Моделирование активности дофаминовых нейронов

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НИУ ВШЭ

Motivation

DA neuron model and VTA curvuit

Dynamical mechanisms substantially increasing the DA neuron frequency:

- NMDA synaptic current
- change of the spike generation class (EtOH)
- Ach and nicotinic inputs
- a strong high-frequency input

Conclusion

QS world university rating 2023

QS World University Rankings by Subject

TOP100 TOP300 ★ — единственный вуз из России

Предмет	Год	Мир	РФ
Mathematics	2023	**68**	2
Economics & Econometrics	2023	**71**	1
Linguistics	2023	**75**	3
Sociology	2023	**91**	1
Education & Training	2023	**94**	2
Psychology	2023	**100**	1
Geography	2023	**51-100**	1
History	2023	**51-100**	1-2
Social Policy & Administration	2023	**51-100**	2-3
Politics	2023	**51-100**	2-4

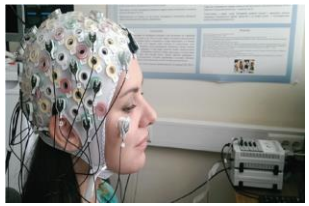
Институт когнитивных нейронаук (https://neuro.hse.ru/)

- **Центр нейроэкономики и когнитивных исследований**
  - Группа нейроэкономики
  - Группа Изучения Когнитивного Контроля, Коммуникации и Восприятия
  - Группа изучения динамики нейрональных процессов
  - Группа изучения моторного контроля
  - МЭГ группа
  - Группа математического моделирования
- **Центр биоэлектрических нейроинтерфейсов**
  - Нейроинтерфейсы
  - Энцефалография реального времени
  - Решение обратной задачи ЭЭГ/МЭГ
- **Международная лаборатория социальной нейробиологии**

Института когнитивных нейронаук

Уникальный набор оборудования:

- транскраниальная магнитной стимуляция (ТМС, NexStim+Magventure)
- транскраниальная электрическая стимуляции (ТЭС, ТЭС+ЭЭГ, ПЭС)
- МЭГ (на базе МГПУ)
- регистрация движения глаз (окулография)
- электроэнцефалография (ЭЭГ, BrainProducts)
- интерфейсы мозг-компьютер и нейрообратная связь
- инфракрасная спектроскопия
- виртуальная реальность + регистрация движений
- магнитометр с оптической накачкой
- регистрация вегетативных ответов (дыхания, ЧСС, КВР)



АСПИРАНТСКАЯ ШКОЛА ПО КОГНИТИВНЫМ НАУКАМ

В **НИУ ВШЭ** на базе **Института когнитивных нейронаук** создана
аспирантура по Специальности 5.12 “Когнитивные науки”:

5.12.1. Междисциплинарные исследования когнитивных процессов.

5.12.2. Междисциплинарные исследования мозга.

5.12.3. Междисциплинарные исследования языка.

5.12.4. Когнитивное моделирование.

Набор – **10 человек в год** (первый набор – март 2023 года)

Виды аспирантуры:

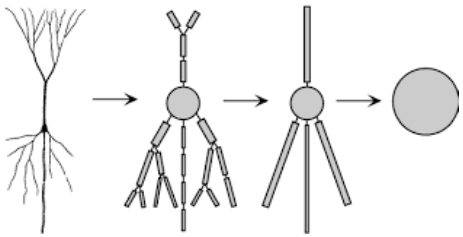
- «обычная»
- академическая (стипендия 40 тыс. руб.)
- «единый» трек: магистратура (стипендия 50 тыс. руб.) + аспирантура (стипендия 70 тыс. руб.)

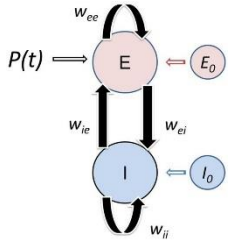
Защита будет проходить в специализированном диссовете по когнитивным наукам

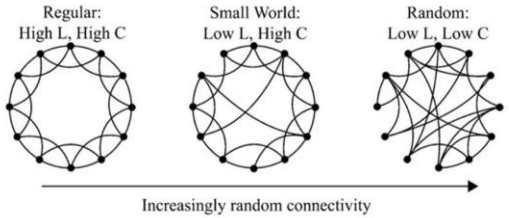
(степени психологических, биологических, филологических и физико-математических наук)

Neuron models

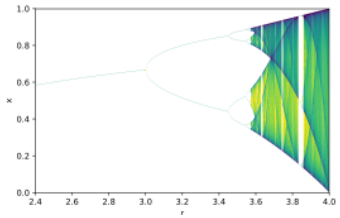
- Mathematical models
  - neurons
    - phenomenological
      - Izhikevich
      - FitzHugh-Nagumo
      - Hindmarsh-Rose
    - biophysical
      - Hodgkin–Huxley
      - Morris–Lecar model
  - networks
    - mean field
      - Wilson–Cowan
    - coupled neurons

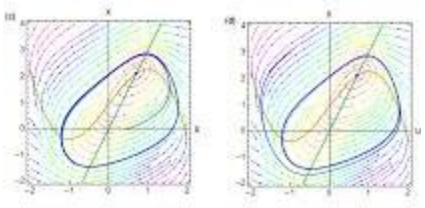


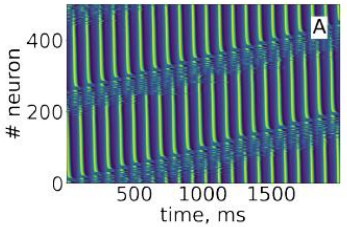




Methods: Bifurcation analysis, Evolution of phase portraits, raster plots, order parameters



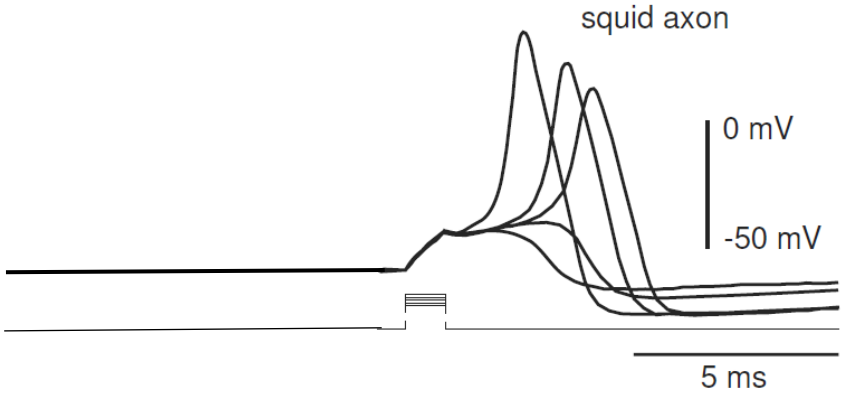




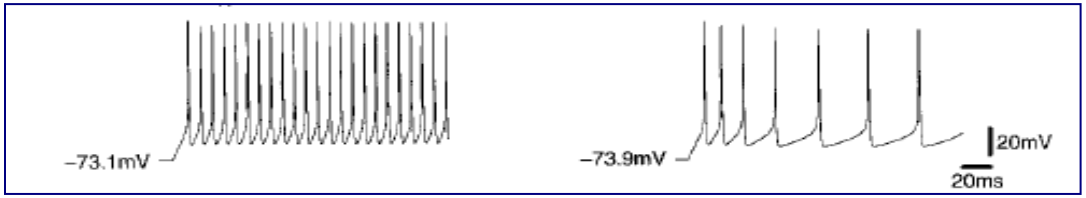
$$re^{i\psi} = \frac{1}{N}\Sigma_{j=1}^{N} e^{i\theta_j}$$

Basic types of neuronal activity

- Rest state (excitable state);

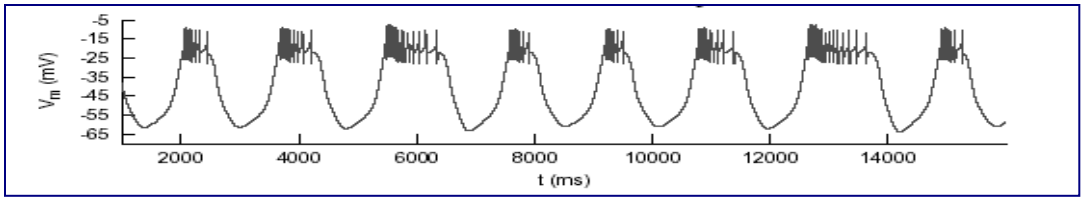


- Generation of action potentials (spiking)



Oscillations of piramidal neurons (*D.Golomb, Y. Amitai, 1998*)

- Bursting activity



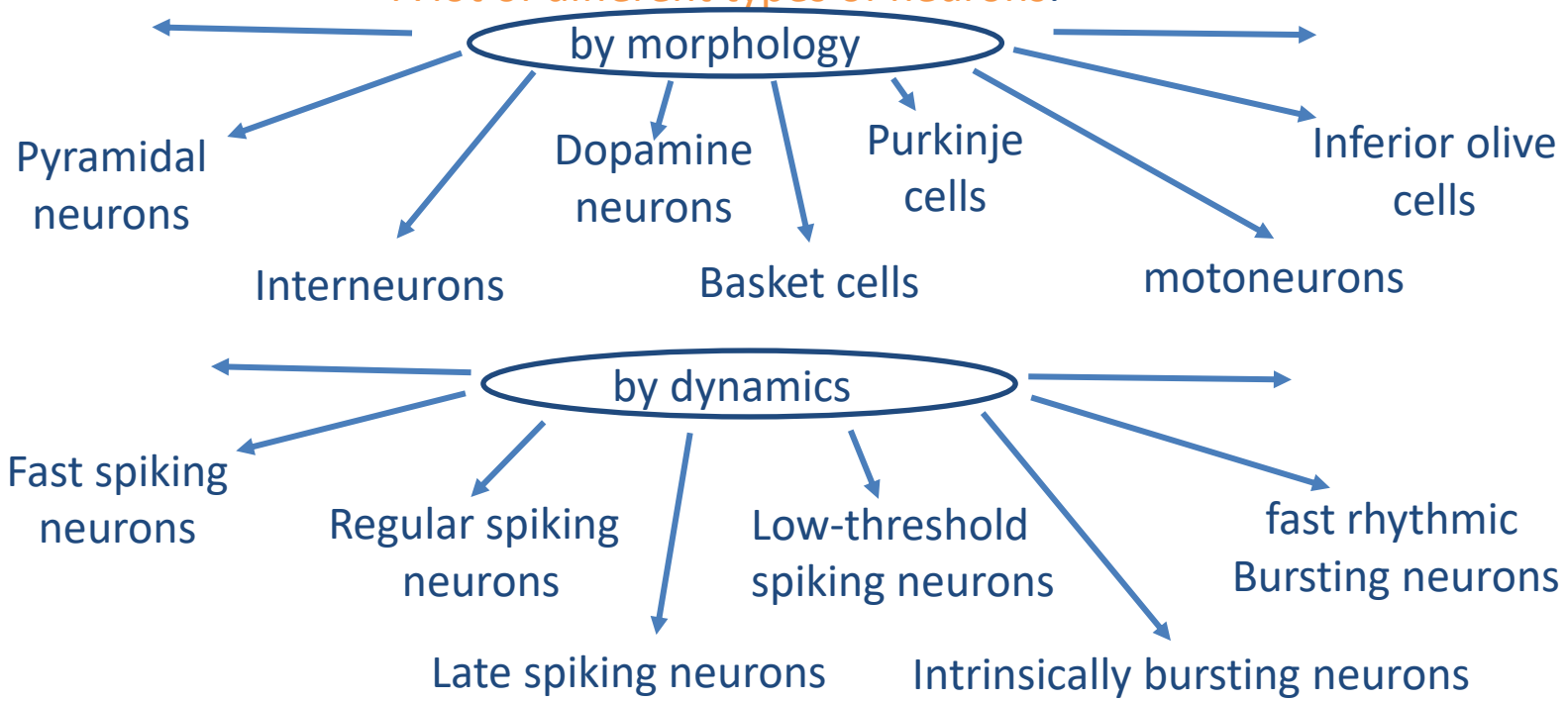
Chaotic oscillations of motor neurons *(P. Varona, et al., Neural Networks 2001*)

Motivation

Brain is a extremely complex system:

10^{11} neurons, much larger number of glial cells, etc.

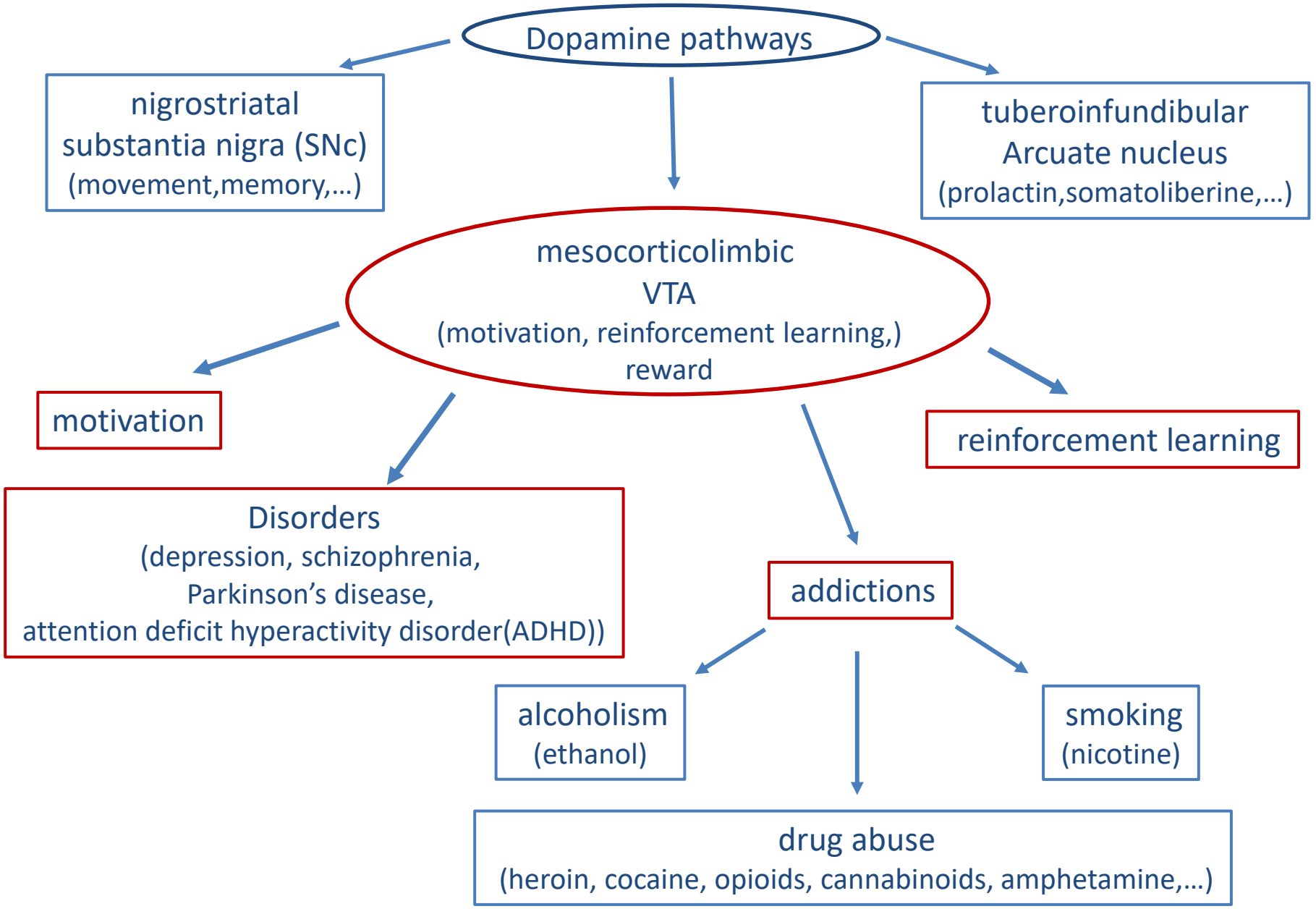
A lot of different types of neurons:



