Modeling and Measurements of Cerebral Signaling Circuits

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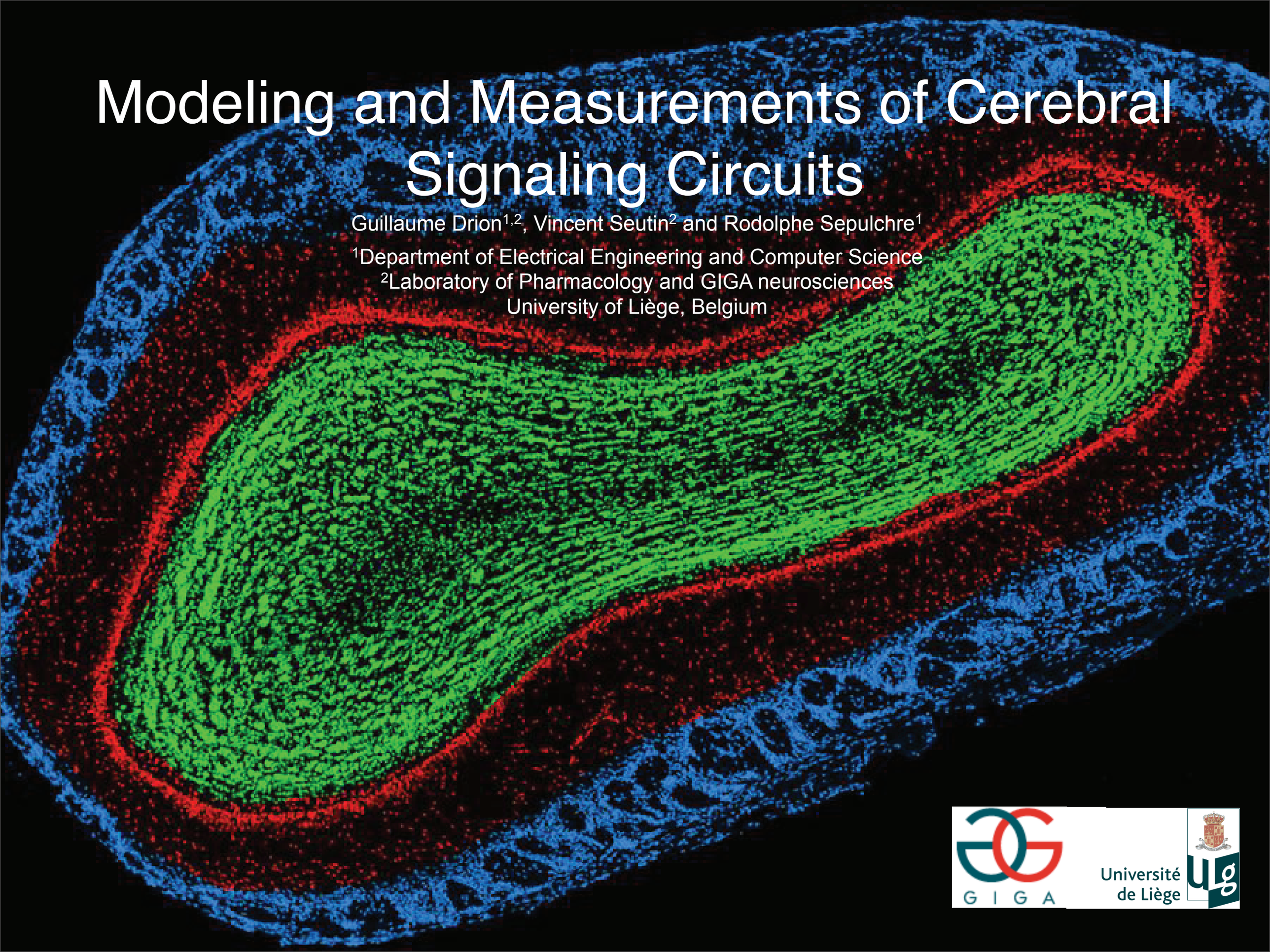
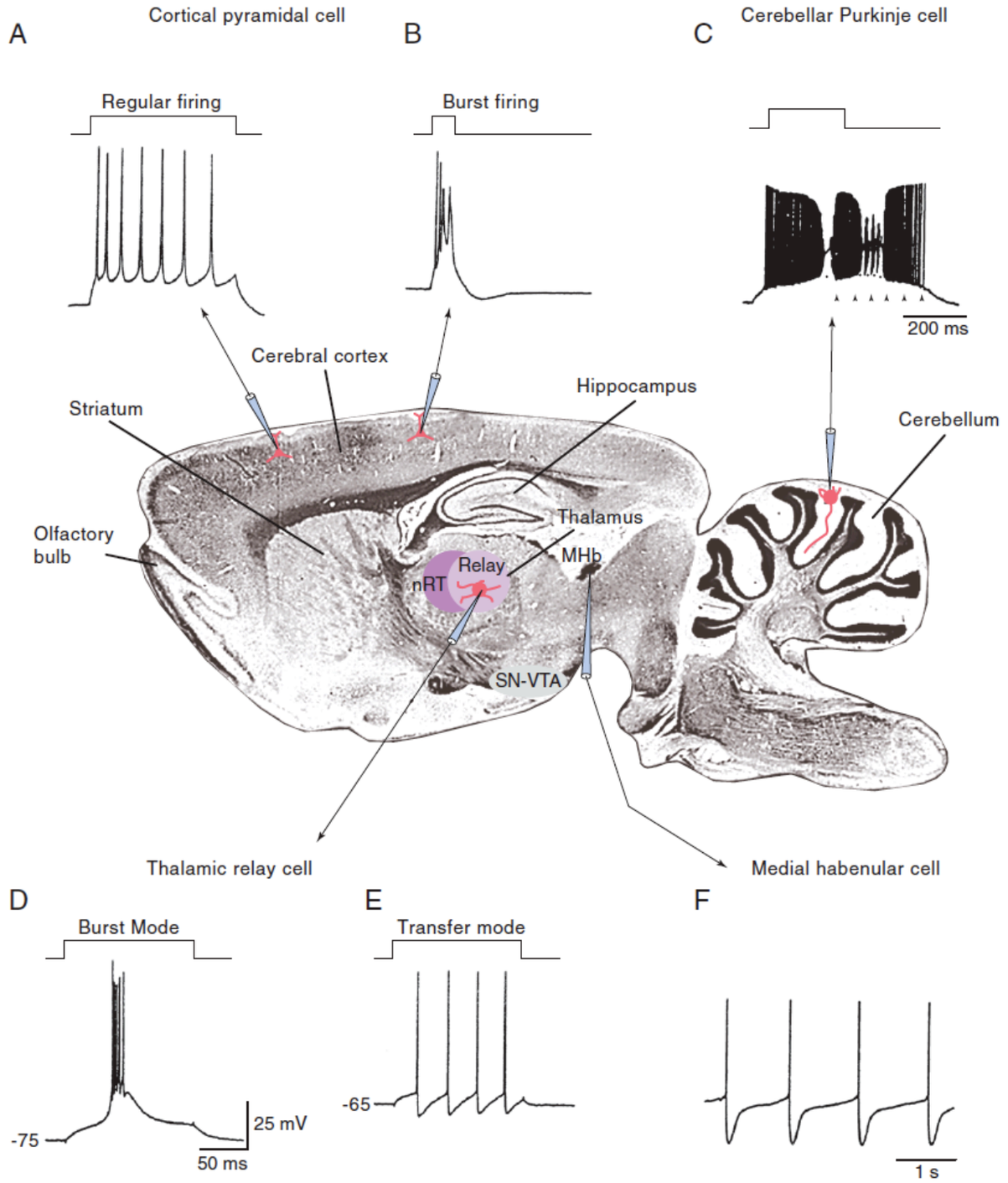


The Way That Action Potentials Are Generated Over Time Defines the Firing Pattern of the Cell.

