajectory for case I. A = 0.5, ω = 0.01, D = 0.01. The estimation of the response time as a first passage time at the boundary x = 0.
(2a) The response time dependence versus frequency of periodic driving for the deterministic case, A = 0.5.

NUMERICAL RESULTS FOR CASE I

- The variable that corresponds to the membrane potential is subjected to fluctuations. N = 5000

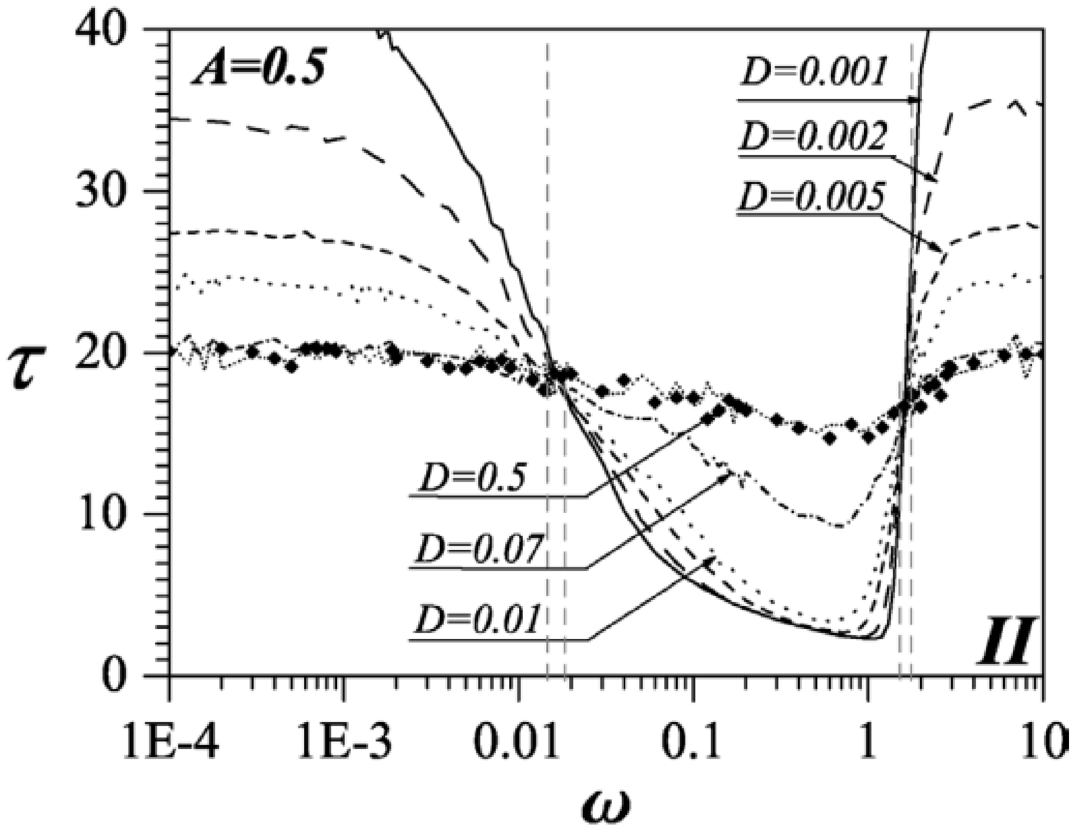


- A **resonant activation-like** phenomenon: the MRT exhibits a minimum as a function of the driving frequency, which is almost independent of the noise intensity
- In a narrow frequency range (ω ∈ (0.6 ÷ 1.3)), we found a nonmonotonic behavior of the MRT. Here the **noise enhanced stability** effect is observed.

Fig. The mean response time dependence versus frequency of periodic driving for case I for four values of noise intensity. Namely: $D = 0.5, 0.07, 0.01, 0.005$. The parameter setting is: $I = 1.1, = 0.05, A = 0.5, and\ \phi = 0$. The right solid lines give the theoretical values of τ for fixed bistable potential. Inset: frequency range where the noise enhanced stability effect is observed.

NUMERICAL RESULTS FOR CASE II

- **Case II** The recovery variable associated with the refractory properties of a neuron is noisy.