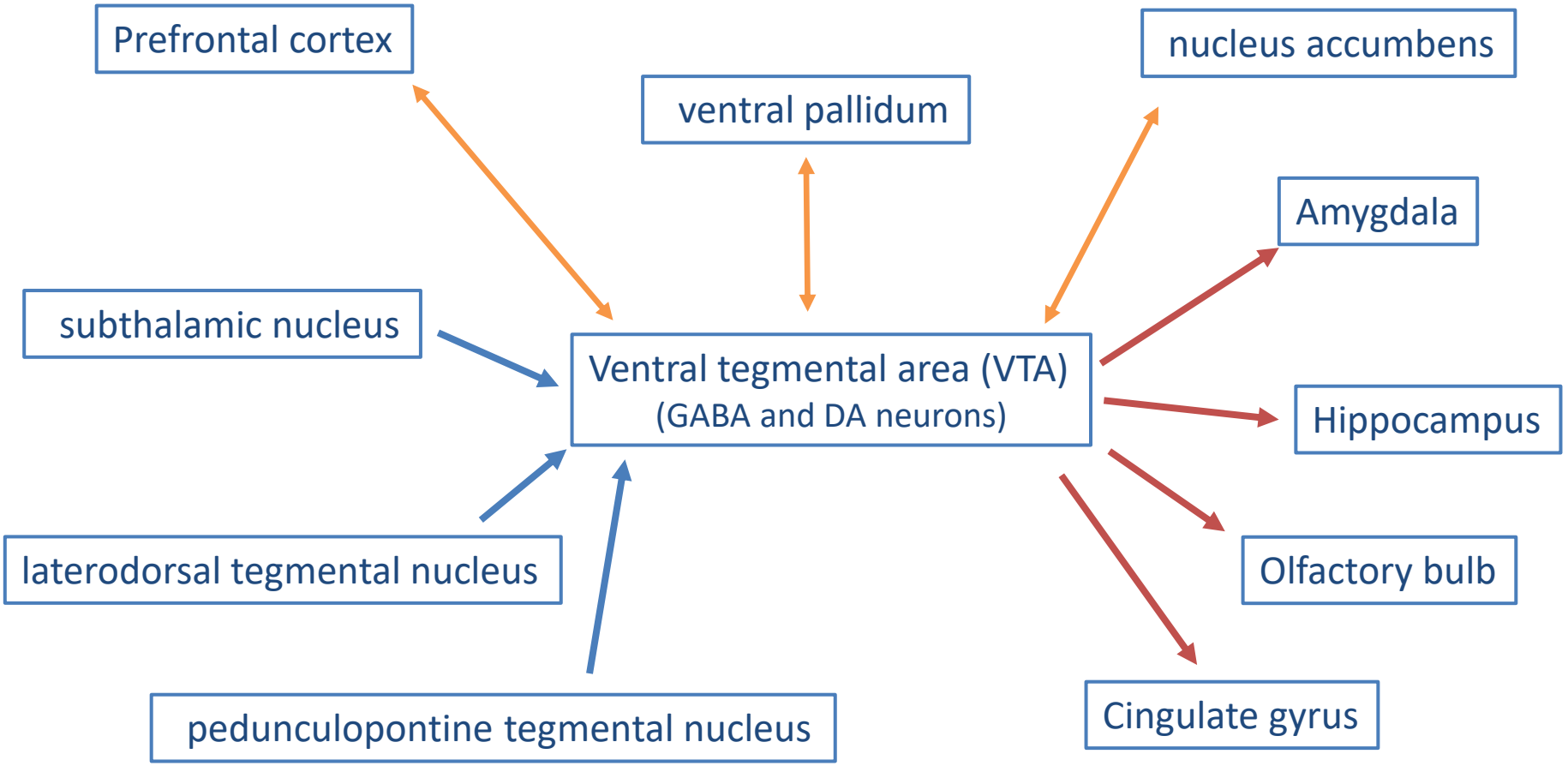
Each neuron has approx. 10^5 couplings $\Rightarrow$ 10^{16} connections between neurons:

- local and nonlocal (including connections between brain areas)
- Gap junctions and excitatory (AMPA, NMDA,…) and inhibitory (GABA, DA, …) chemical synapses
- Synaptic plasticity (Short and long term plasticity)
- etc.

Dopamine system

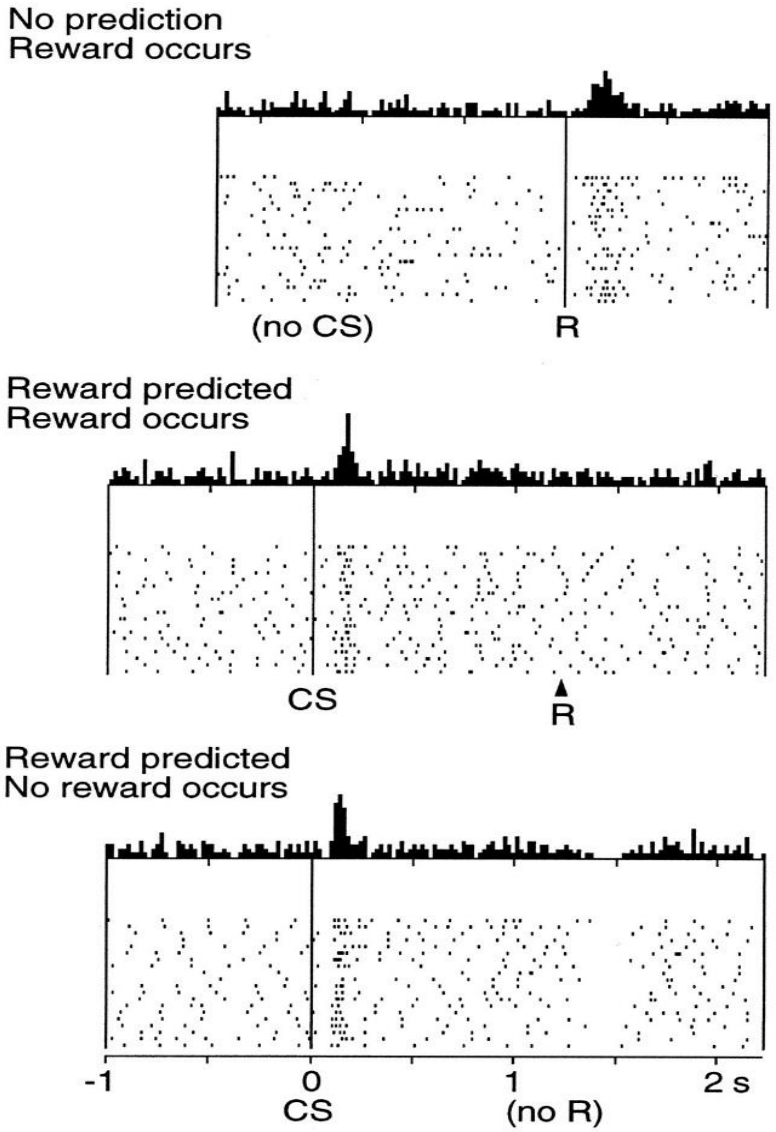


DA system


Prefrontal cortex
ventral pallidum
nucleus accumbens
Amygdala
subthalamic nucleus
Ventral tegmental area (VTA)
(GABA and DA neurons)
Hippocampus
laterodorsal tegmental nucleus
Olfactory bulb
pedunculopontine tegmental nucleus
Cingulate gyrus

DA neurons

Dopaminergic neurons (DA neurons) are the main source of dopamine in the mammalian central nervous system.



W. Schultz, J. Neurophysiol. 80:1-27(1997)

Experimental facts about DA neuron activity

Types of firing activity:

- Tonic activity, 1-5 Hz (without external stimuli);
- Phasic activity, >20 Hz (NMDA, NMDA+AMPA)

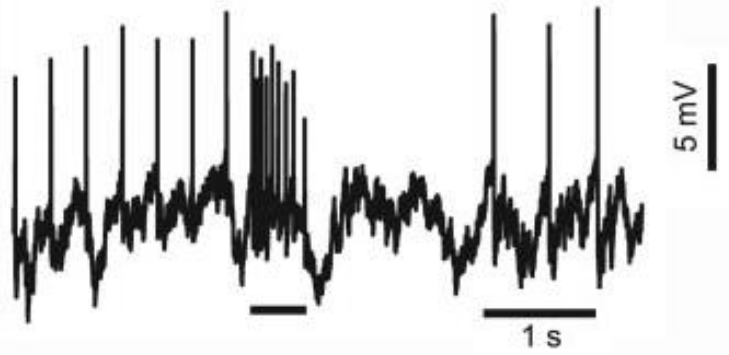
Response differentiation:

- NMDA current ⇒ high-frequency activity >20Hz
- AMPA current or applied current

⇓

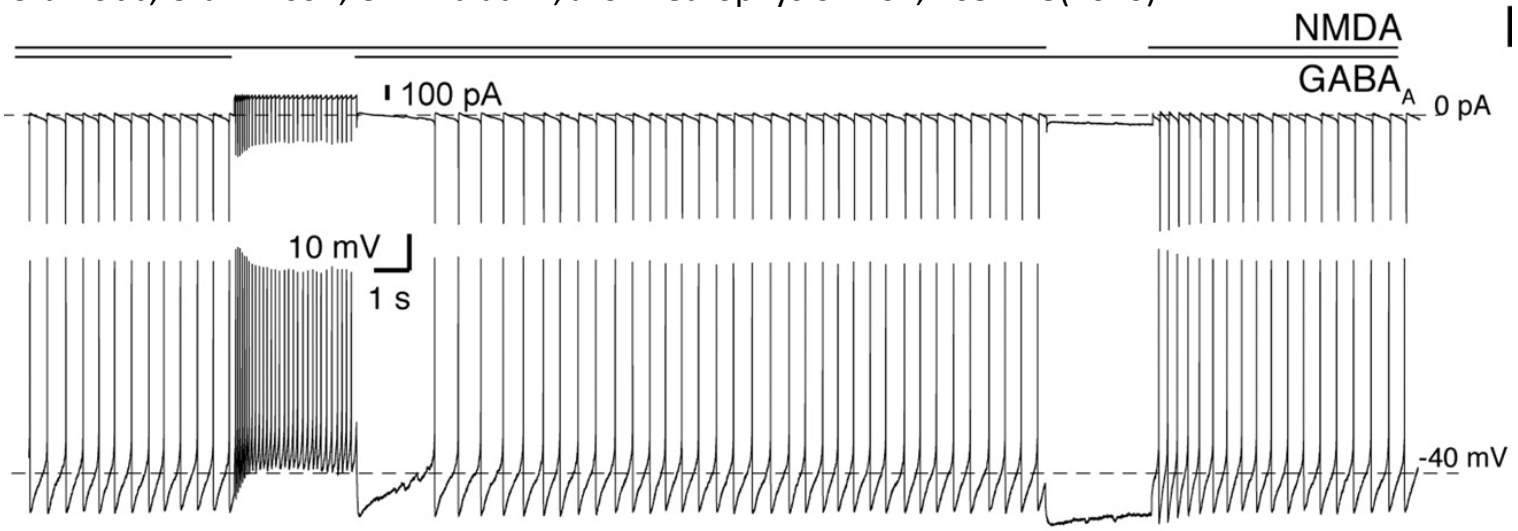
low-frequency activity <10Hz or activity suppression;

S. N., J. F. Atherton, and M. D. Bevan, *J. Neurophysiol.* **97,** 2837 (2007): A time series of high-frequency activation *in vitro* of a DA neuron (stimulation duration is shown by black line).



Compensation of actions of NMDA and GABA currents:

C. J. Lobb, C. J. Wilson, C. A. Paladini, J. of Neurophysiol. **104**, 403-413(2010)



Types of neuronal excitability

A.L. Hodgkin, J. Physiol., 107, 165, 1948:

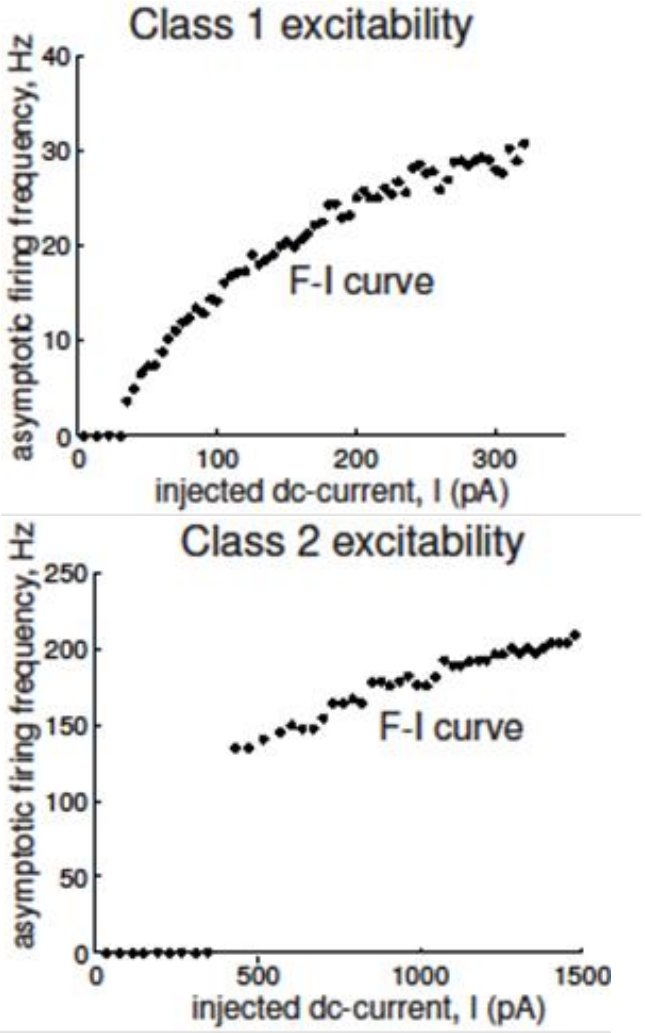
- **Type I.** Spikes can be generated with arbitrary low frequency, depending on the strength of the stimulus (applied current, synaptic currents, etc.);
- **Type II.** Spikes can be generated in a certain frequency band that is relatively insensitive to changes in the strength of the stimulus;
- **Type III.** A single spike can be generated in response to a pulse current. Repetitive spiking can be generated only for extremely strong injected current or not at all.

Why is it important for DA neuron dynamics:

- accurate encoding of reward level in firing frequency
- synchronization properties (leading to changing in dopamine release)

etc.

Izhikevich E. M. (2007) *Dynamical Systems in Neuroscience*: *The Geometry of Excitability and Bursting*, Cambridge, Mass: MIT Press.