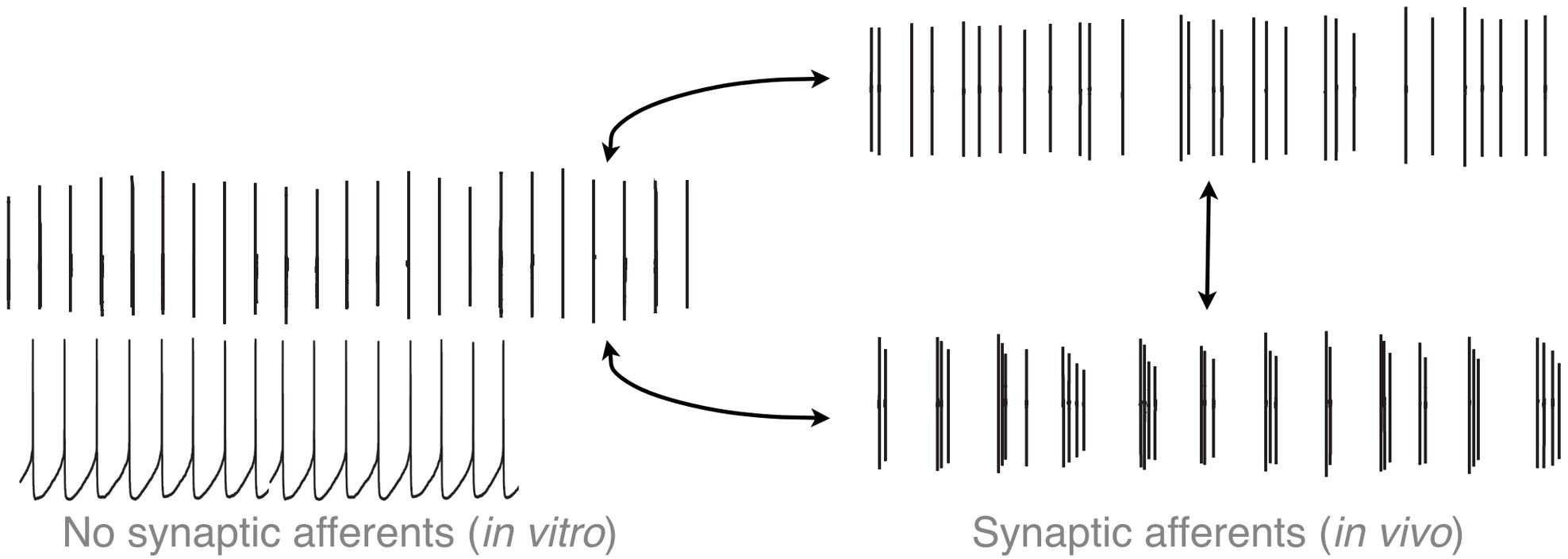
- **Excitable cells can exhibit different firing patterns**
  - Regular single spike firing
  - Irregular single spike firing
  - Burst firing
- **The firing pattern is a critical component of the signaling**



Byrne et. al, 2004

Our Focus: The Control of Firing Patterns of Particular Pacemaker Neurons, Such as Dopaminergic Neurons.

- Dopaminergic (DA) neurons are pacemaker cells (firing in regular single-spikes endogenously) that can switch between irregular tonic firing and burst firing *in vivo*.

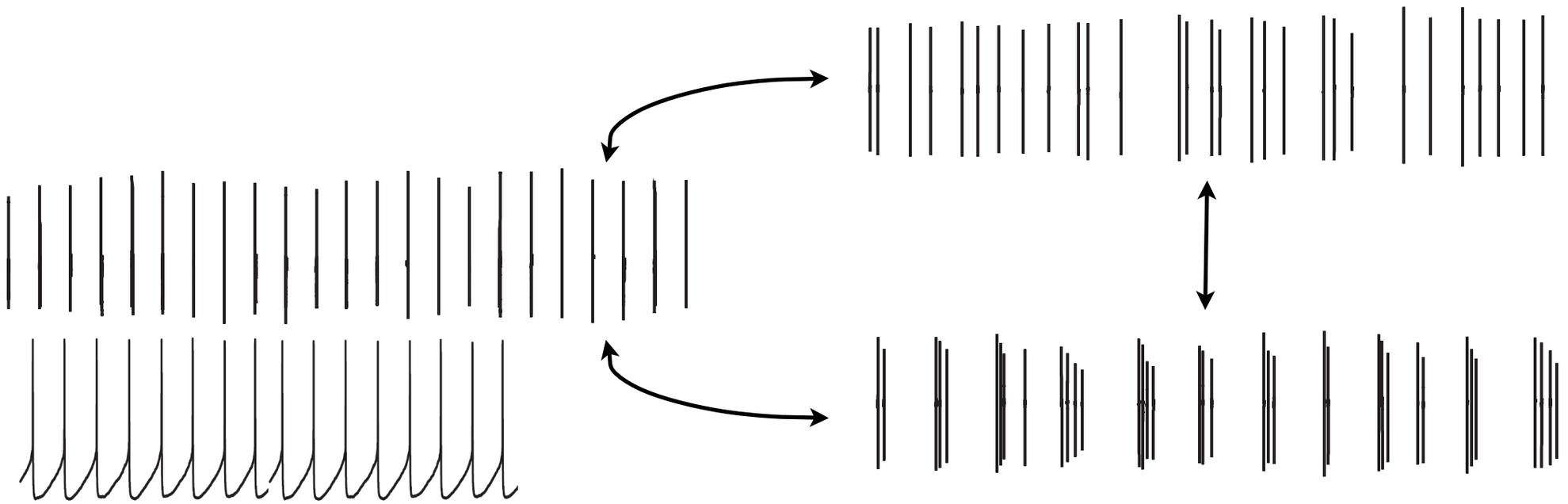


No synaptic afferents (*in vitro*)

Synaptic afferents (*in vivo*)

Why Are We Interested in Burst Firing of Dopaminergic Neurons?

- Dopaminergic (DA) neurons are pacemaker cells (firing in regular single-spikes endogenously) that can switch between irregular tonic firing and burst firing *in vivo*.



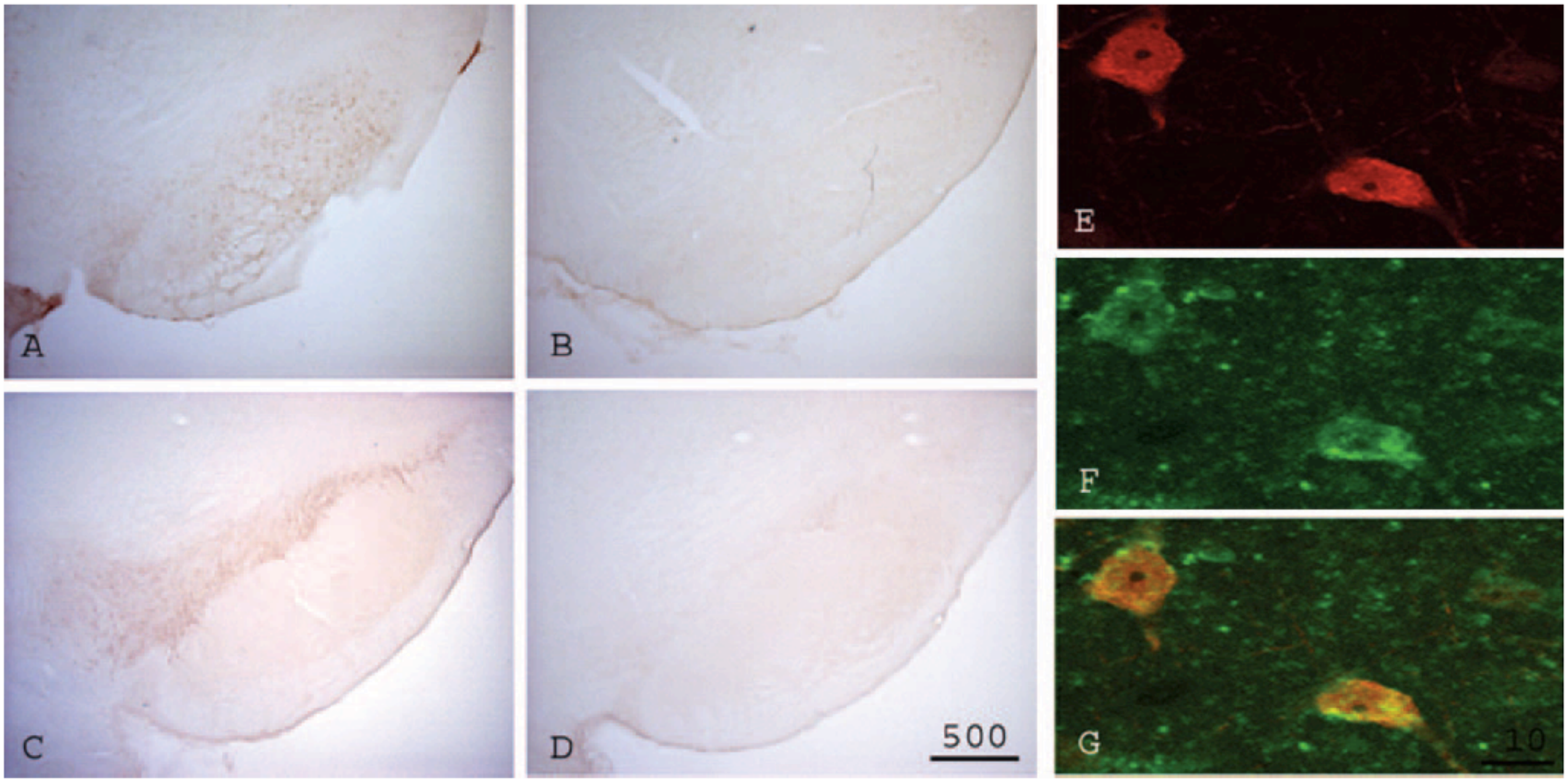
No synaptic afferents (*in vitro*)

Synaptic afferents (*in vivo*)

- Burst firing of DA neurons is of particular interest because it strongly increases the release of dopamine compared to a tonic firing pattern.
  - Enhancing burst firing in dopaminergic neurons (thus increasing the amount of released dopamine) could be an interesting way to treat symptoms that are generated by a deficiency in dopamine, such as in Parkinson's disease.