- An independent noise **resonant activation-like** phenomenon is observed until D reaches the value of parameter ε
- The minimum tends to disappear for greater noise intensities.
- In a larger frequency range $(\omega \in (0.02 \div 1.6))$, we found, as noise intensity increase, a monotonic growth of the MRT respect to deterministic case.
- For noise intensity values greater than $\varepsilon = 0.05$, the recover variable can be approximate by a Wiener process, which acts now as noise source in a double well potential.

Fig. The mean response time dependence vs frequency of periodic driving for case II. The curve with diamonds gives the values of τ for fixed bistable potential, when the noise source is a Wiener process.

CONCLUSION

- Two dimensional model that can be derived from Hodgkin-Huxley via reduction of variables
- A lot of phenomena are explained with the FHN model
- Increasing input current led to an Hopf-bifurcation, i.e. sustained periodic spiking
- Two noise-induced effects are observed in the noisy case with a suprathreshold periodic driving (NES and RA phenomena).
- Investigation of these noise induced effects in the stochastic FitzHugh–Nagumo model is not only important for the response time of a neuron (to realize high-rate signal transmission with the suppression of noise), but also in all excitable systems, ranging from chemistry to physics and biology, where this model can be used.

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GRAZIE PER L’ATTENZIONE

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APPENDIX A: EULER - MARUYAMA INTEGRATION METHOD

Given the stochastic differential equation:

$$dX_t = u(X_t, t)dt + v(X_t, t)dB_t$$

where $u(X, t)$ represents the deterministic part, $v(X, t)$ the stochastic one and dB_t is a differential Wiener process. We want to find a solution X_t or a numerically approximation. The aim is to mimic the deterministic Euler method. The primary tool is to approximate the integrals by a one-point quadrature:

$$\int_t^{t+h} u(s, X_s)ds + \int_t^{t+h} v(s, X_s)dB_s \approx hu(t, X_t) + v(t, X_t)(B_{t+h} - B_t)$$

where the increment $(B_{t+h} - B_t)$ is a normal random variable with mean 0 and standard deviation $\sqrt{t}$. This develops the iterative method by creating a discretization Y_t of the process X_t over a desired time interval.

APPENDIX A: EULER - MARUYAMA INTEGRATION METHOD

Euler - Maruyama method

The stochastic differential equation:

$$dX_t = u(X_t, t)dt + v(X_t, t)dB_t$$

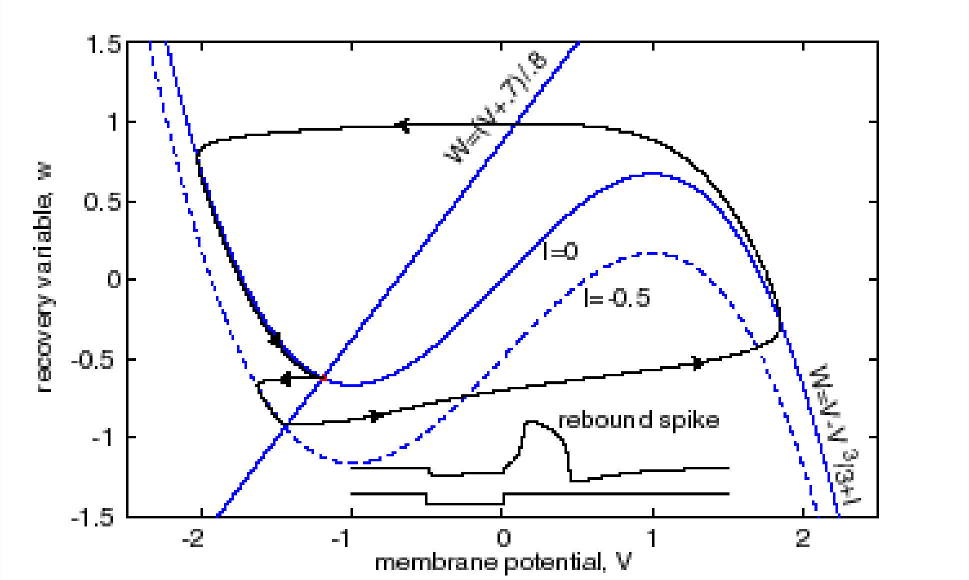
can be numerically approximated by the Markov chain partitioned on the time interval $[0, T]$ with N equally spaced points