A biophysical model of a DA neuron

E. Morozova, M. Myroshnychenko, D.Zakharov, M. di Volo , C. Lapish, B. Gutkin, A. Kuznetsov, Journal of Neurophysiology 116(4):1900–1923, 2016;
E. Morozova, D.Zakharov, C. Lapish, B. Gutkin, A. Kuznetsov, PLOS CB 12(12): e1005233, 2016.

Subthreshold oscillations:

$$C_m \frac{dv}{dt} = \overbrace{g_{Ca}(v)(E_{Ca} - v)}^{I_{Ca}} + \overbrace{(g_{KCa}([Ca^{2+}]) + g_K(v))(E_K - v)}^{I_{KCa}+I_K} + \overbrace{g_{sNa}(v)(E_{Na} - v)}^{I_{sNa}} + g_l(E_l - v) + I_{sti},$$

$$\frac{d[Ca^{2+}]}{dt} = \frac{2\beta}{r}\left(\frac{g_{Ca}(v) + 0.1g_L}{zF}\right)(E_{Ca} - v) - P_{Ca}([Ca^{2+}])$$

Spike producing model:

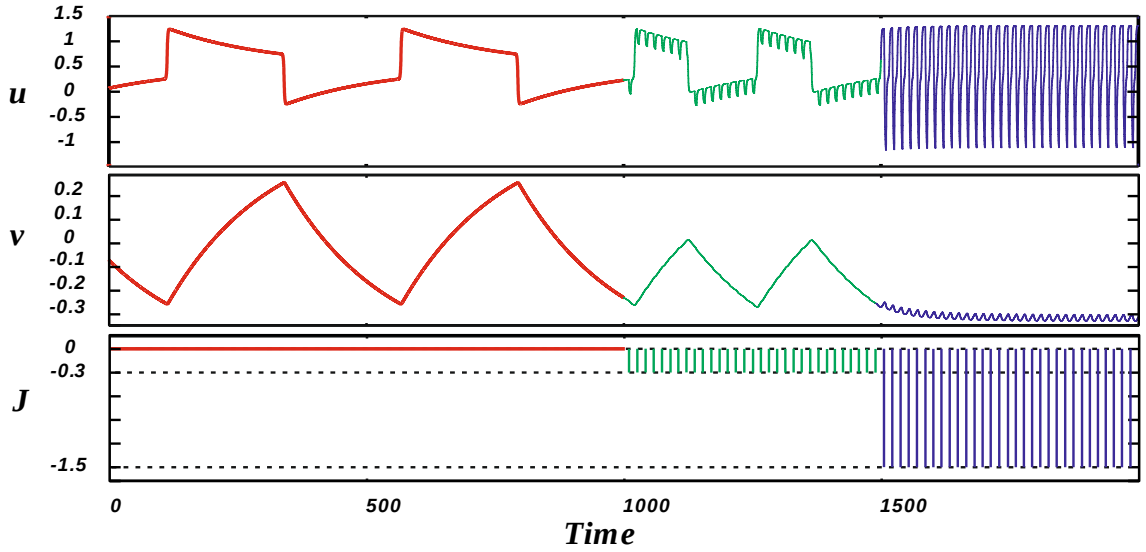
$$C_m \frac{dv}{dt} = \cdots + \overbrace{g_{Na}m^3h(E_{Na} - v)}^{I_{Na}} + \overbrace{g_{DR}n^4(E_K - v)}^{I_{DR}},$$

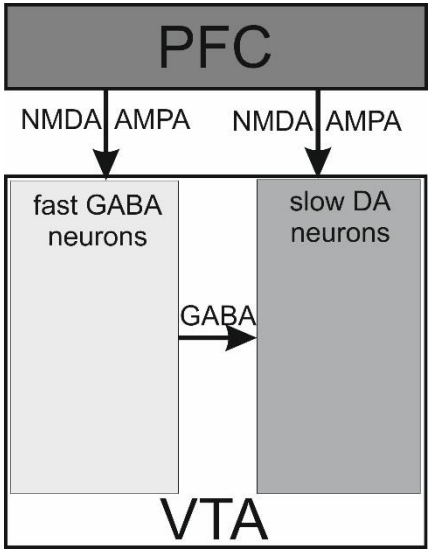
External stimuli (tonic case):

$$I_{sti} = I_{app} + g_{AMPA}(E_{AMPA} - v) + g_{GABA}(E_{GABA} - v) + \frac{g_{NMDA}}{1 + 0.1[Mg^{2+}]e^{-m_e v}}(E_{NMDA} - v)$$

Ways to initiate high-frequency activity of a DA neuron

- **Tonic activation of NMDA receptors or simultaneously activation of NMDA and AMPA receptors (**experimental fact**)**
- **A strong (excitatory or inhibitory) high-frequency input (**Zakharov et al., PRE 97, 062211, 2018**)**





- **Change of excitability type from I to II**

⇓

improvement of synchronization properties

⇓

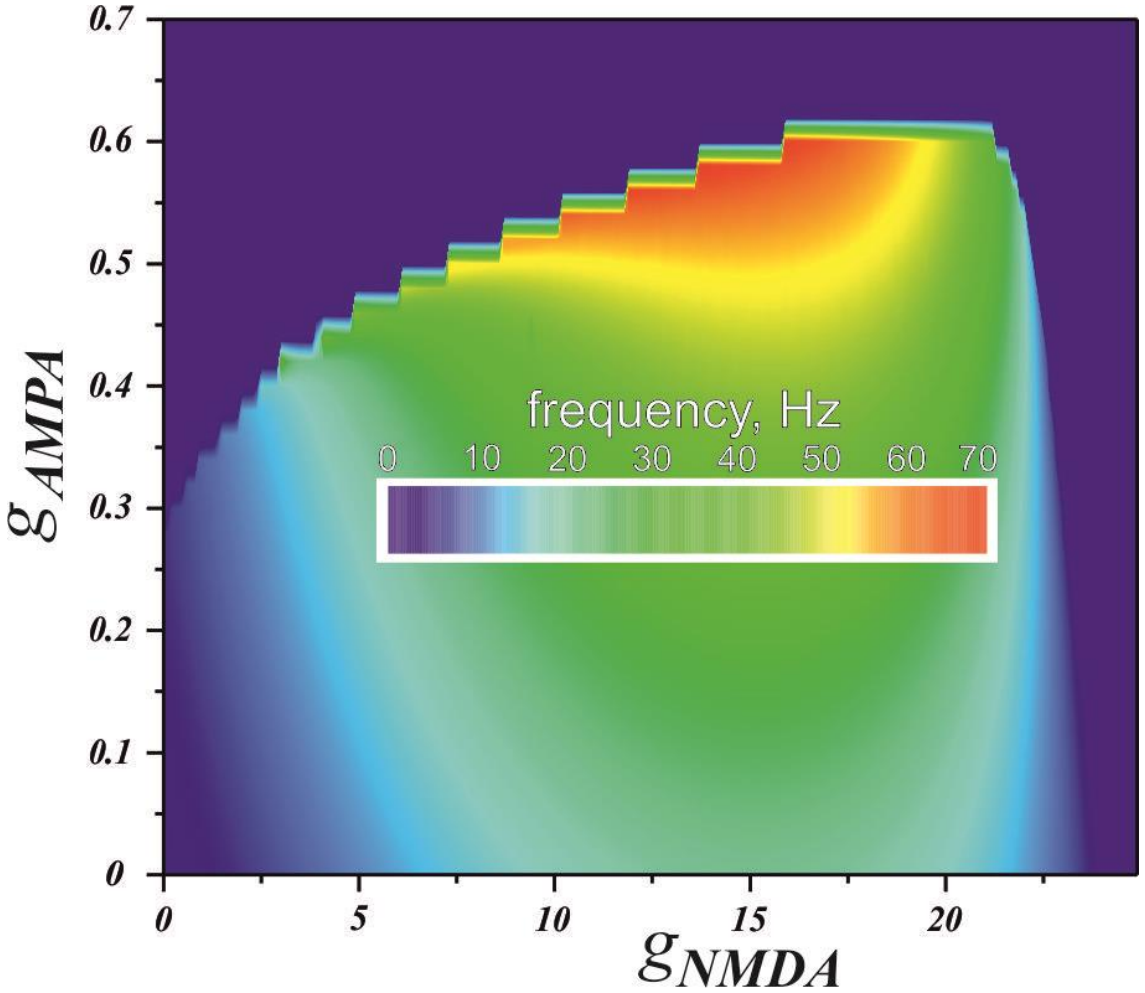
higher firing rate

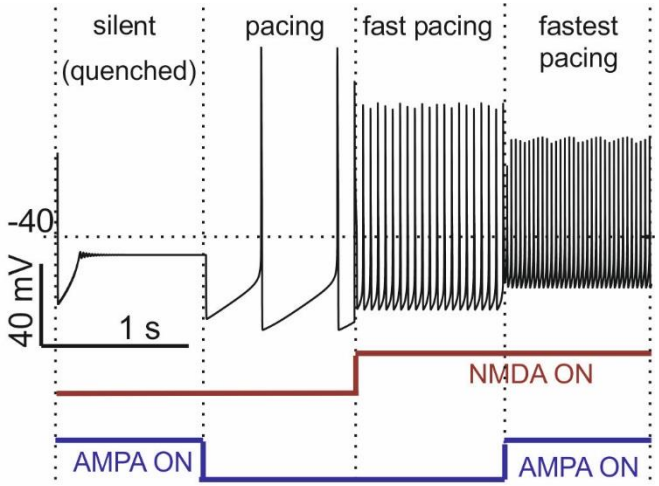
⇓

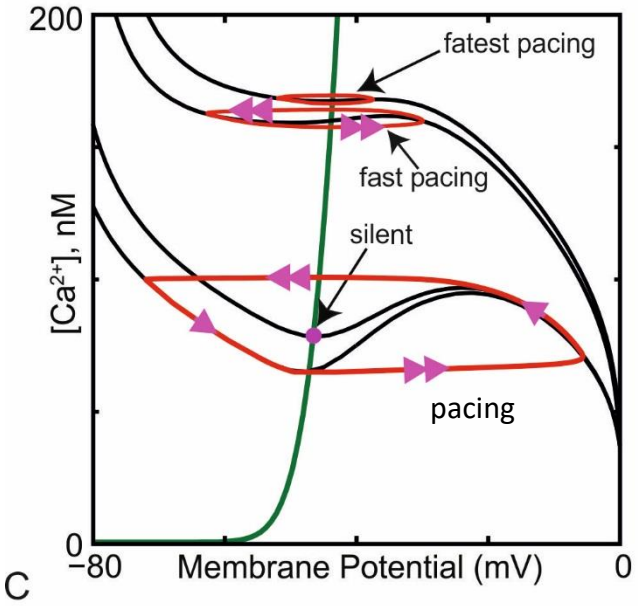
increased dopamine release

(E. Morozova et al., Journal of Neurophysiology, 116(4), 1900–1923, 2016**)**

Different responses on AMPA and NMDA current







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E. Morozova, D.Zakharov, C. Lapish, B. Gutkin, A. Kuznetsov, PLOS CB 12(12): e1005233, 2016.

D. Zakharov, C. Lapish, B. Gutkin, A. Kuznetsov, Front. Comput. Neurosci. 10: article 48(2016)

A phenomenological model of a DA neuron (subthreshold oscillations)

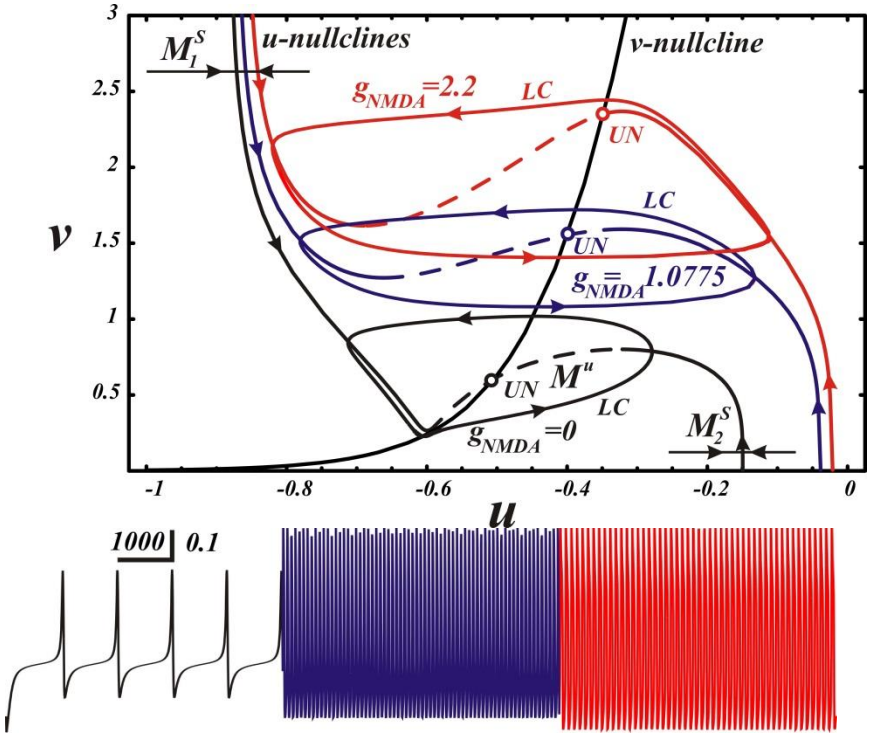
$$\frac{du}{dt} = -(u - 1.35)(u - 0.54)(u - 0.0539) + \boldsymbol{j_{KCa}\,(u,v)} + I_{sti},$$

$$\frac{dv}{dt} = \varepsilon\,(\tanh(5u - 3.85) - v).$$

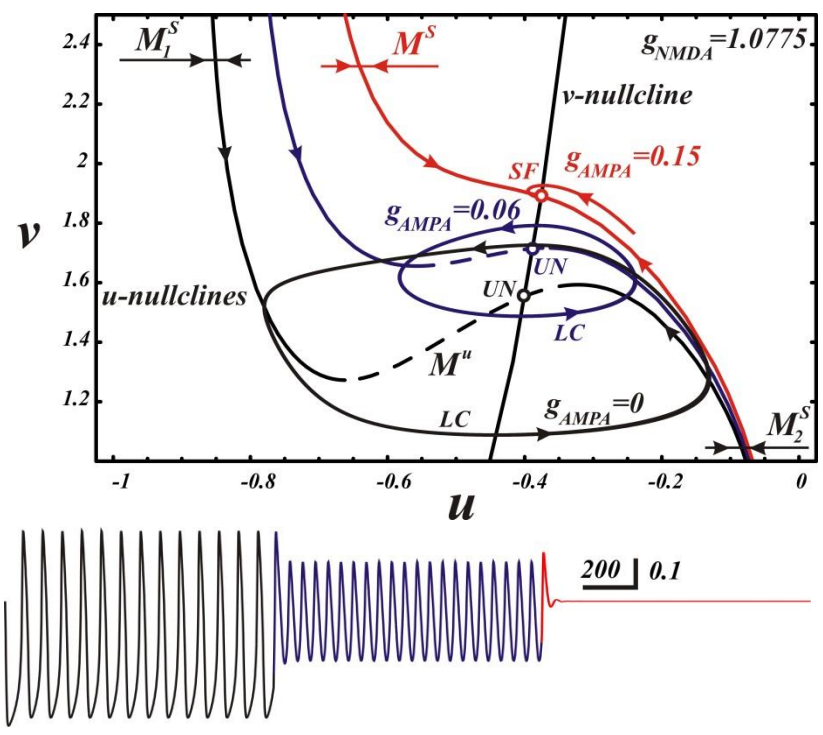
$$I_{sti} = I_{app} + g_{AMPA}(E_{AMPA} - v) + g_{GABA}(E_{GABA} - v) + \frac{g_{NMDA}}{1 + 0.1[Mg^{2+}]e^{-m_e v}}(E_{NMDA} - v)$$