A M-type Potassium Current $I_{K,M}$, Carried by KCNQ4 Channels, is Present in DA Neurons.

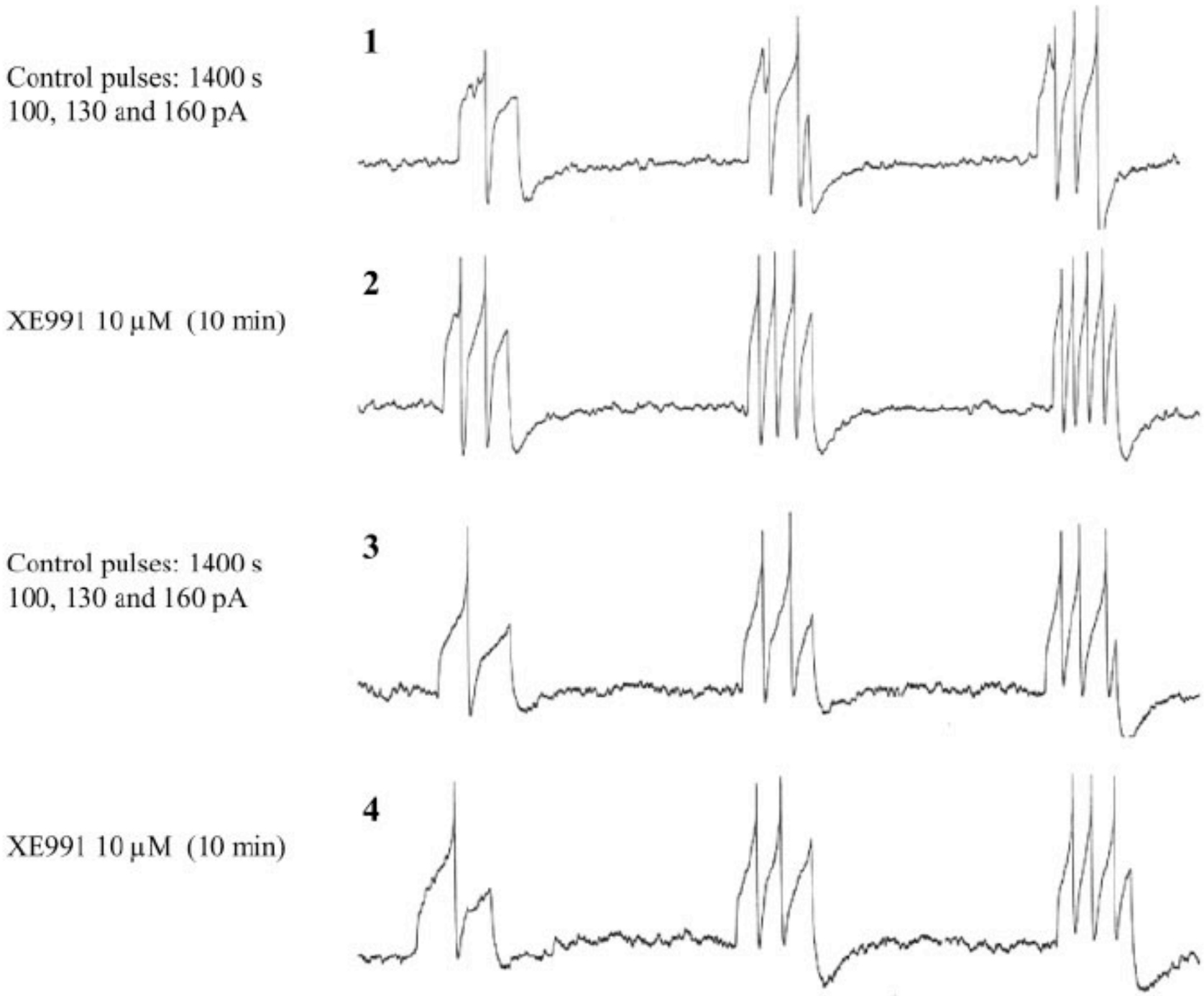
- A M-current was characterized in DA neurons (Hansen et. al., 2006 ; Koyama and Appel, 2006).



From A to D : KCNQ2 to KCNQ5 E : KCNQ4 F : Tyrosine hydroxylase
(KCNQ1 is mainly expressed in the heart) G : Overlap

Hansen et. al, 2006

Blockade of the M-Current had Only Minor Effects on the Spontaneous Firing of DA Neurons



Hansen et. al, 2006

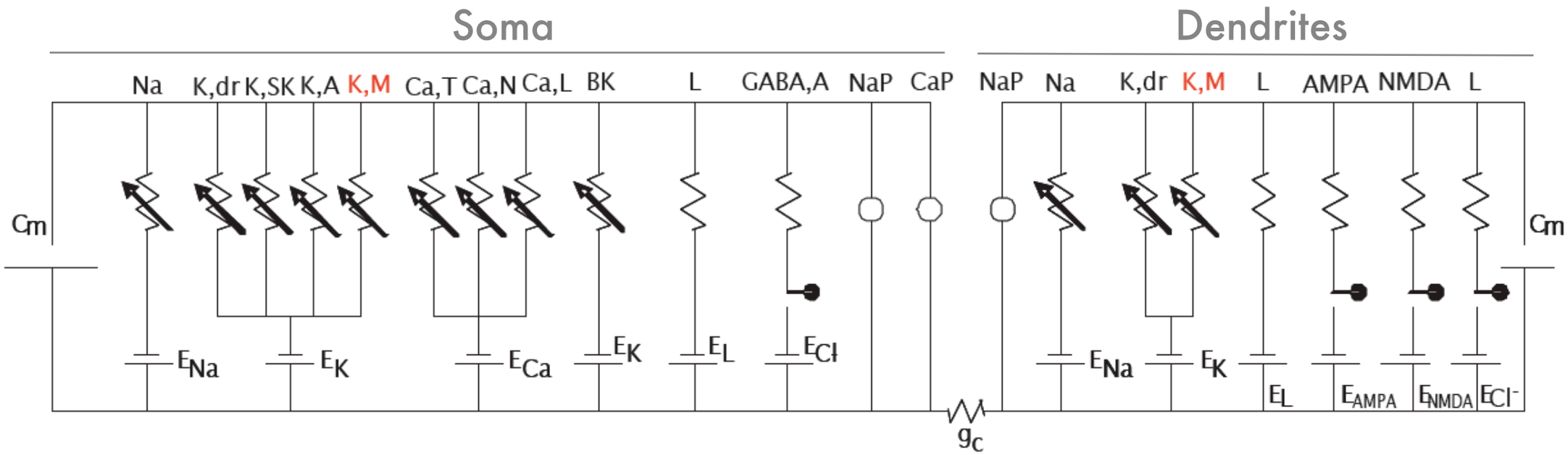
Analysis of the Effect of a M-type current $I_{K,M}$ on the Firing of Dopaminergic Neurons

- A new potassium current has been described in DA neurons (Hansen et. al., 2006; Koyama and Appel, 2006). This current had the typical electrophysiological signature and pharmacology of the M-current.
- Moreover, one of the subunits carrying M-currents (KCNQ4) was highly expressed in DA neurons (Hansen et al., 2006).
- Blockade of the M-current had only minor effects on the pacemaker firing of DA neurons in rat brain slices and *in vivo*.

What would be the effect of a blockade of the M-current on the burst firing of DA neurons?

Tools for the Analysis of the Effect of $I_{K,M}$ on the Firing of Dopaminergic Neurons : Mathematical Modeling

- A model of a dopaminergic neuron (from Canavier and Landry, 2006).



- The equations describe the temporal variations of variables such as membrane potential, intracellular calcium concentration, channel activation and inactivation, etc.
- The model can exhibit the three firing patterns of DA neurons.
- Burst firing is induced by an inhibition of the SK current, which is in agreement with experimental data (Waroux et al., 2005).