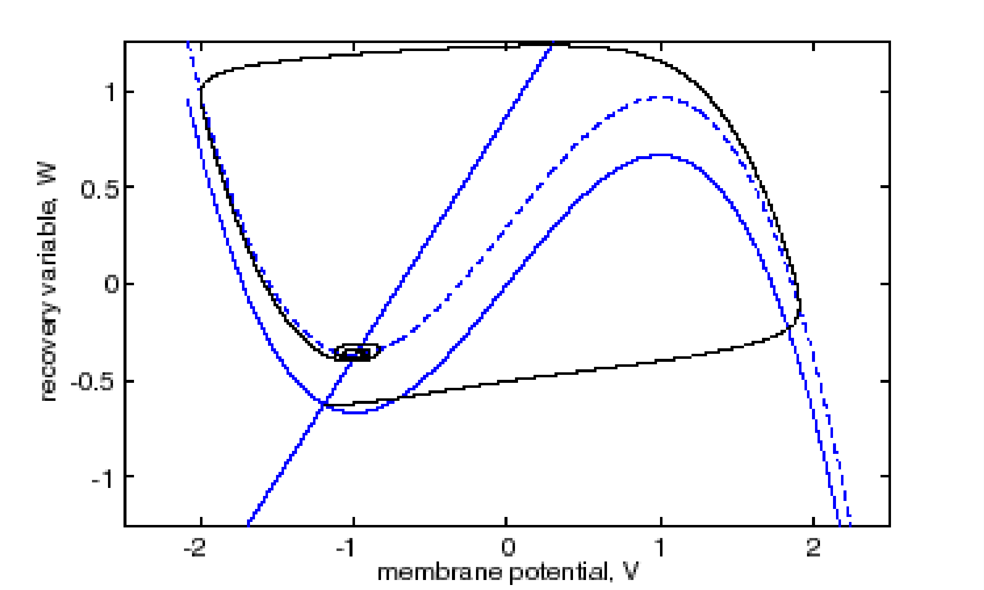
$$Y_n = Y_{n-1} + hu(t_{n-1}, X_{t_{n-1}}) + v(t_{n-1}, X_{t_{n-1}})(B_{t_{n-1}} - B_{t_n})$$

where $Y_0 = X_0$, $h = T/N$ and $n = 0, 1, ..., N$.

APPENDIX B: ANODAL BREAK EXCITATION & SPIKE ACCOMMODATION (NO NUMERICAL SIMULATION)

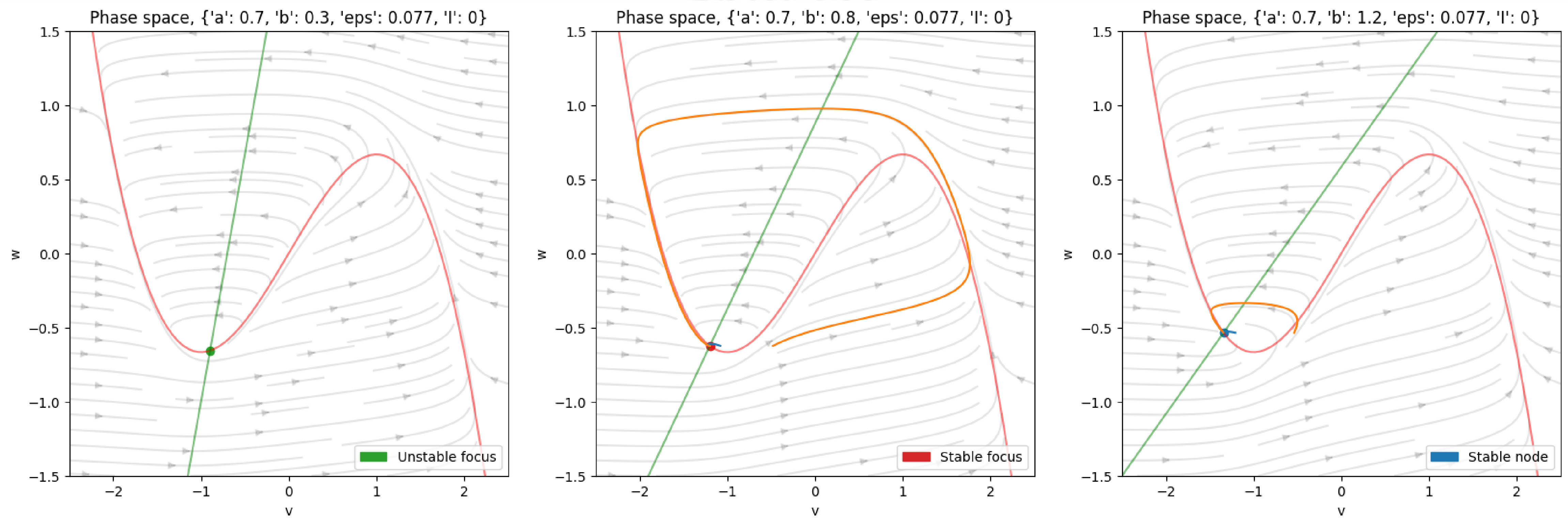
- Another two well known phenomena explained by FHN model are:



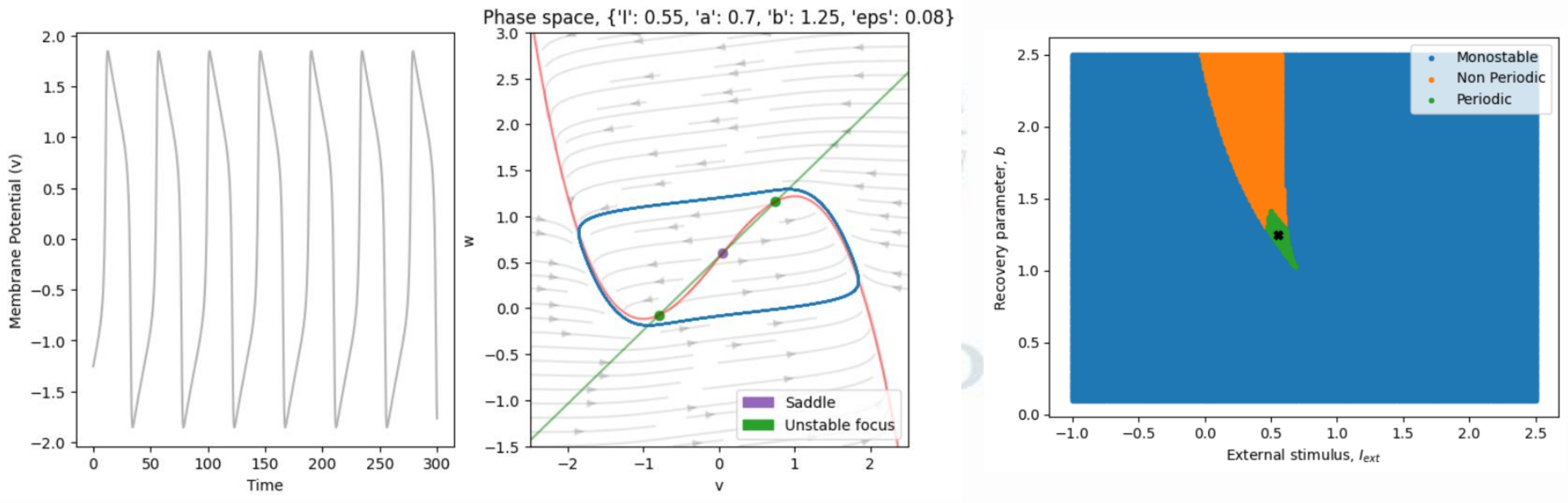


Figs. Both figures adapted from http://www.scholarpedia.org/article/FitzHugh-Nagumo_equation. **A** represents Anodal break excitation (post-inhibitory rebound spike) in the FHN model. **B** Spike accommodation to slowly increasing stimulus in the FHN model.

APPENDIX C: VARYING THE PARAMETER B



APPENDIX C: VARYING THE PARAMETER B



Figs. A Membrane potential e phase space. It's possible to obtain periodic orbit also with 3 fixed points, only if there is one saddle and two unstable points (focus or nodes), as in figure. **B** Bifurcation diagram varying I on recovery parameter b.