Response differentiation:

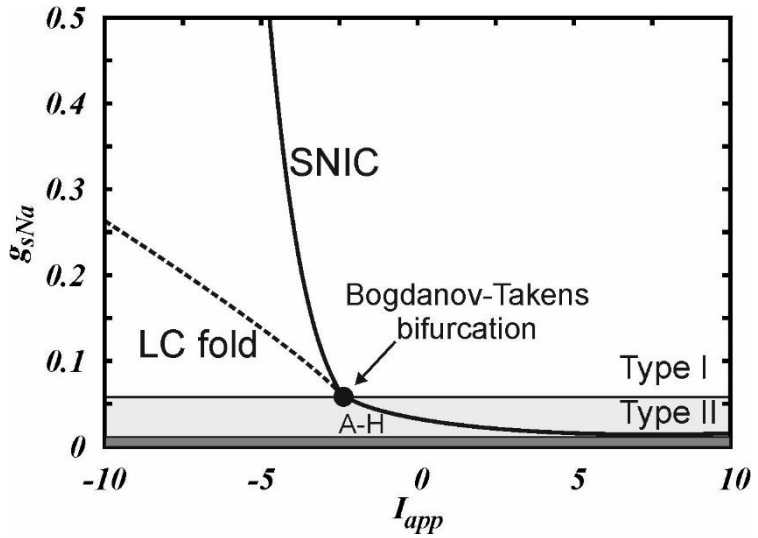
NMDA

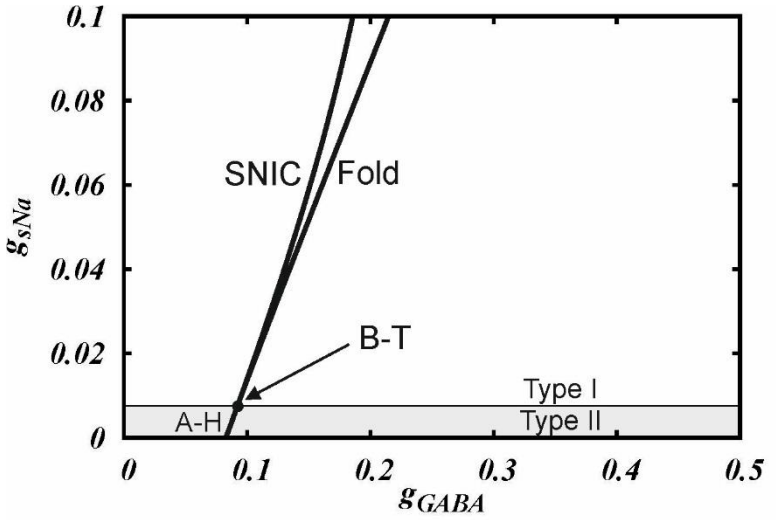


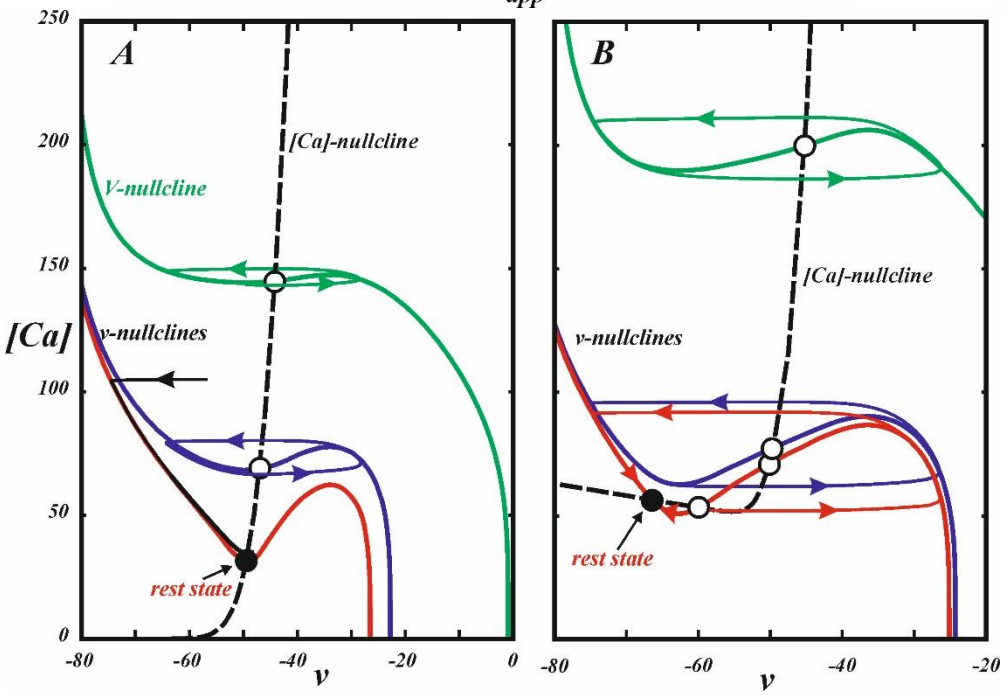
AMPA

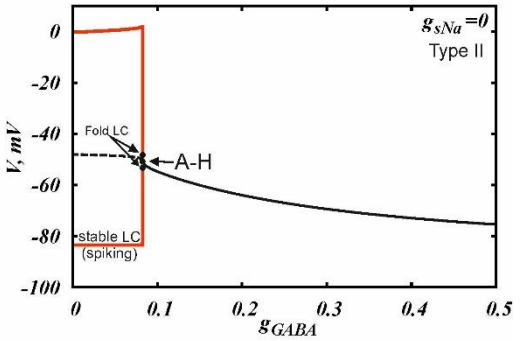


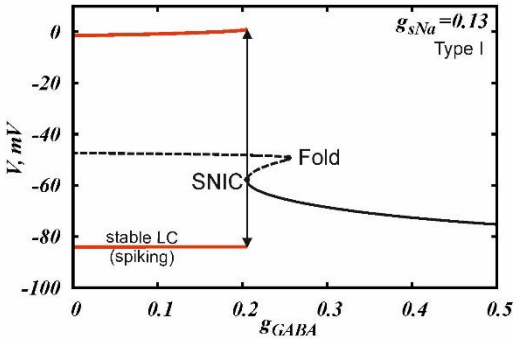
Role of a subthreshold Na^+ current



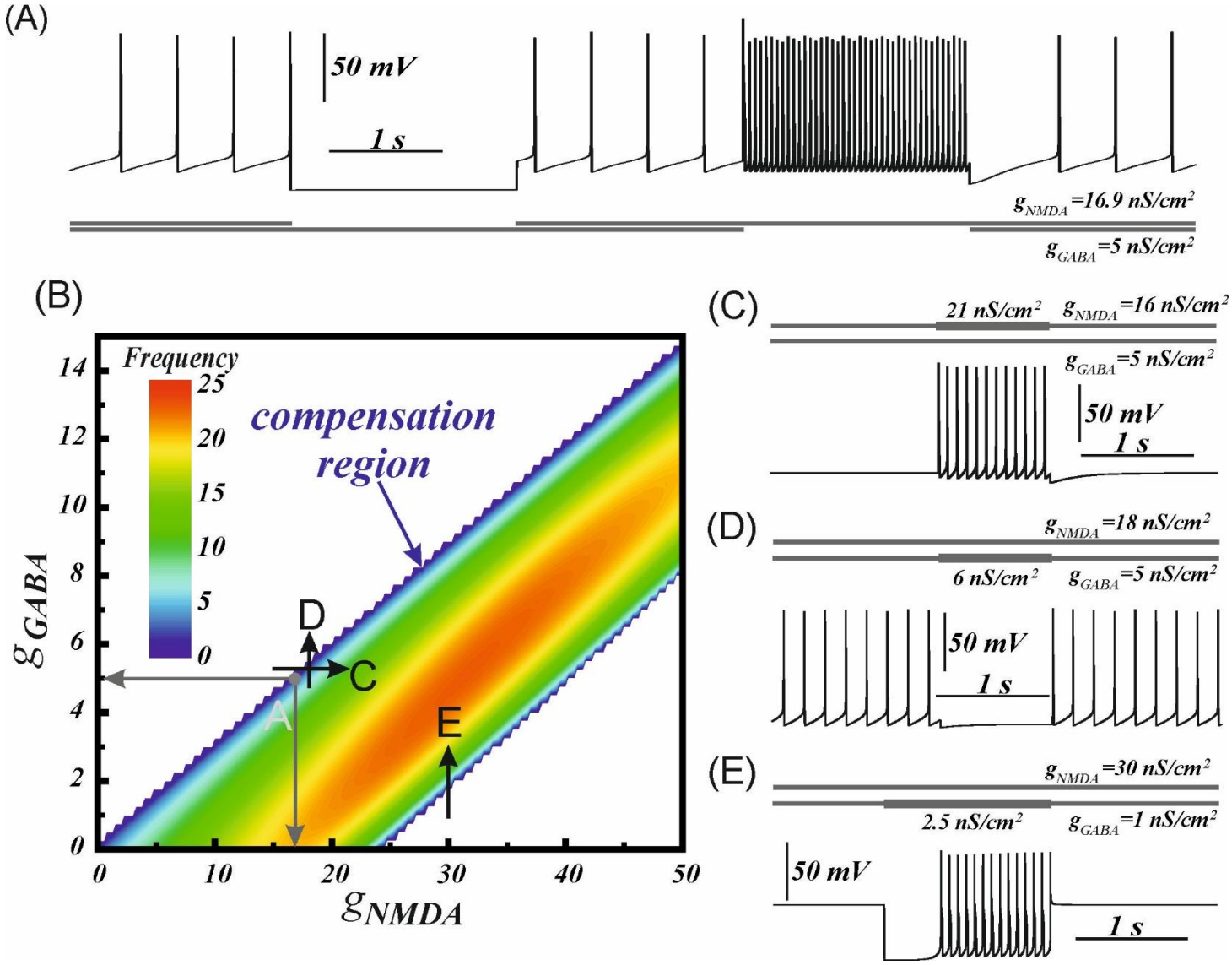








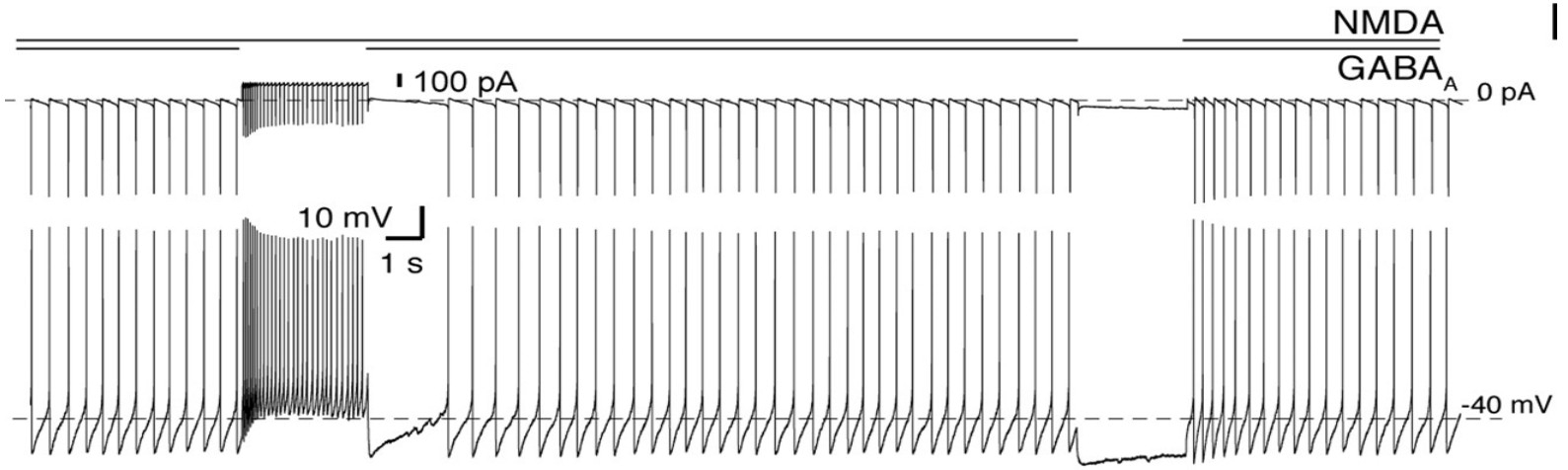
Compensation of the GABA and NMDA current



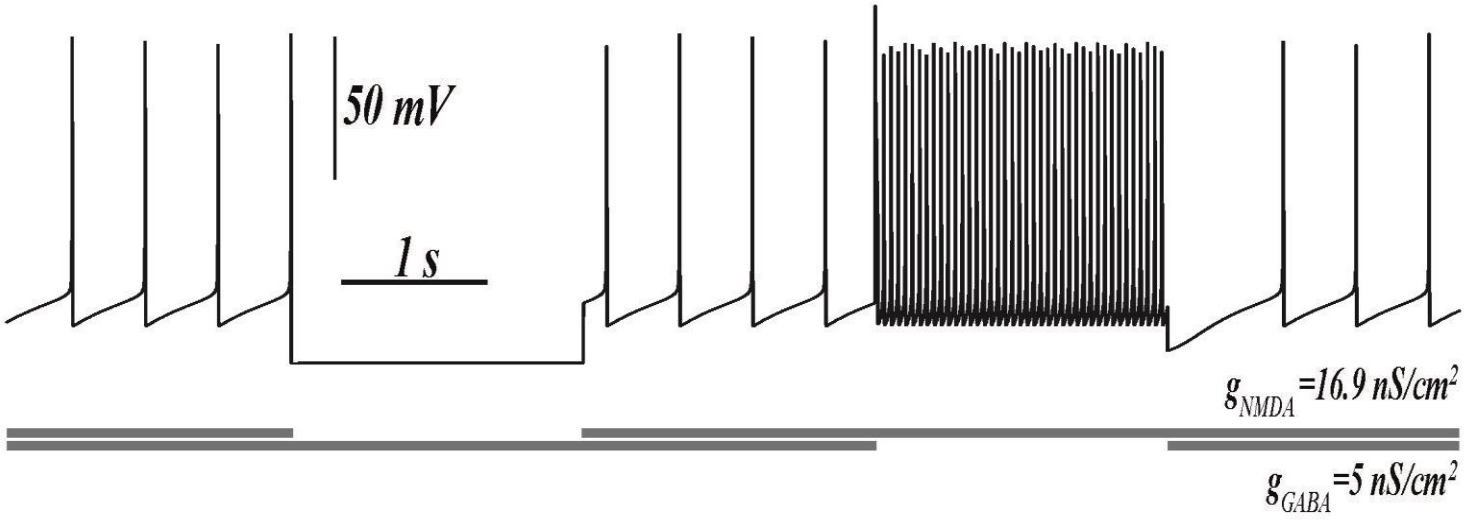
E. Morozova, D.Zakharov, C. Lapish, B. Gutkin, A. Kuznetsov, PLOS CB 12(12): e1005233, 2016.