Tools for the Analysis of the Effect of $I_{K,M}$ on the Firing of Dopaminergic Neurons : Mathematical Modeling

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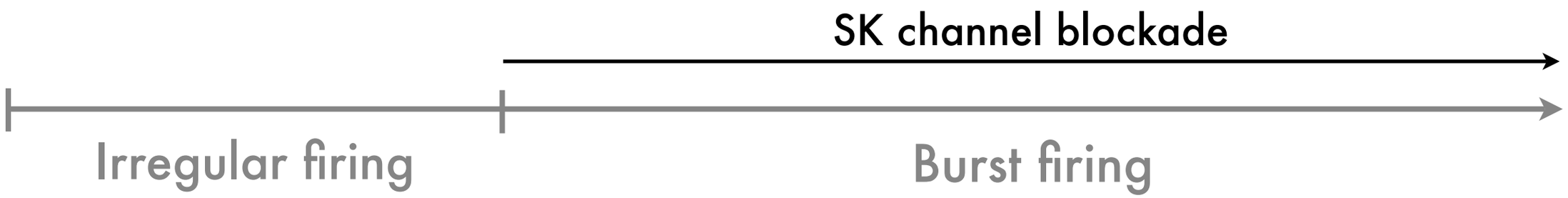

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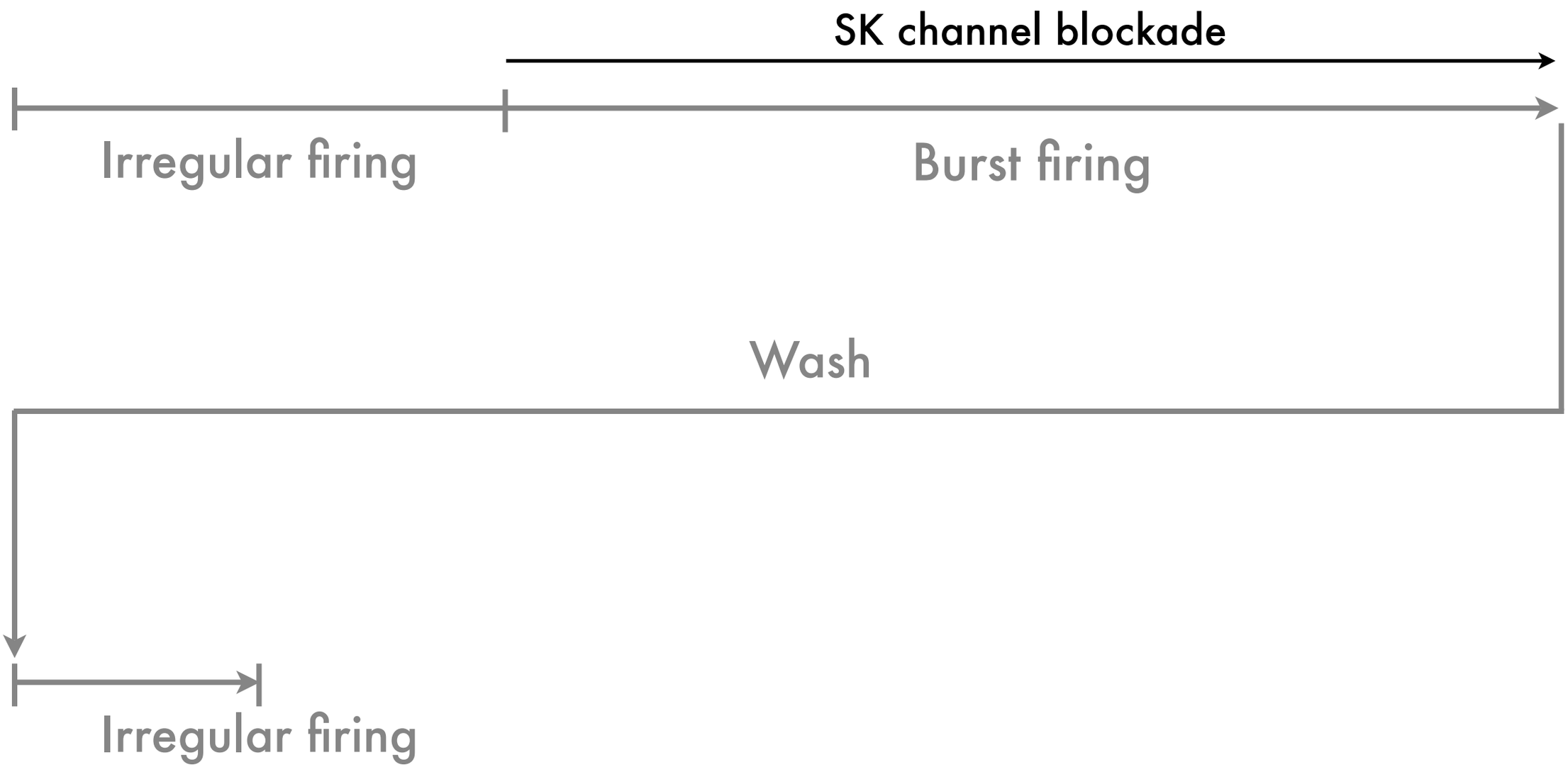

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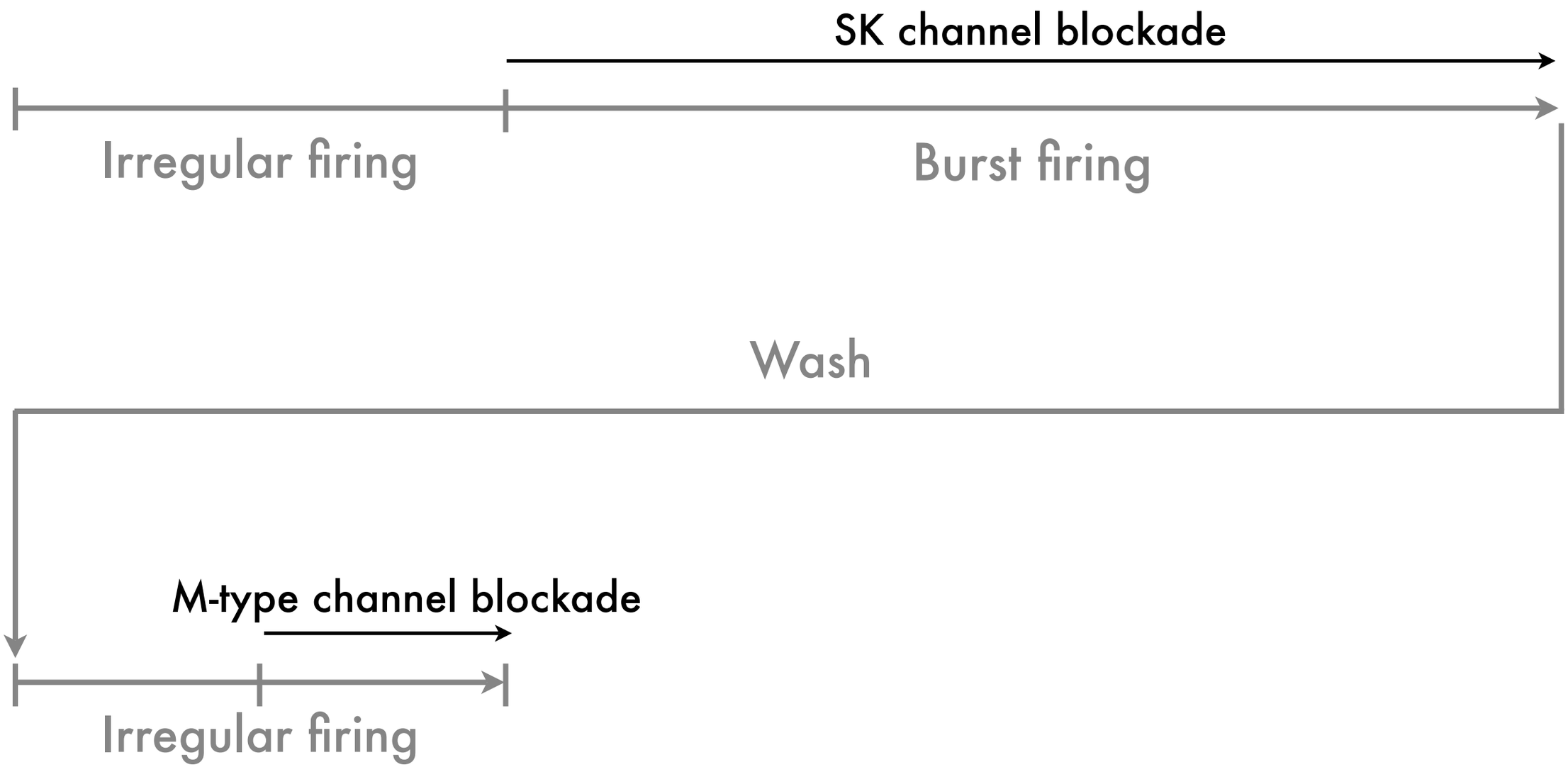