APPENDIX D: QUASI THRESHOLD PHENOMENON

- Da rivedere

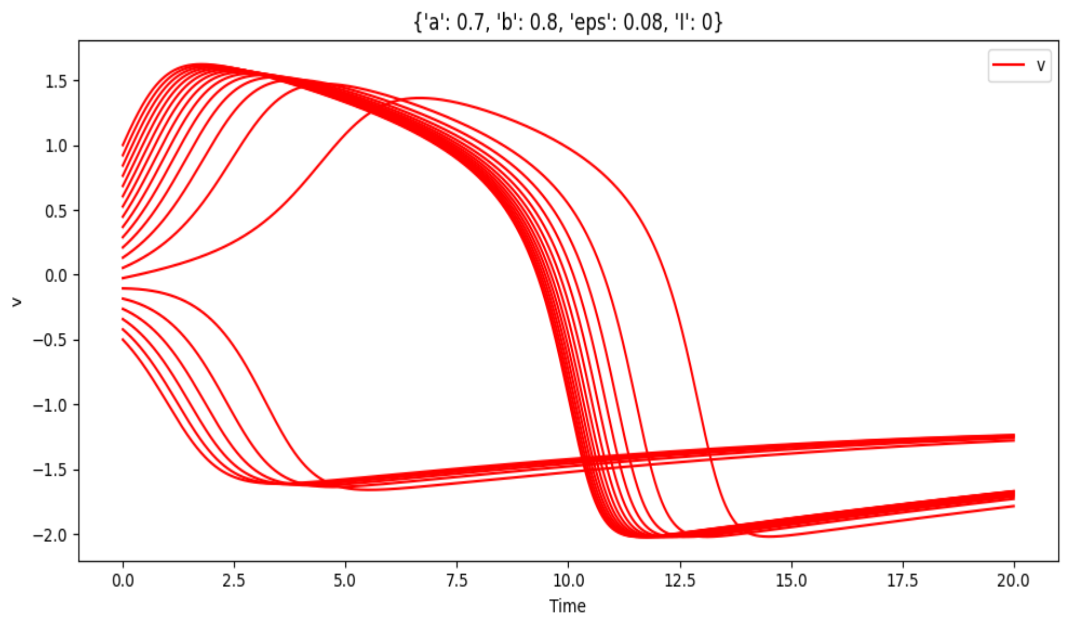


Fig A. Threshold behavior in a model with Hopf bifurcation. Projection of the trajectories on the voltage axis, for different initial condition v0. For v0 < 0 , the trajectories return rapidly to rest. The trajectories with v0 ≥ 0 start with positive slope.