Compensation of the GABA and NMDA current

Experiment, dynamical patch clamp (C. J. Lobb, C. J. Wilson, C. A. Paladini, J. of Neurophysiol. **104**: 403-413, 2010):



Biophysical model (E. Morozova, D. Zakharov, C. Lapish, B. Gutkin, A. Kuznetsov, PLOS CB 12(12): e1005233, 2016):

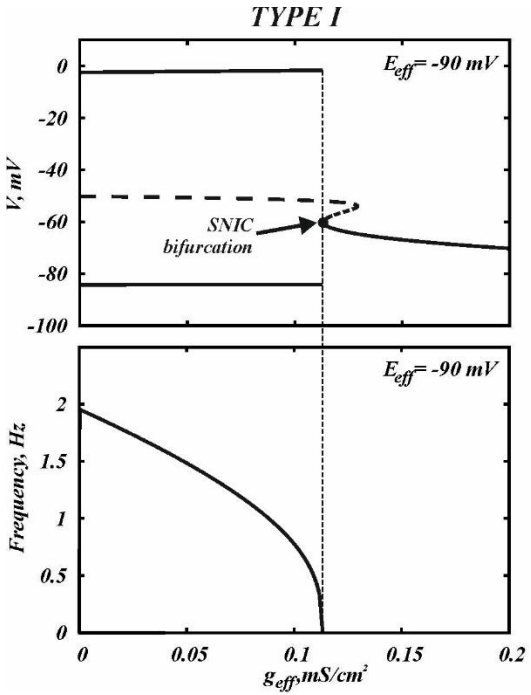


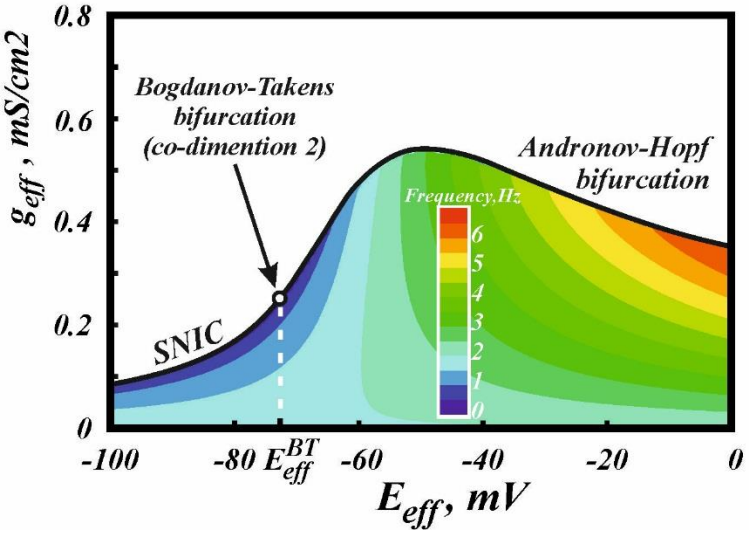
Role the GABA and AMPA current

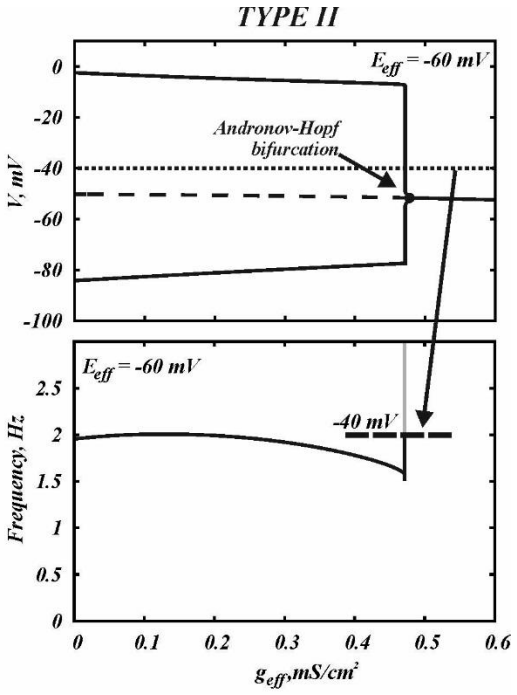
The AMPA and GABA currents are ohmic (they linearly depend on the membrane potential) and, thus, it is possible to introduce “effective ohmic current”:

$$I_{AMPA} + Ig_{GABA} = g_{eff}(E_{eff} - v),$$

$$g_{eff} = g_{AMPA} + g_{GABA}\ ,\quad E_{eff}\Big|_{E_{AMPA}=0} = \frac{g_{GABA}}{g_{GABA} + g_{AMPA}} E_{GABA}$$



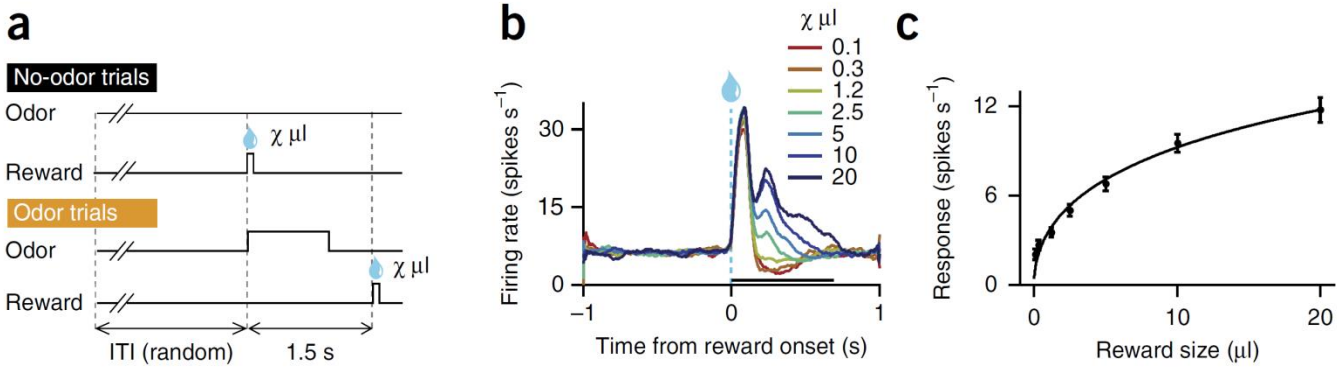




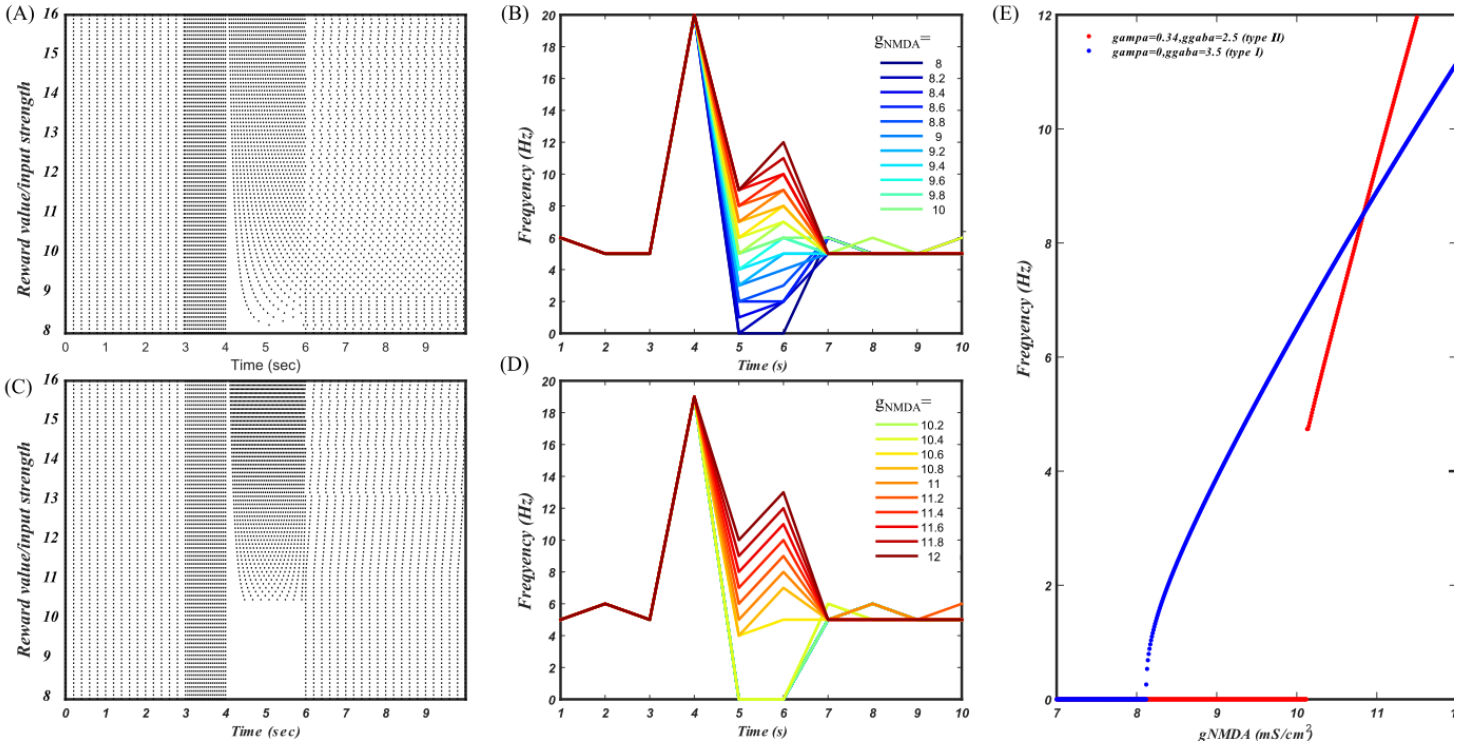
E. Morozova, D.Zakharov, C. Lapish, B. Gutkin, A. Kuznetsov, PLOS CB 12(12): e1005233, 2016.

Coding of the reward value by type I and type II DA neurons

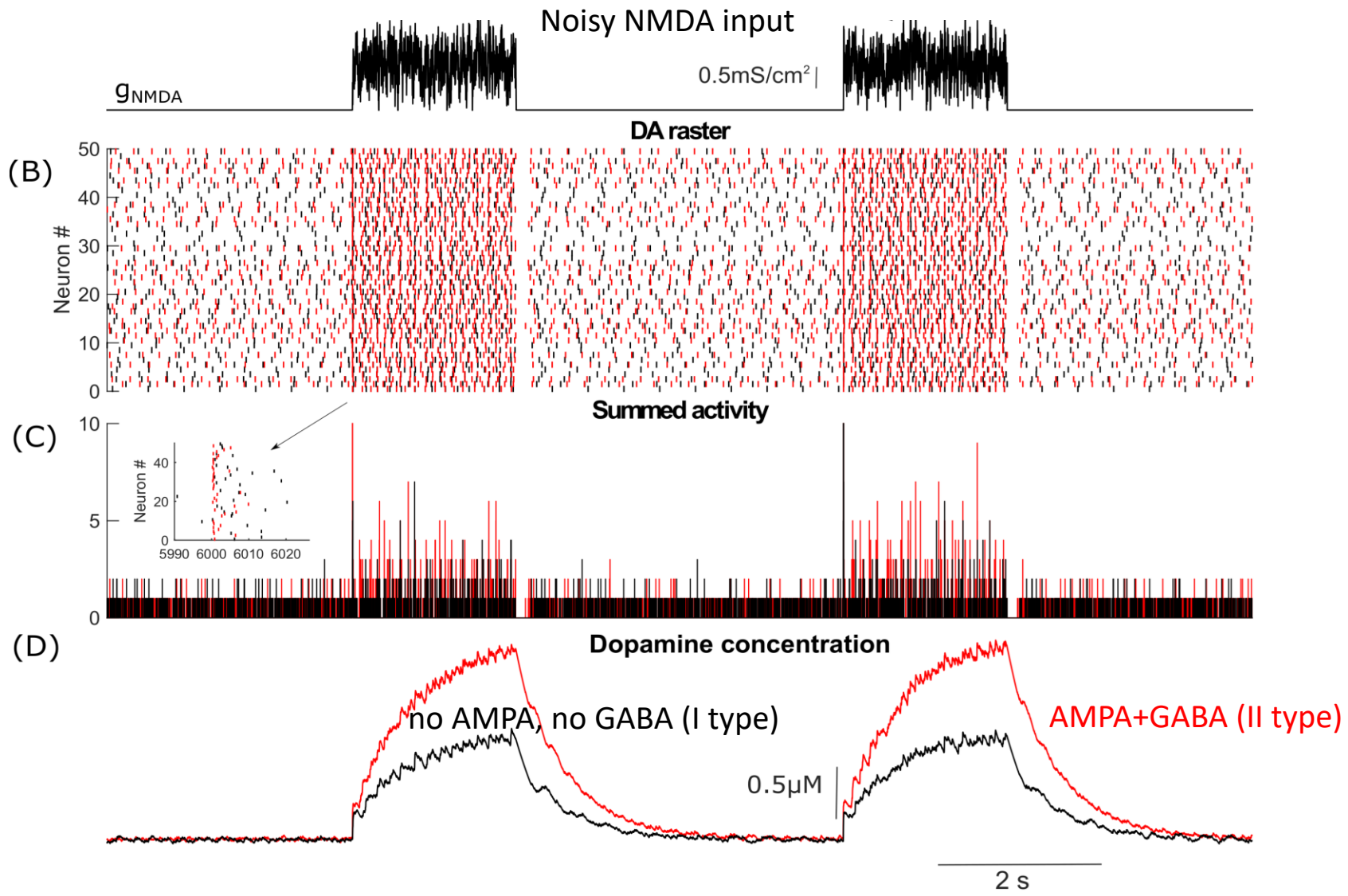
Experiment (N. Eshel et al. Nature Neurosci., 2016,1–11):



Biophysical model (E. Morozova, D.Zakharov, C. Lapish, B. Gutkin, A. Kuznetsov, PLOS CB, 2016):