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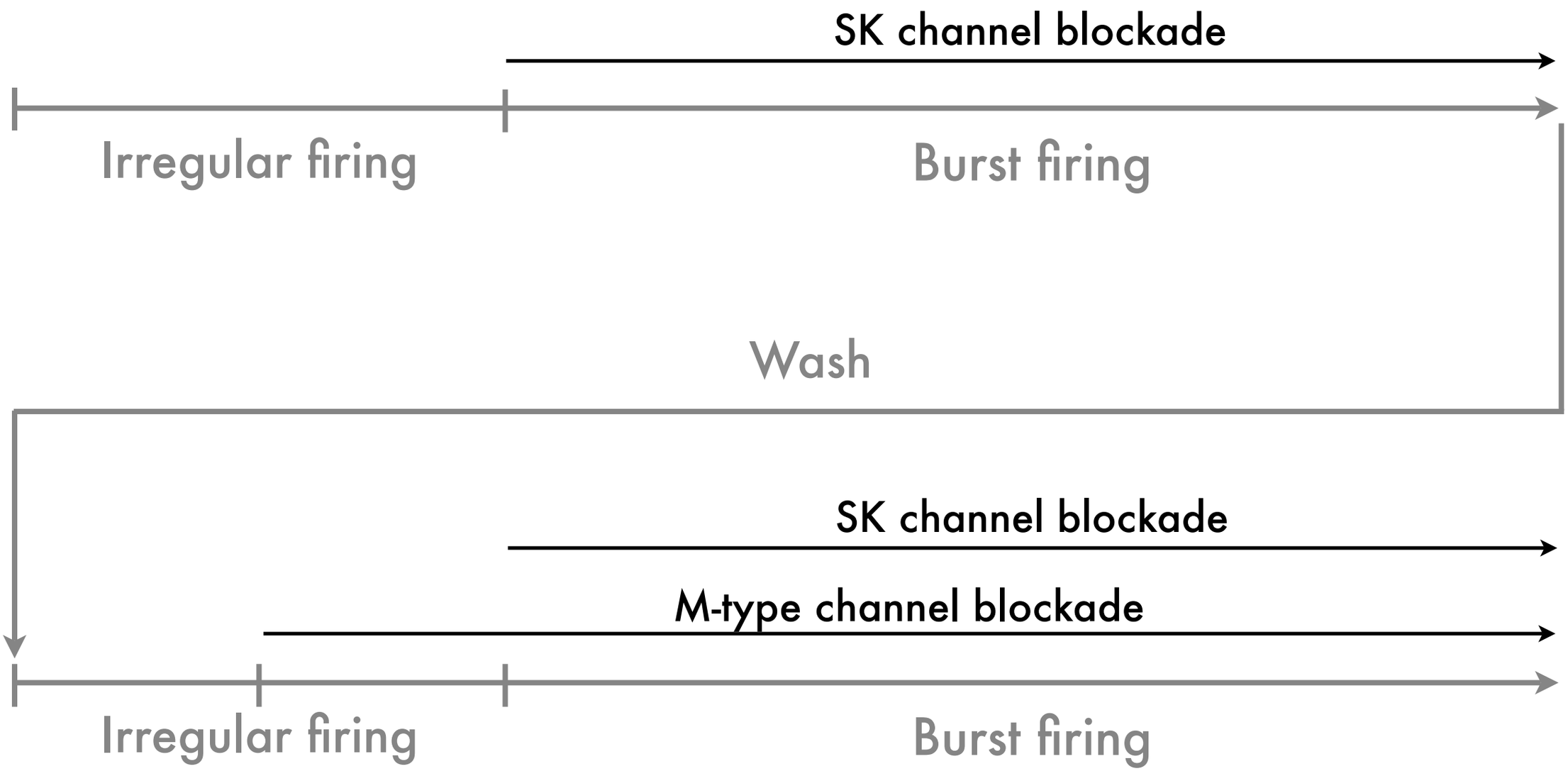

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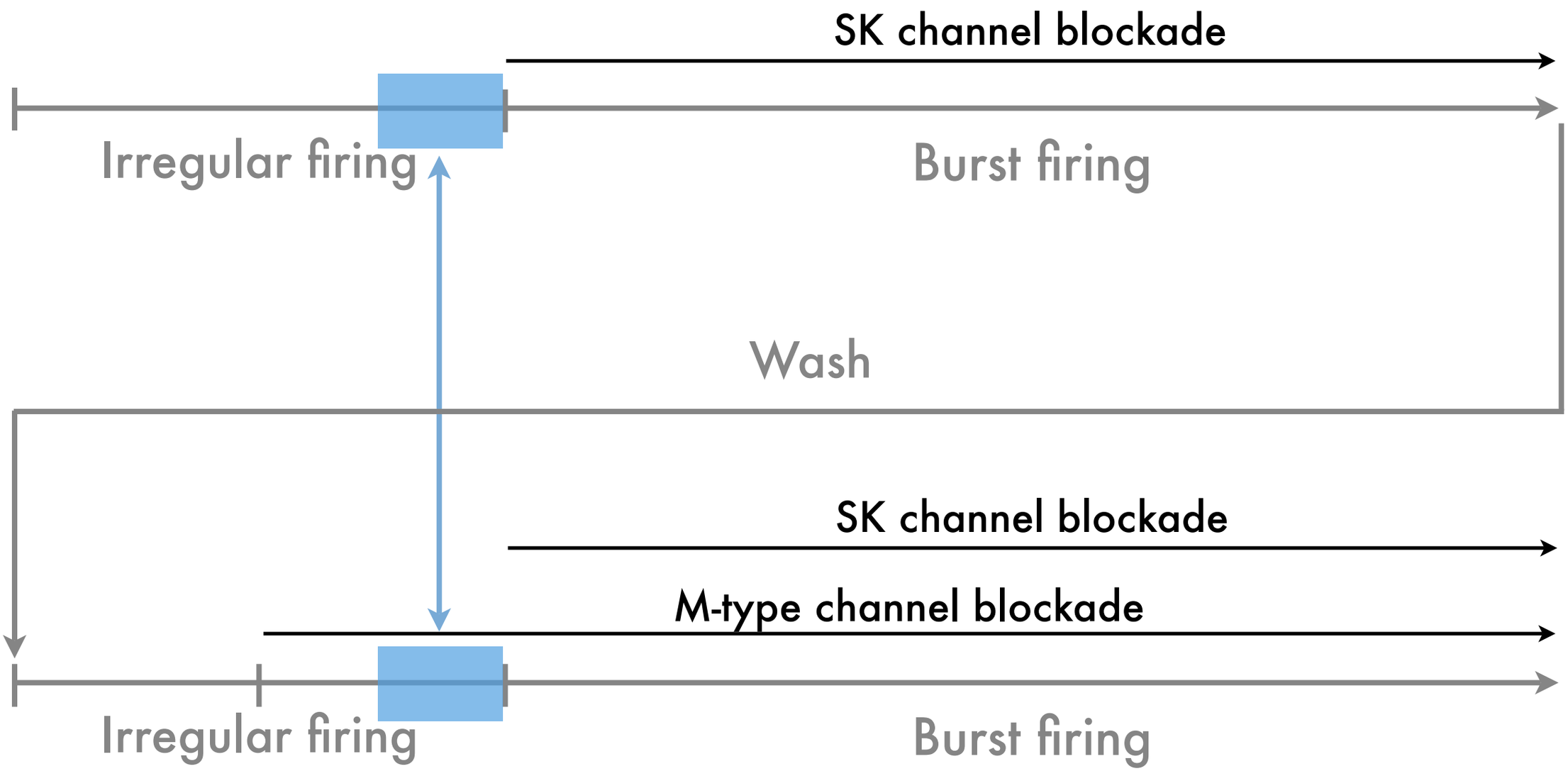