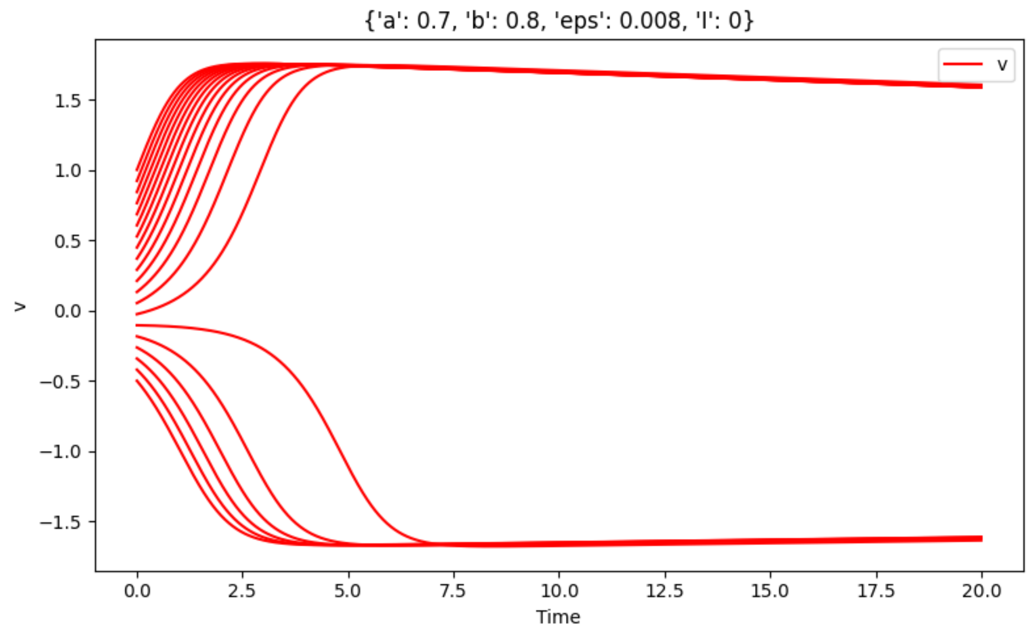
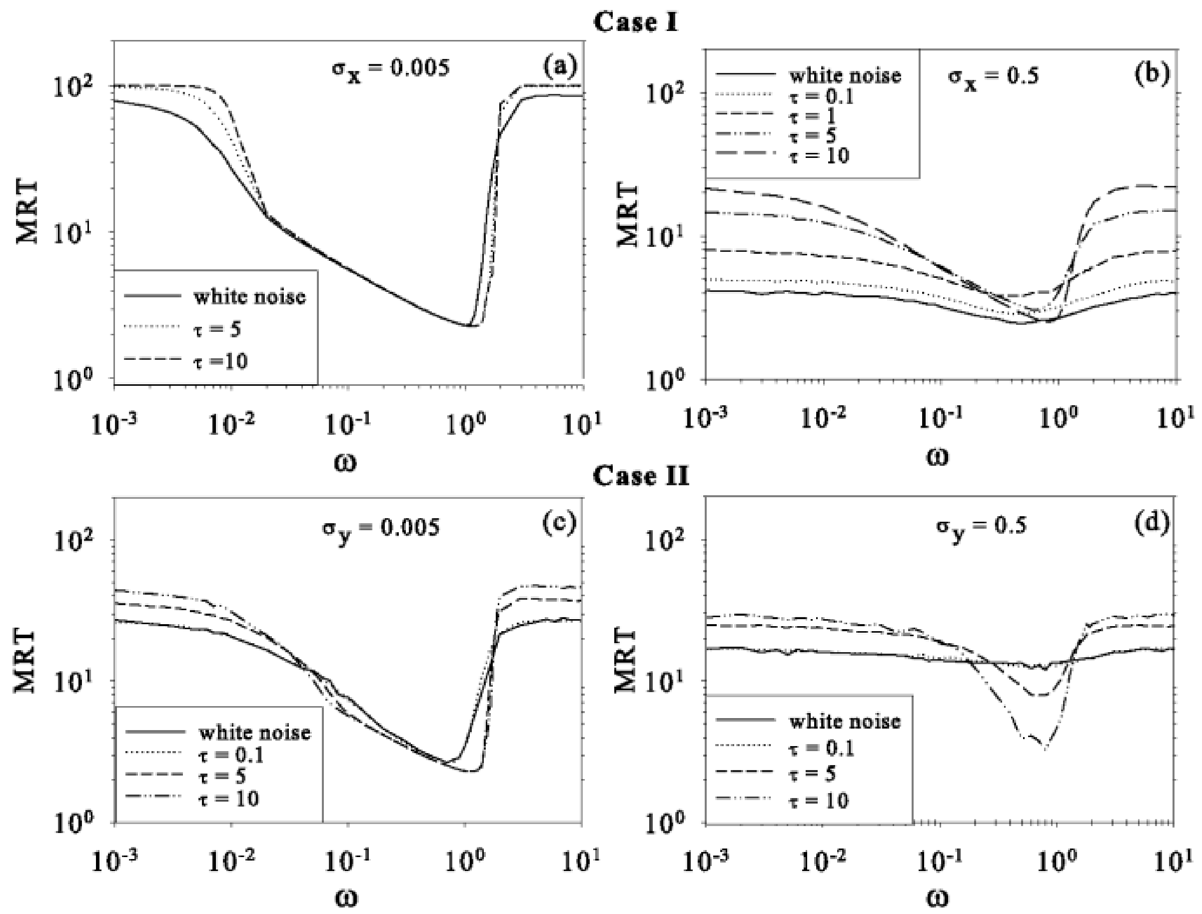


Fig B. FitzHugh–Nagumo model with separated time scales. All parameters are identical to those of fig A except for ε. which has been reduced by a factor of 10. Owing to slow w-dynamics, pulses are much broader than in Fig. A.