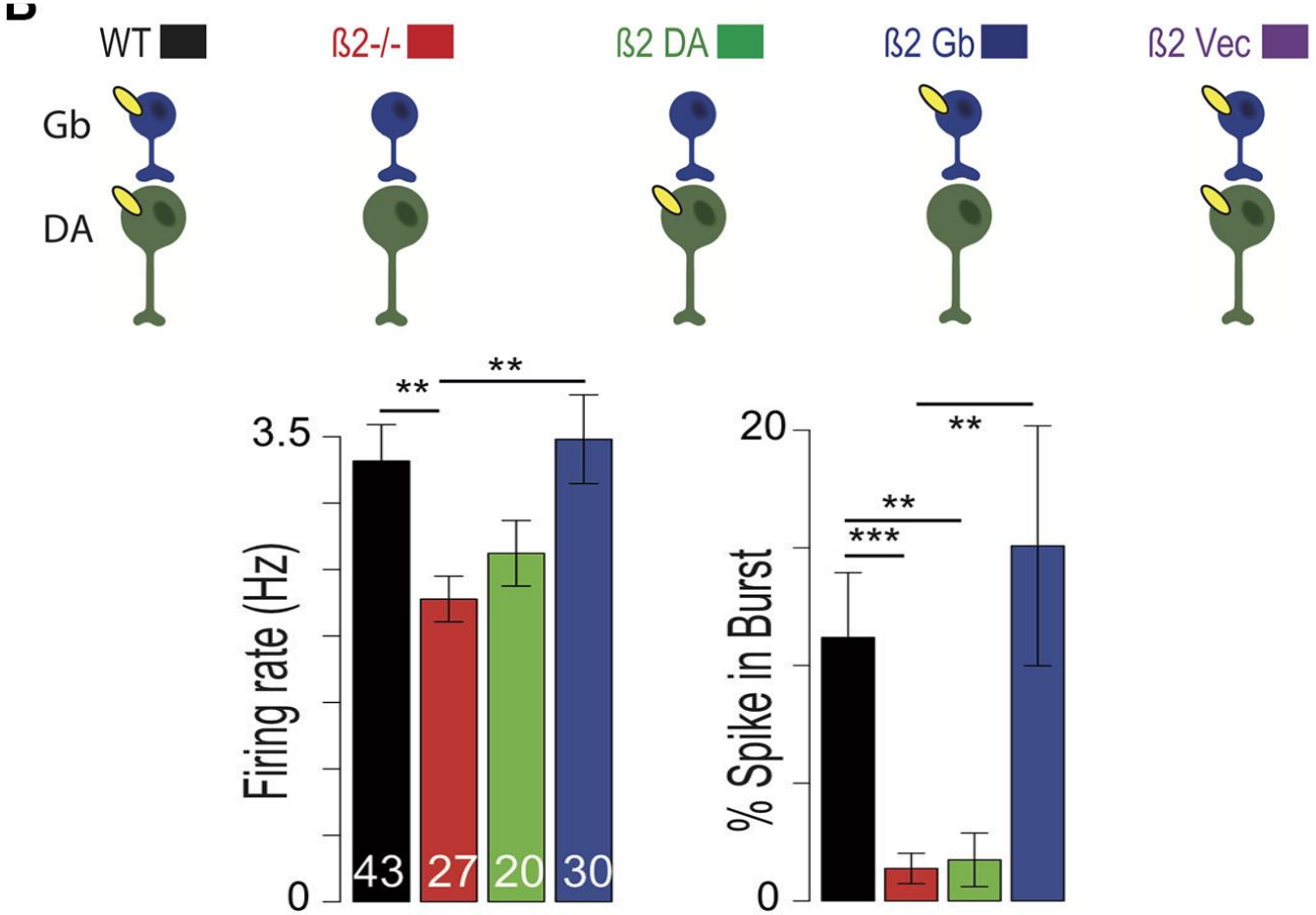


Role the GABA and AMPA current (change of excitability type)



E. Morozova, D.Zakharov, C. Lapish, B. Gutkin, A. Kuznetsov, PLOS CB 12(12): e1005233, 2016.

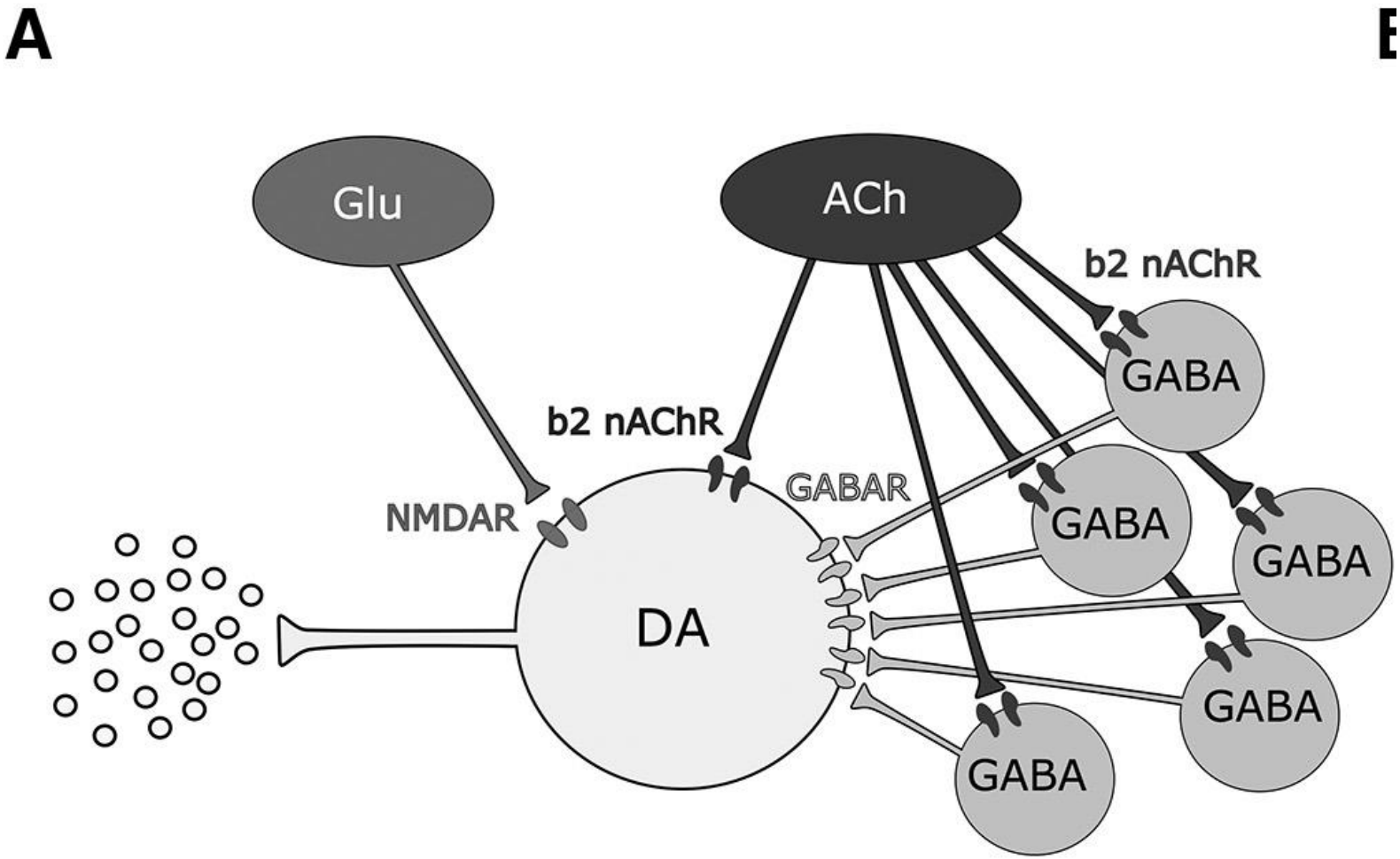
Responses of VTA Neurons to Endogenous ACh and Nicotine



Quantification of firing rate and pattern of the VTA DA neurons in WT mice (black) after systemic deletion of b 2-containing nAChRs (red) and their subsequent re-expression on VTA DA (green), on VTA GABA (blue), and on both neurons (purple). A

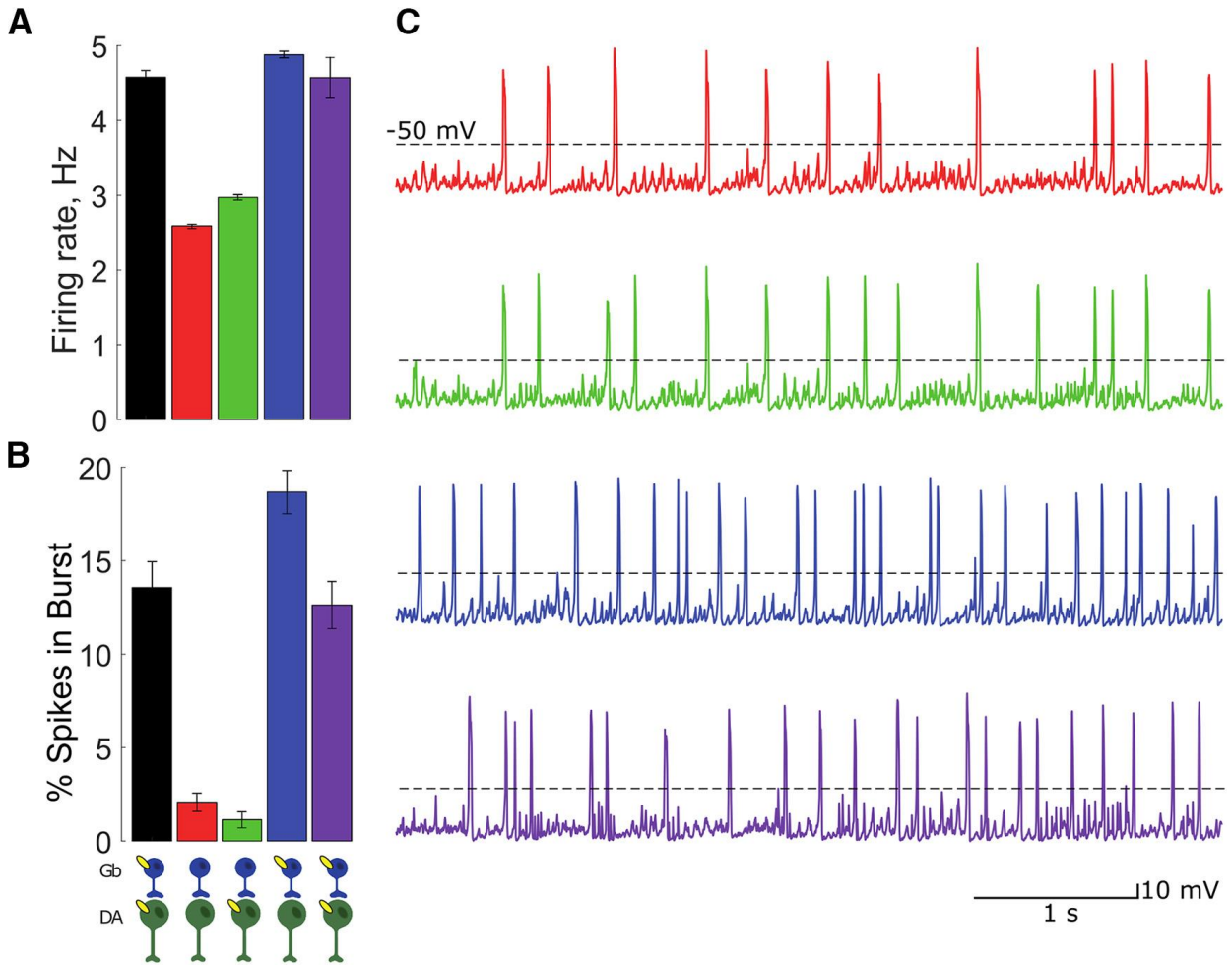
Morozova et al. 7(4) ENEURO.0418-19.2020, 2020, 1–13

Responses of VTA Neurons to Endogenous ACh and Nicotine



Morozova et al. 7(4) ENEURO.0418-19.2020, 2020, 1–13

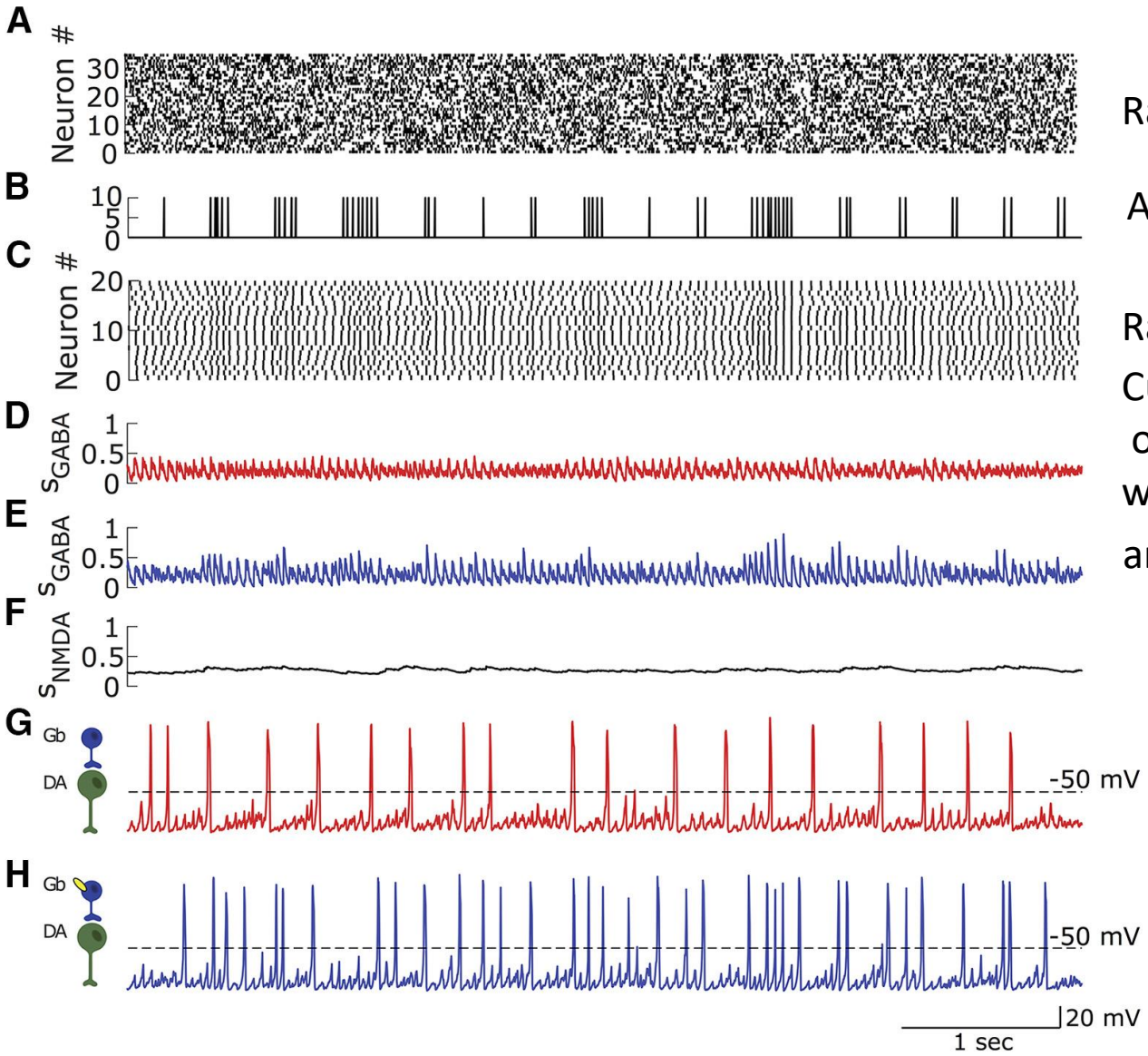
Responses of VTA Neurons to Endogenous ACh and Nicotine



Quantification of the spontaneous firing of simulated DA neurons: WT case (black), KO (red), b 2-containing nAChRs on DA neurons (green), the nAChRs on GABA neurons (blue), and the nAChRs on DA and GABA neurons (purple).