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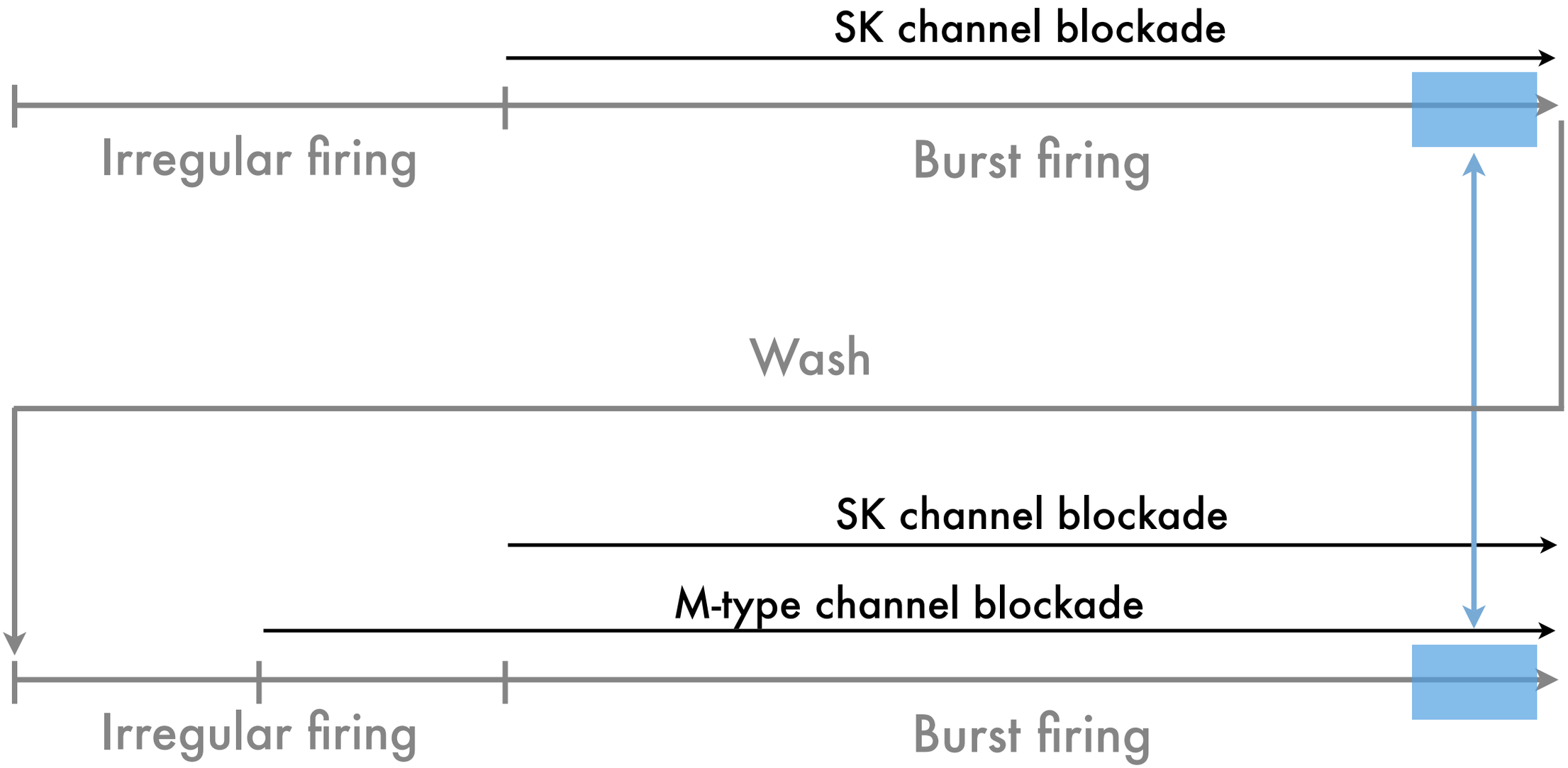
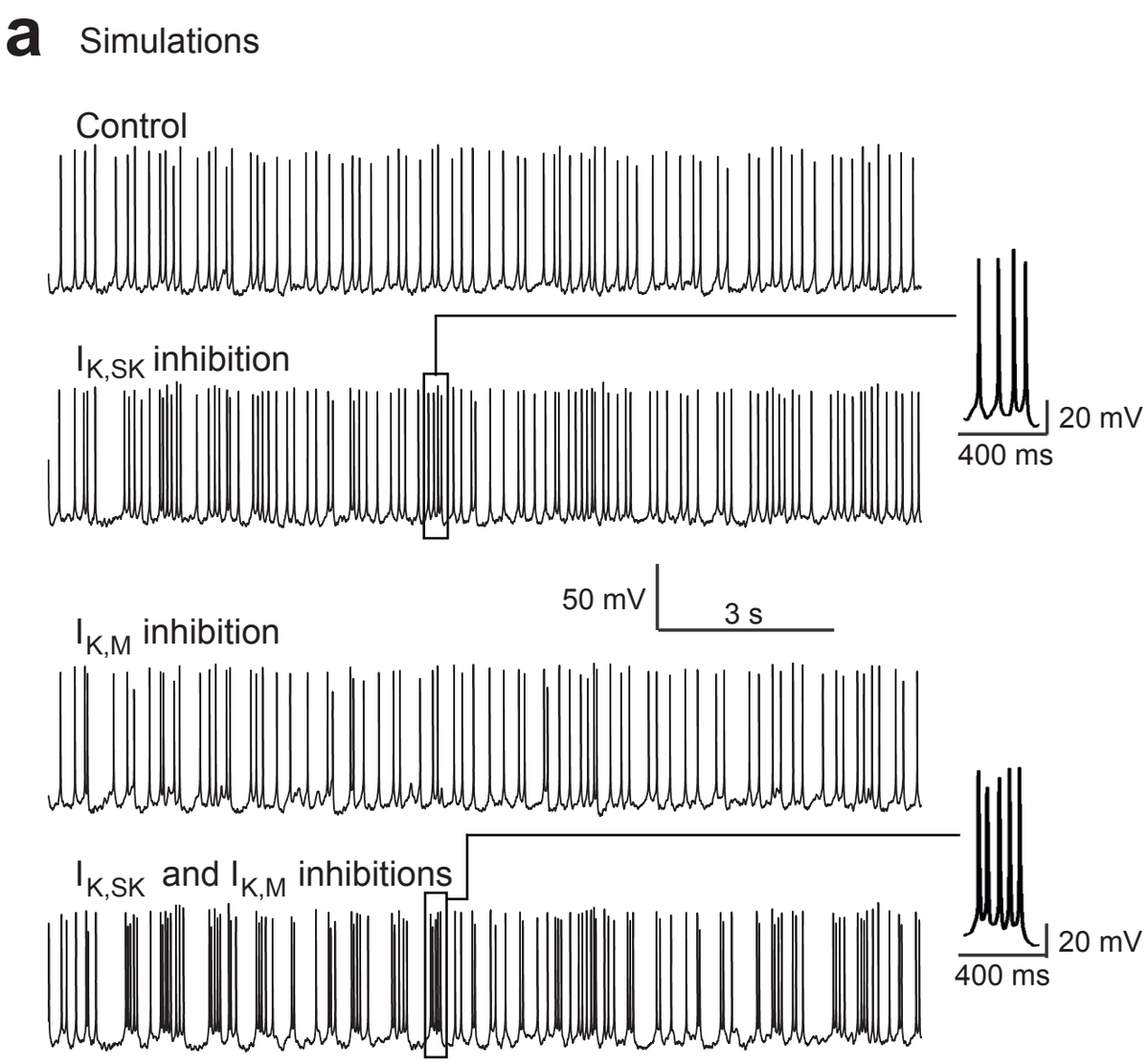
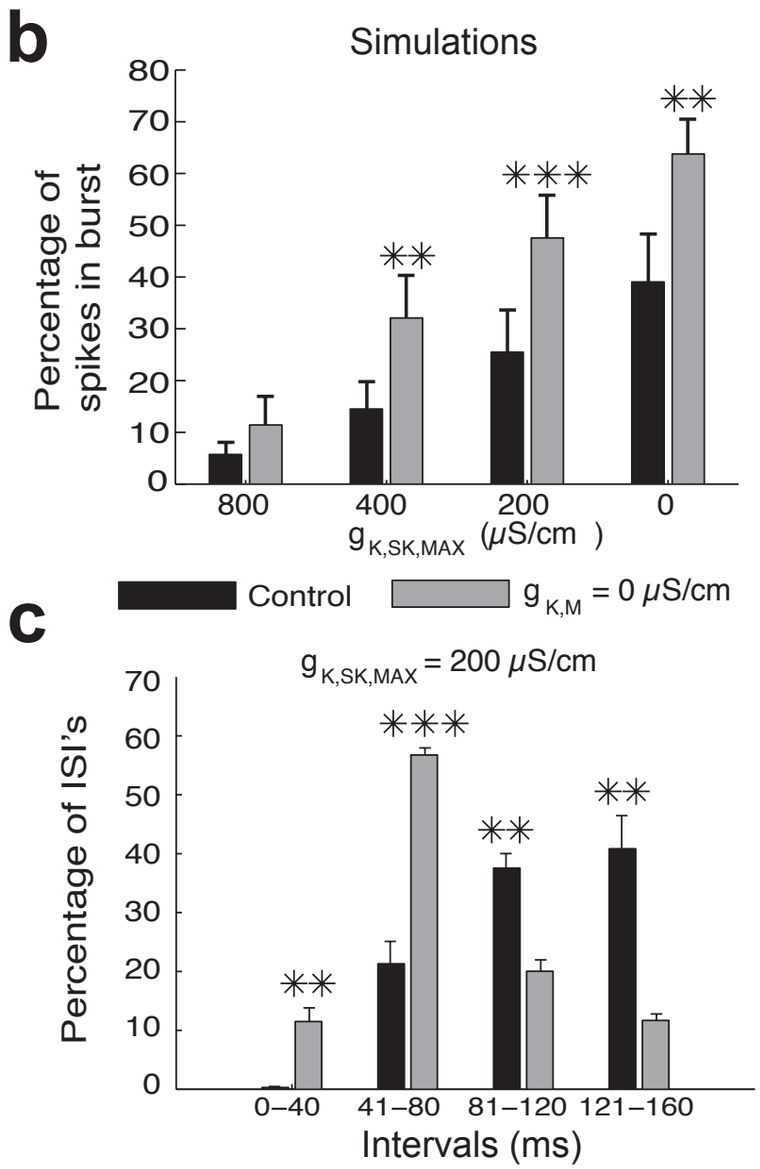