APPENDIX E: MRT WITH COLORED NOISE AT DIFFERENT CORRELATION TIME



See *D. Valenti*, G. Augello, B. Spagnolo - Role of the colored noise in a FitzHugh-Nagumo system driven by a periodic signal*

Figs. (a) and (c) For low noise intensities a slight displacement of the RA minimum is observed as the correlation time T increases (weak suppression of the noise effects), (b) and (d) For higher noise intensities the minimum of RA is strongly affected by the value of T. Both in cases I and II the RA minimum almost disappears for white noise, while it is more pronounced for high values of T (strong suppression of the noise effects).

APPENDIX F: NUMERICAL RESULTS FOR STANDARD DEVIATION BOTH CASES

- Standard deviation σ has a minimum too, in both cases, as a function of driving frequency.
- The noise has minimal effect in the same range of frequencies where we observe resonant activation-like phenomenon.

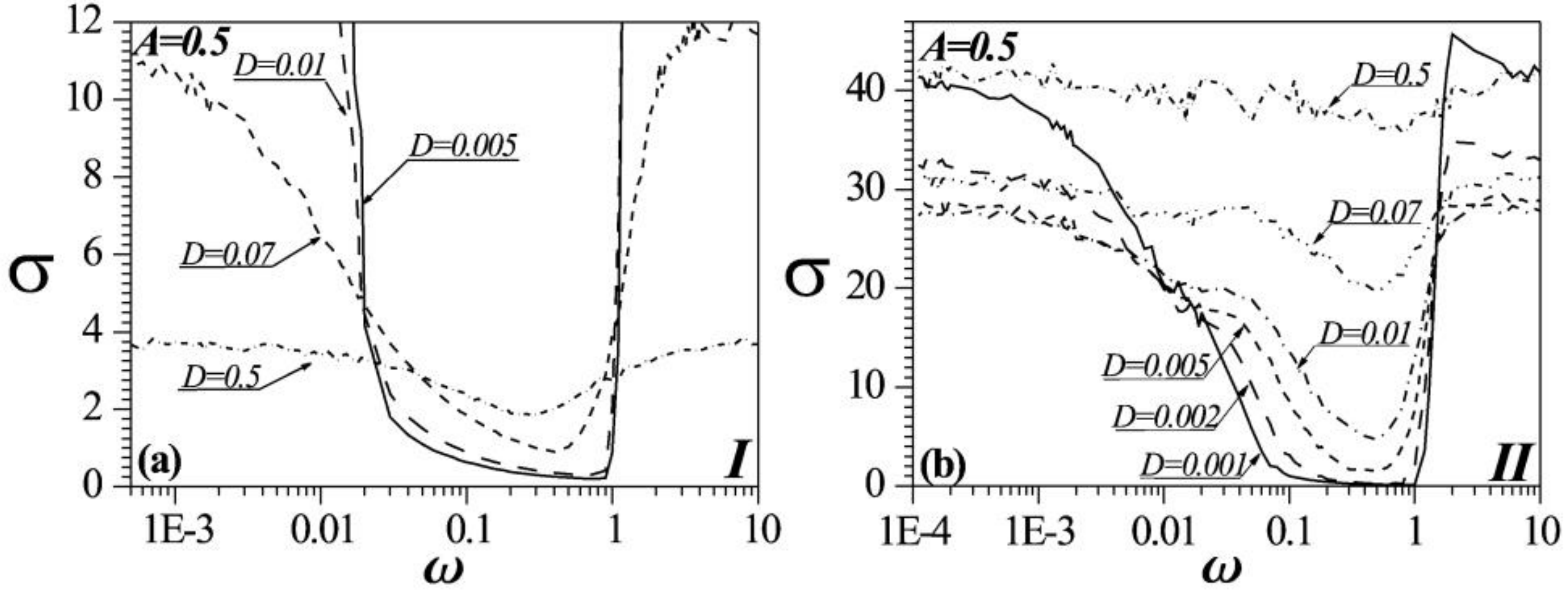


Fig. 5. The standard deviation of the response time dependence vs frequency of periodic driving for case I (a) and case II (b). The parameter values are respectively equal to those of Figs. 3 and 4.