Morozova et al. 7(4) ENEURO.0418-19.2020, 2020, 1–13

Responses of VTA Neurons to Endogenous ACh and Nicotine



Raster of Glu neurons

ACh input

Raster of VTA GABA neurons

Cumulative activation variable of GABAR current without ACh input and with ACh input

Voltages of the DA neurons

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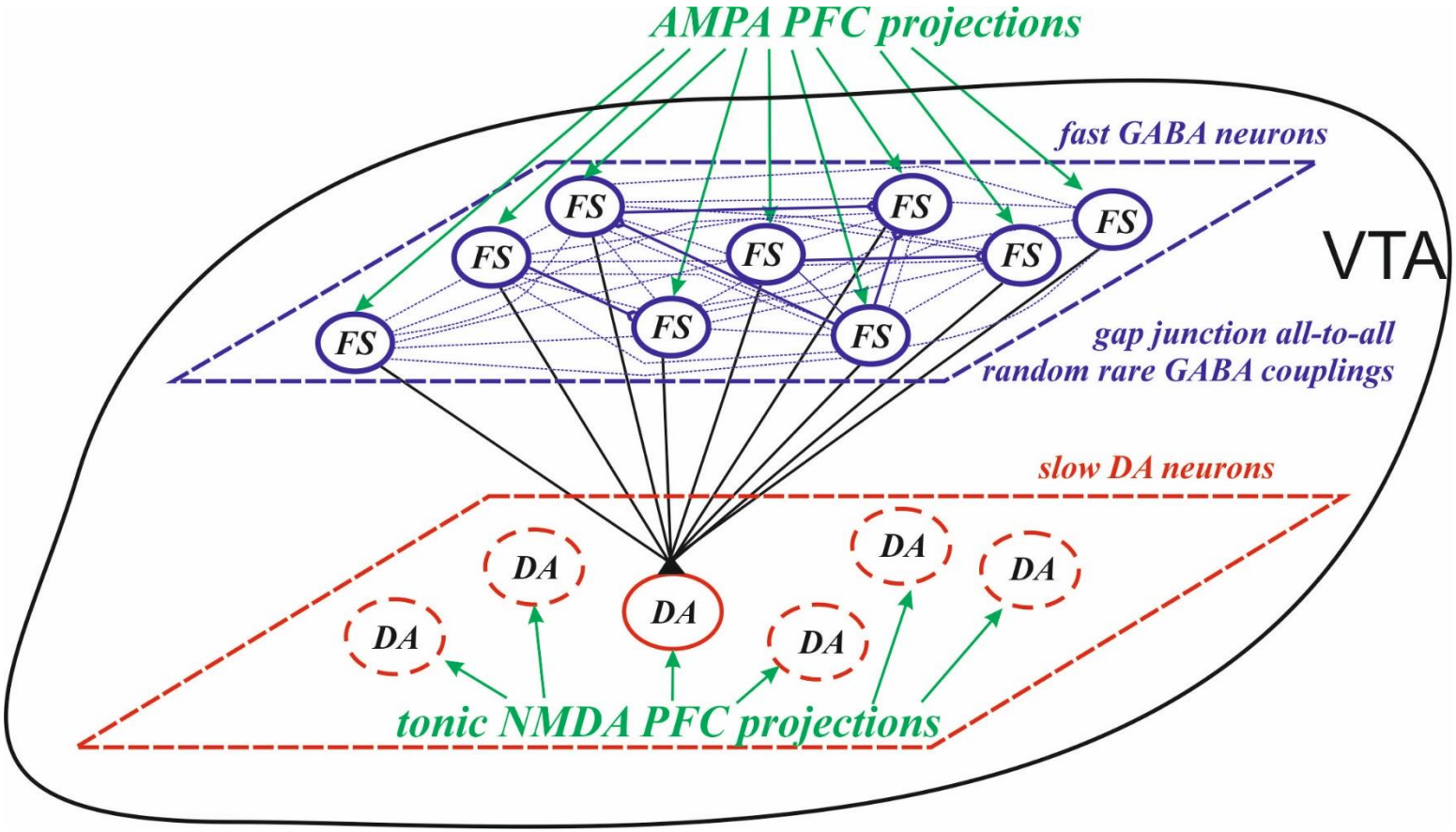
Inhibitory high-frequency input



GABA network:

- asynchronous dynamics without the AMPA PFC projections
- synchronous dynamics with the AMPA PFC projections

DA neuron:

- compensation of asynchronous GABA and tonic NMDA inputs
- high-frequency oscillations under strong synchronous GABA input

Inhibitory high-frequency input

Wang-Buszaki equations for the GABA network (Wang and Buzsáki,J Neurosci 16: 6402– 6413, 1996):

$$C_m \frac{dv_i}{dt} = \bar{g}_{Na} m^3(v_i) h (E_{Na} - v_i) + g_l (E_l - v) + \sum_{j=1}^{N} g_{gap}(v_j - v_i) +$$

$$\sum_{j=1}^{N} g_{GABA} B_{ij} r_j (E_{GABA} - v_i) + I_{PFC-AMPA},$$

$$\frac{dh_i}{dt} = \alpha_h(v_i)(1 - h_i) - \beta_h(v_i) h_i,$$

$$\frac{dn_i}{dt} = \alpha_n(v_i)(1 - n_i) - \beta_n(v_i) n_i, i = \overline{1,30}$$

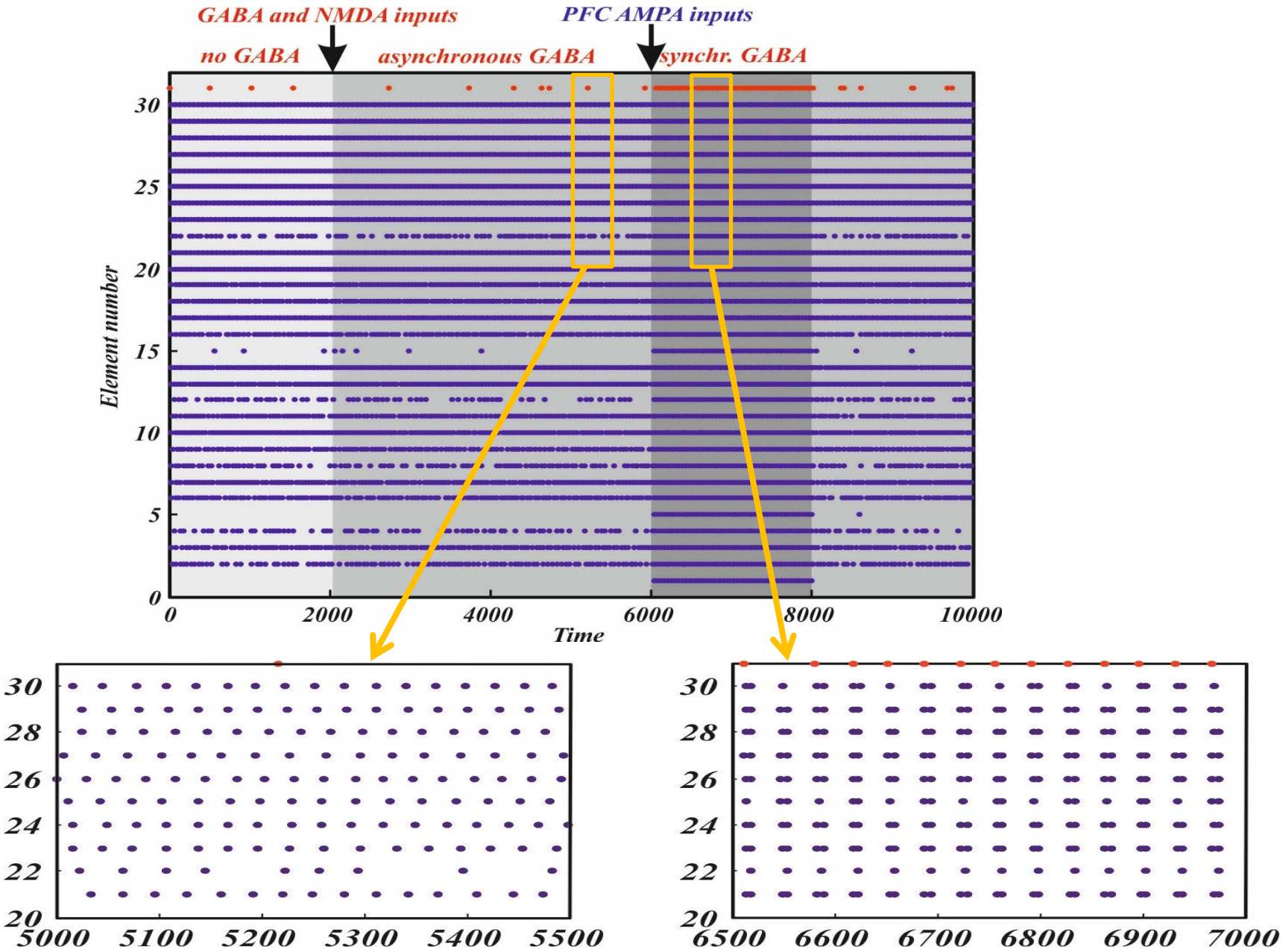
Biophysical model of DA neuron:

$$C_m \frac{dv}{dt} = g_{Ca}(v)(E_{Ca} - v) + (g_{KCa}([Ca^{2+}]) + g_K(v))(E_K - v) + g_{sNa}(v)(E_{Na} - v)$$

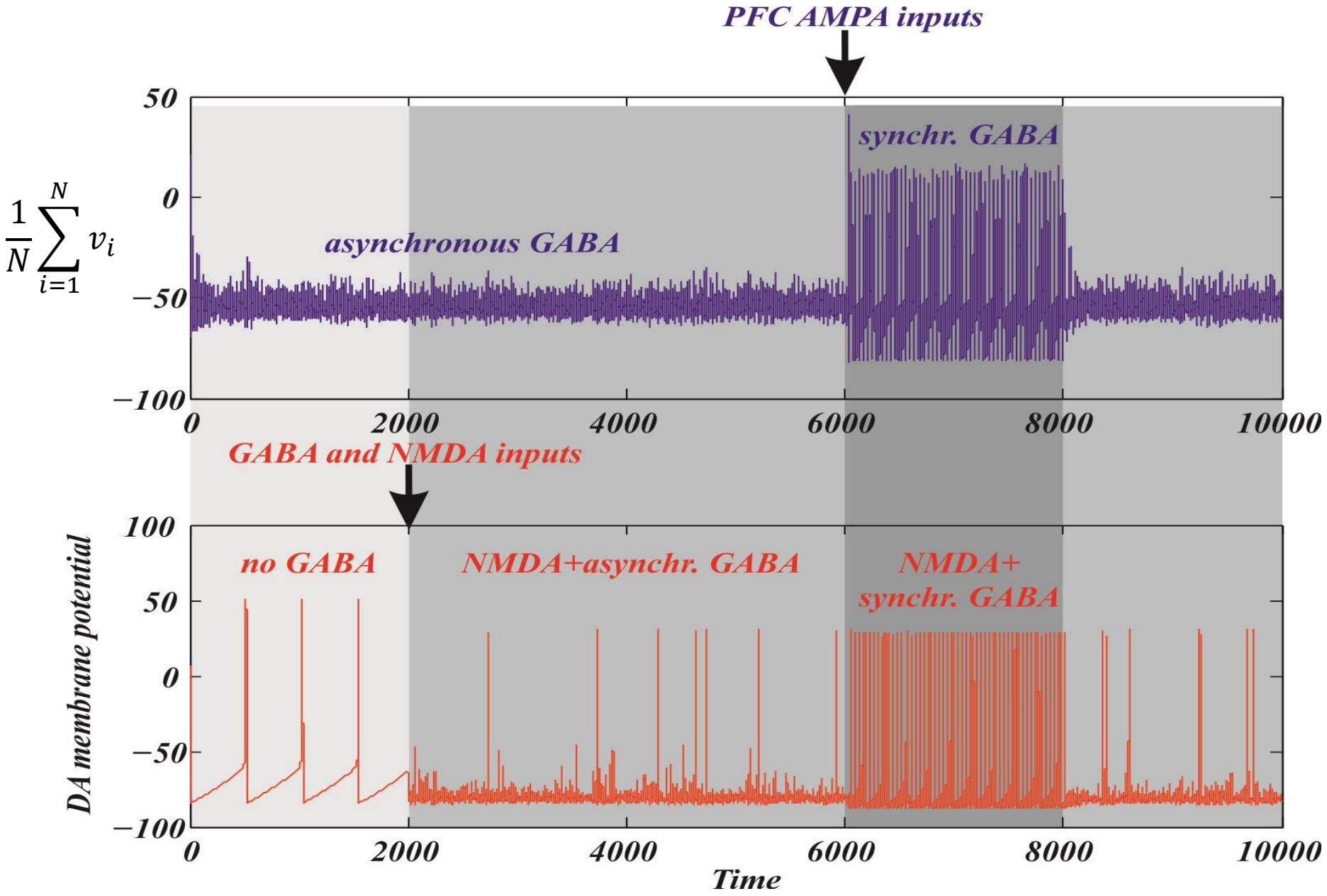
$$+ g_l(E_l - v) + \sum_{i=1}^{N} g_{DA-GABA} r_i (E_{GABA} - v) + \frac{g_{NMDA}}{1 + 0.1[Mg^{2+}] e^{-m_e v}} (E_{NMDA} - v),$$

$$\frac{d[Ca^{2+}]}{dt} = \frac{2\beta}{r} \left(\frac{g_{Ca}(v) + 0.1 g_L}{zF} \right) (E_{Ca} - v) - P_{Ca}([Ca^{2+}])$$

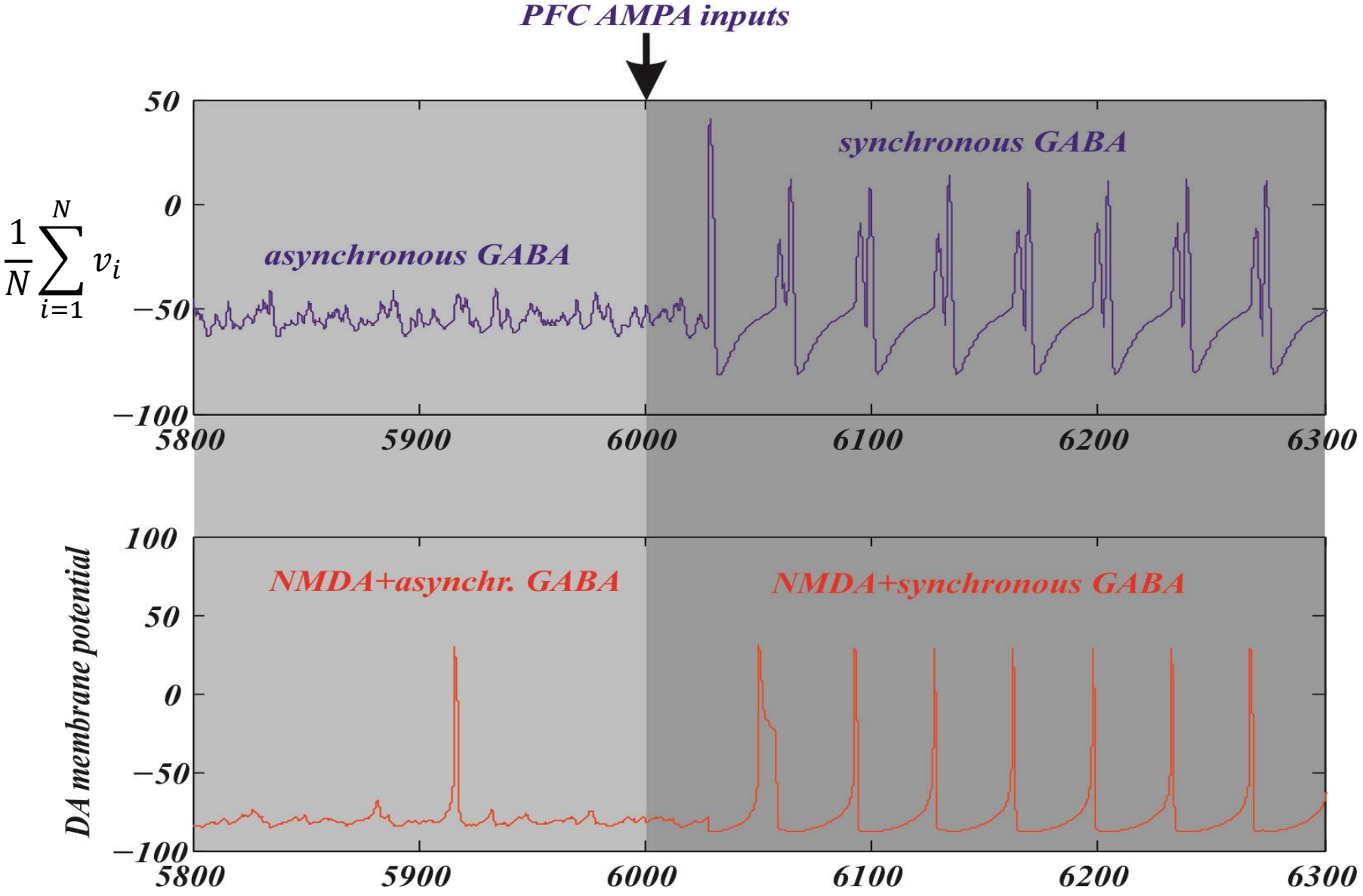
Inhibitory high-frequency input



Inhibitory high-frequency input



Inhibitory high-frequency input



High-frequency forced oscillations

Periodically forced McKean equations:

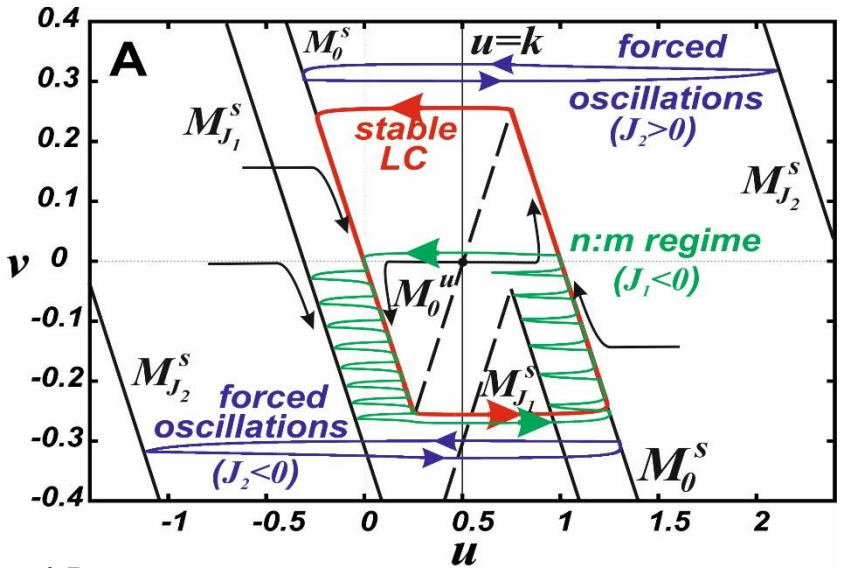
(Zakharov et al., PRE **97**, 062211, 2018)

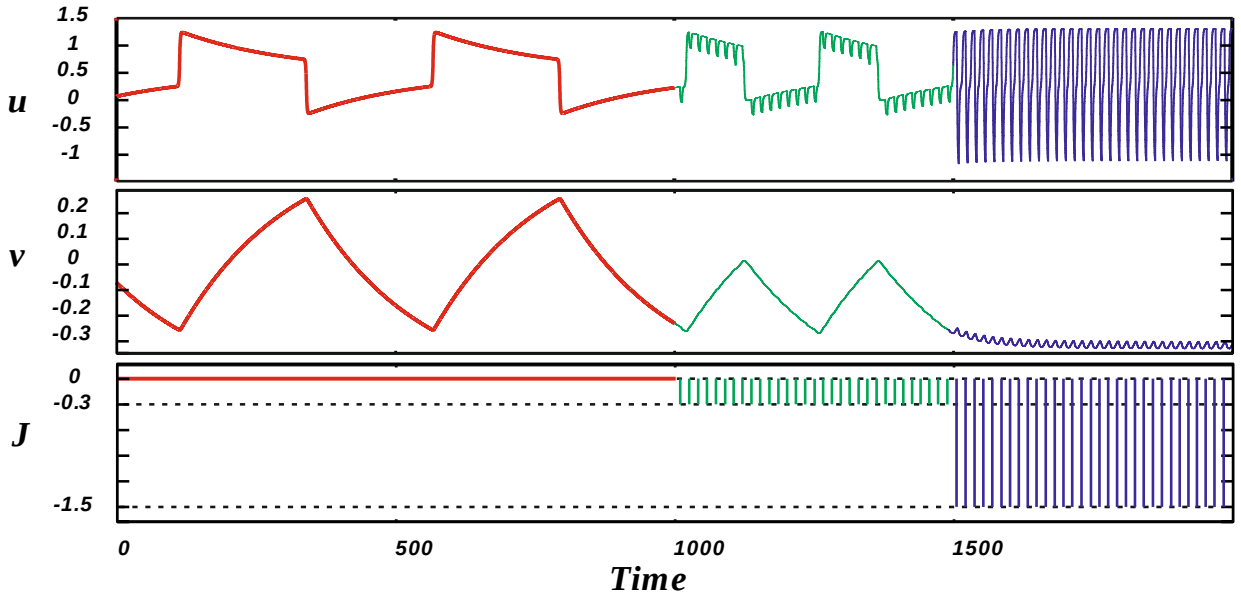
$$du/dt = f(u) - v + \varphi(t),$$

$$dv/dt = \epsilon(u - k),$$

$$f(u) = \begin{cases} -u, u \leqslant 0.25, \\ u - 0.5, 0.25 < u \leqslant 0.75, \\ 1 - u, u > 0.75. \end{cases}$$

$$\varphi(t) = \begin{cases} J, t \in [nT, nT + \tau], & n = 0,1,2,\ldots, \\ 0, t \in [nT + \tau, (n+1)T], & n = 0,1,2,\ldots. \end{cases}$$





A T-map for the forced oscillations

$$v_{n+1} = v_n + \epsilon P(v_n).$$

If $J > 0$, then

$$P(v_n) = -Tv - Je^{\tau - T\frac{(v+0.25)^2}{(v-0.25)^2}} + Je^{-\tau\frac{(0.0625+J^2+(v_n-0.5)v-J(2v-0.5))}{(0.25-J+v)^2}} + \tau(1+J) - kT + ln\frac{1}{0.25-v} + 2(v+0.25)ln\frac{v+0.25}{v-0.25} + +2(-J+v-0.25)ln(-J+v-0.25) - 2(-J+v-0.75)ln(0.25+J+v).$$

If $J < 0$, then

$$P(v) = T(1-v) - Je^{\tau - T\frac{(v-0.25)^2}{(v+0.25)^2}} + Je^{-\tau\frac{(0.0625+J^2+(v+0.5)v-2J(v-0.25))}{(0.25-J+v)^2}} + \tau(1-J) - kT + ln(-0.25-v) + 2(v-0.25)ln\frac{v-0.25}{v+0.25} + 2(-J+v+0.25)ln(-J+v+0.25) - 2(-J+v+0.75)ln(-0.25+J+v).$$

A T-map for the forced oscillations

$$v_{n+1} = v_n + \epsilon P(v_n).$$

If $J > 0$, then

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If $J < 0$, then

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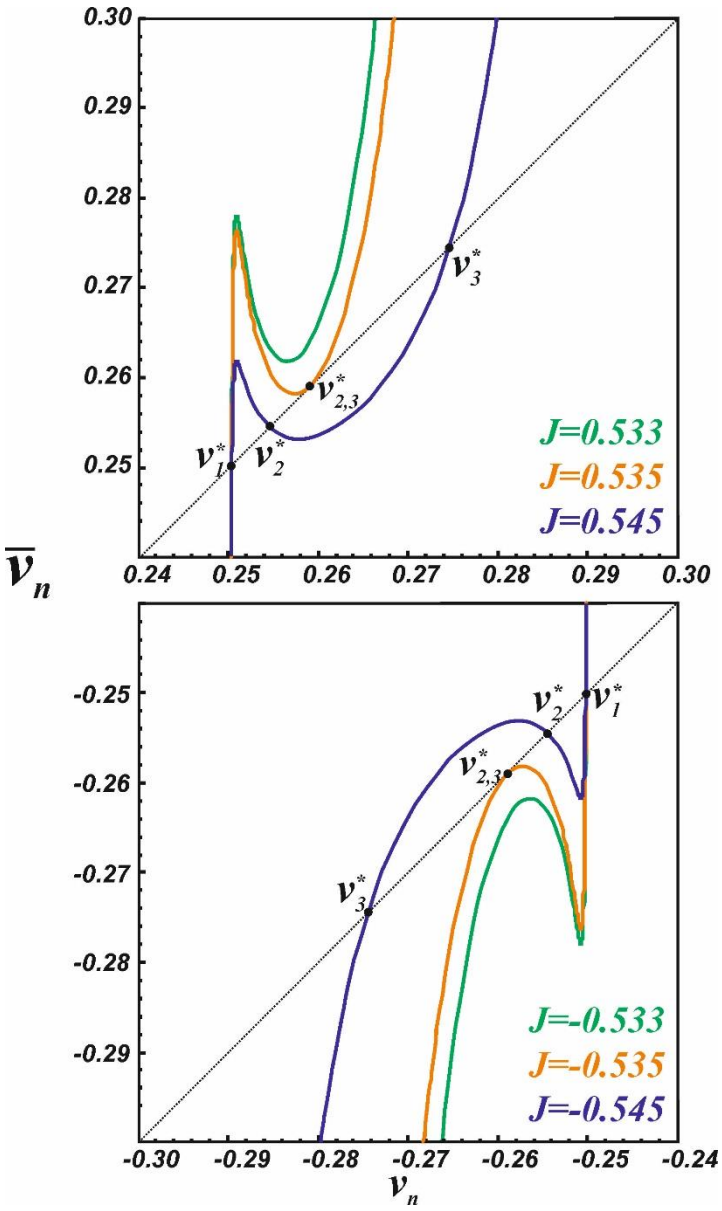
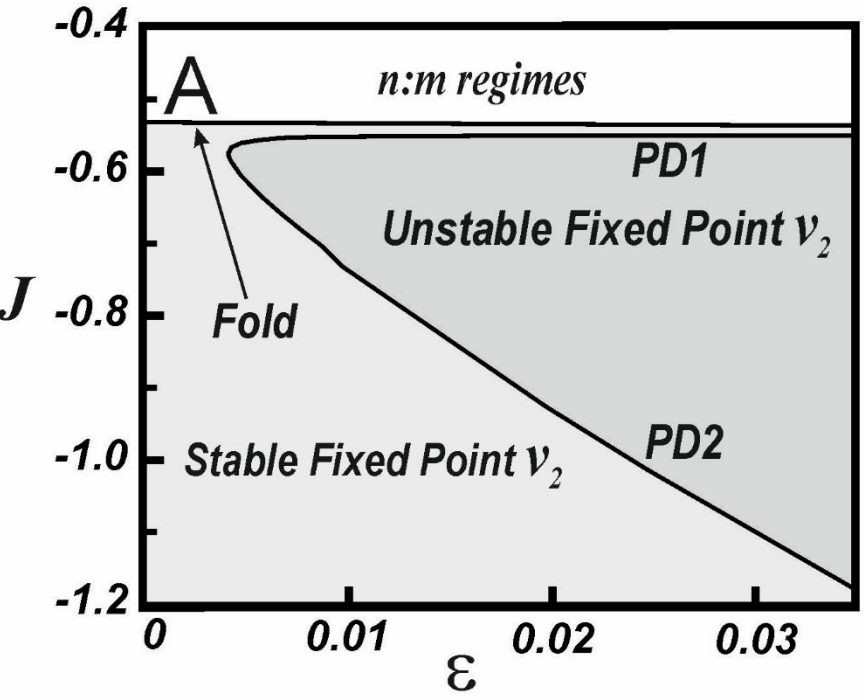
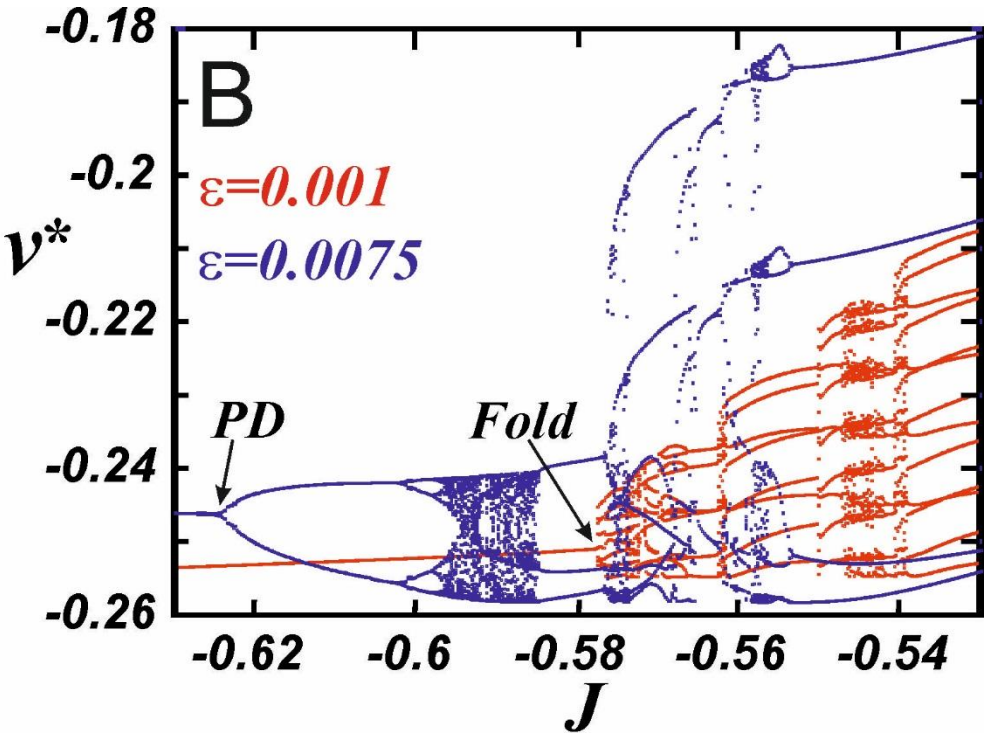


A T-map for the forced oscillations

Two parametric bifurcation diagram for the T-map



One parametric bifurcation diagram for the McKean system



Discussion

In this lecture we consider the dynamical mechanisms “overclocking” DA neuron:

- The first based on the NMDA current. Note that in case of simultaneous action of AMPA and NMDA currents the highest frequency may substantially increase.
- The second mechanism is provided by the strong high-frequency input (for example, from a synchronized GABA network). Necessary conditions: the N-shaped manifold of slow motion, high enough amplitude of periodical forcing and “slow enough” slow variable (almost constant value of the slow variable in such high-frequency regime).

Such raising activity of DA neuron results in greater release of dopamine that is important neuromodulator and responsible for instance for reinforcement learning.

Another point is possibility of changing excitability type (from I to II and vice versa) by variation of the neuronal and synaptic parameters. Depending on the excitability type, the DA neurons may provide different coding features, different response mechanisms on external stimulations providing various amount of releasing dopamine and, thus, dissimilar reward.

ACh and nicotine also cam act to the Dynamic of the VTA circuit leading to additional dopamine release

Thank you for attention!

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