Analysis of the Effect of $I_{K,M}$ on the Firing of Dopaminergic Neurons : Results of Modeling

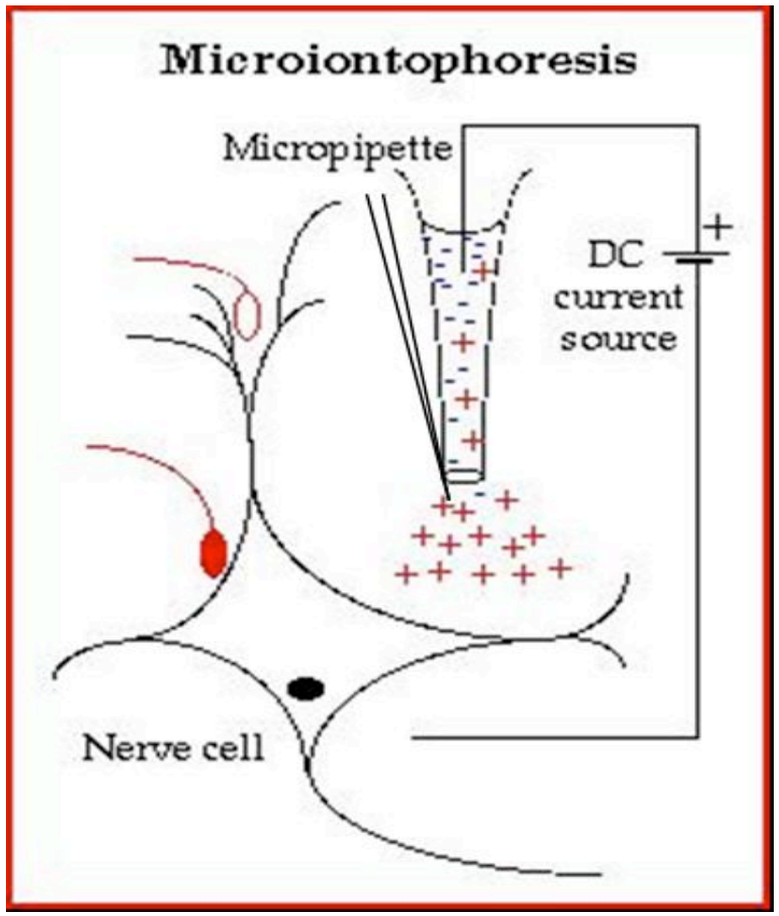
- Simulations suggest that M-type current inhibition may increase burst firing of DA neurons through a facilitation of fast firing, while it probably does not affect tonic firing.

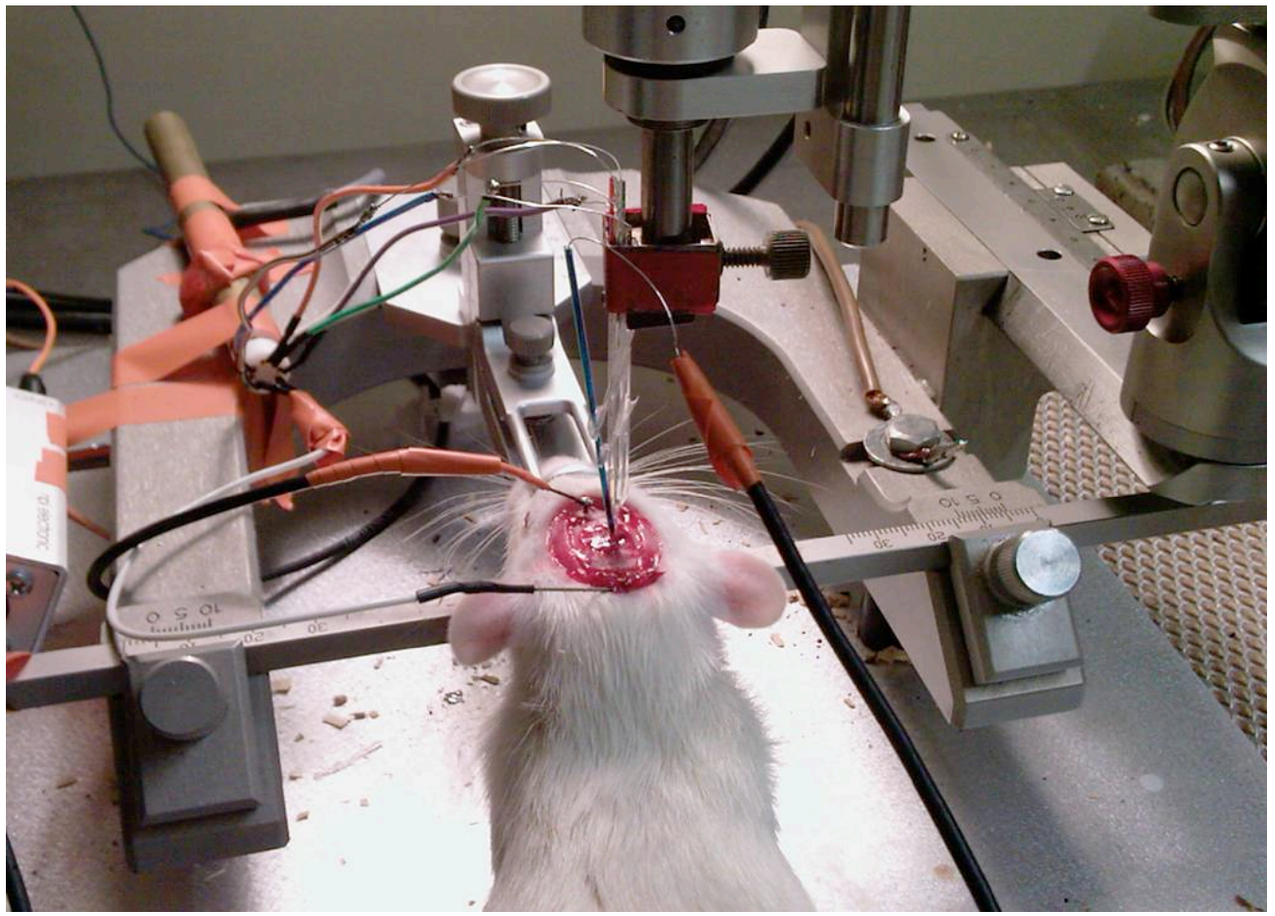




Tools for the Analysis of the Effect of $I_{K,M}$ on the Firing of Dopaminergic Neurons : *in vivo* extracellular recordings

- *In vivo* recording of single DA neurons (from the SNc or the VTA) and application of drugs by iontophoresis





- Burst firing was induced by a blockade of SK channels (Waroux et. al., 2005).

SK Channel Blockade Induces a Switch of Firing Pattern (from Single-Spike Firing to Bursting)

- Small-conductance calcium-activated (SK) potassium channels gating is sensitive to the intracellular calcium concentration BUT NOT to the membrane potential.

- Firing of a dopaminergic neuron in the anesthetized rat

SK Channel Blockade Induces a Switch of Firing Pattern (from Single-Spike Firing to Bursting)

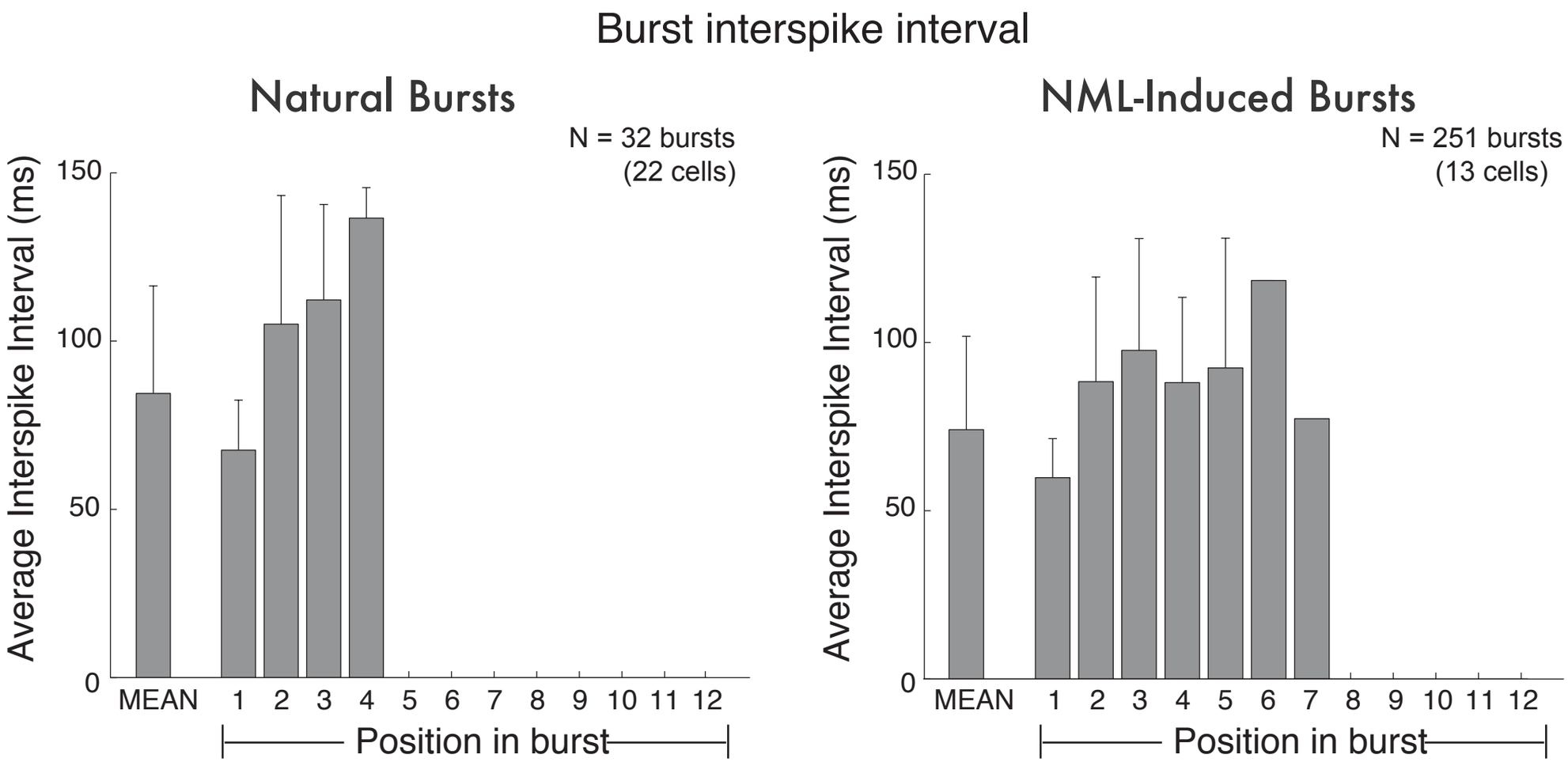
- Small-conductance calcium-activated (SK) potassium channels gating is sensitive to the intracellular calcium concentration BUT NOT to the membrane potential.

- Firing of a dopaminergic neuron in the anesthetized rat

- Change of firing pattern induced by a pharmacological blockade of SK channels

Analysis of the Effect of $I_{K,M}$ on the Firing of Dopaminergic Neurons : Experimental Results

- Bursts induced by a SK blockade are physiological.



- These data are in agreement with original data (Grace and Bunney, 1984)

Drion et. al, 2010

Analysis of the Effect of $I_{K,M}$ on the Firing of Dopaminergic Neurons : Experimental Results

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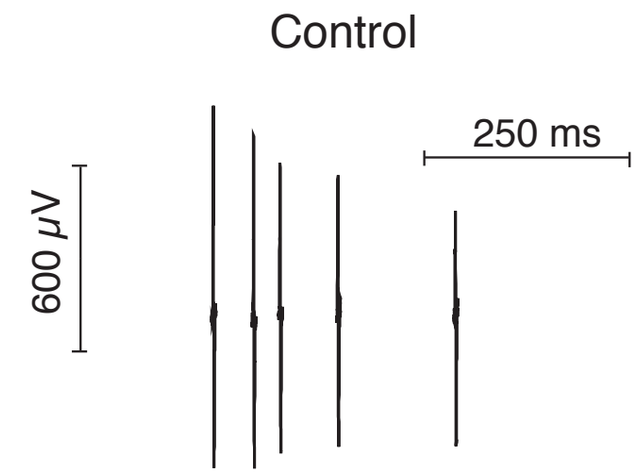
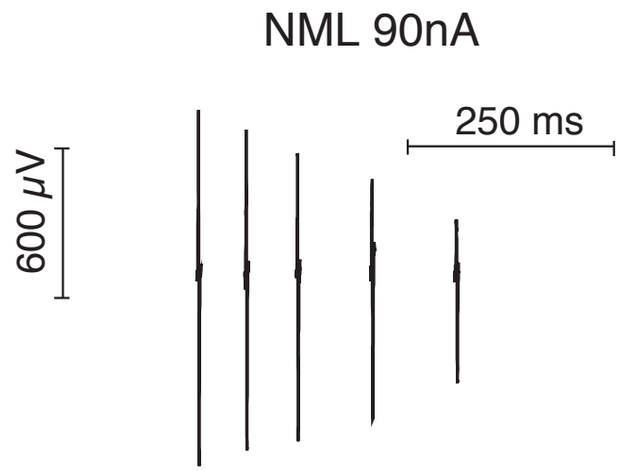
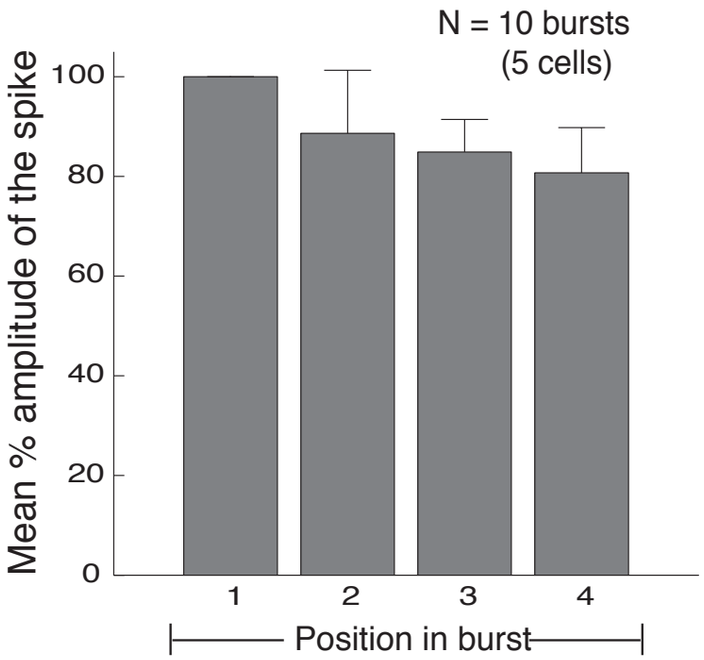
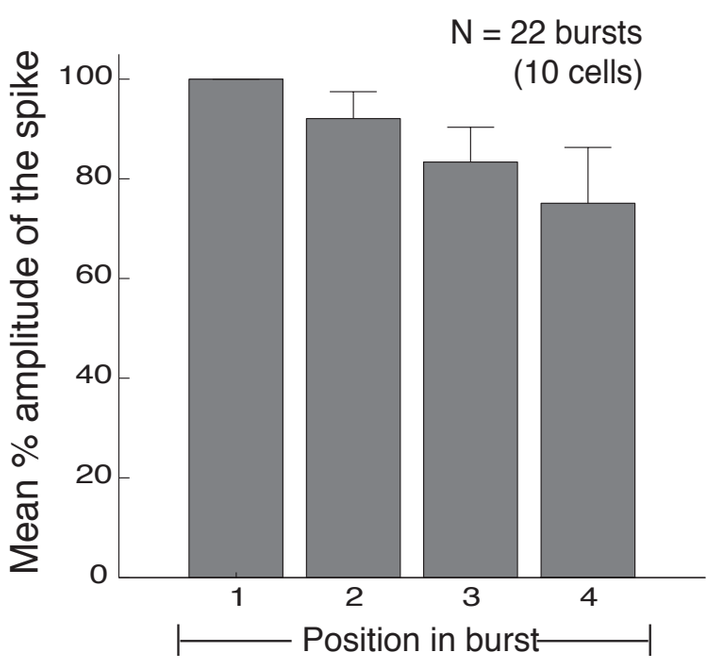




Grace and Bunney, 1984

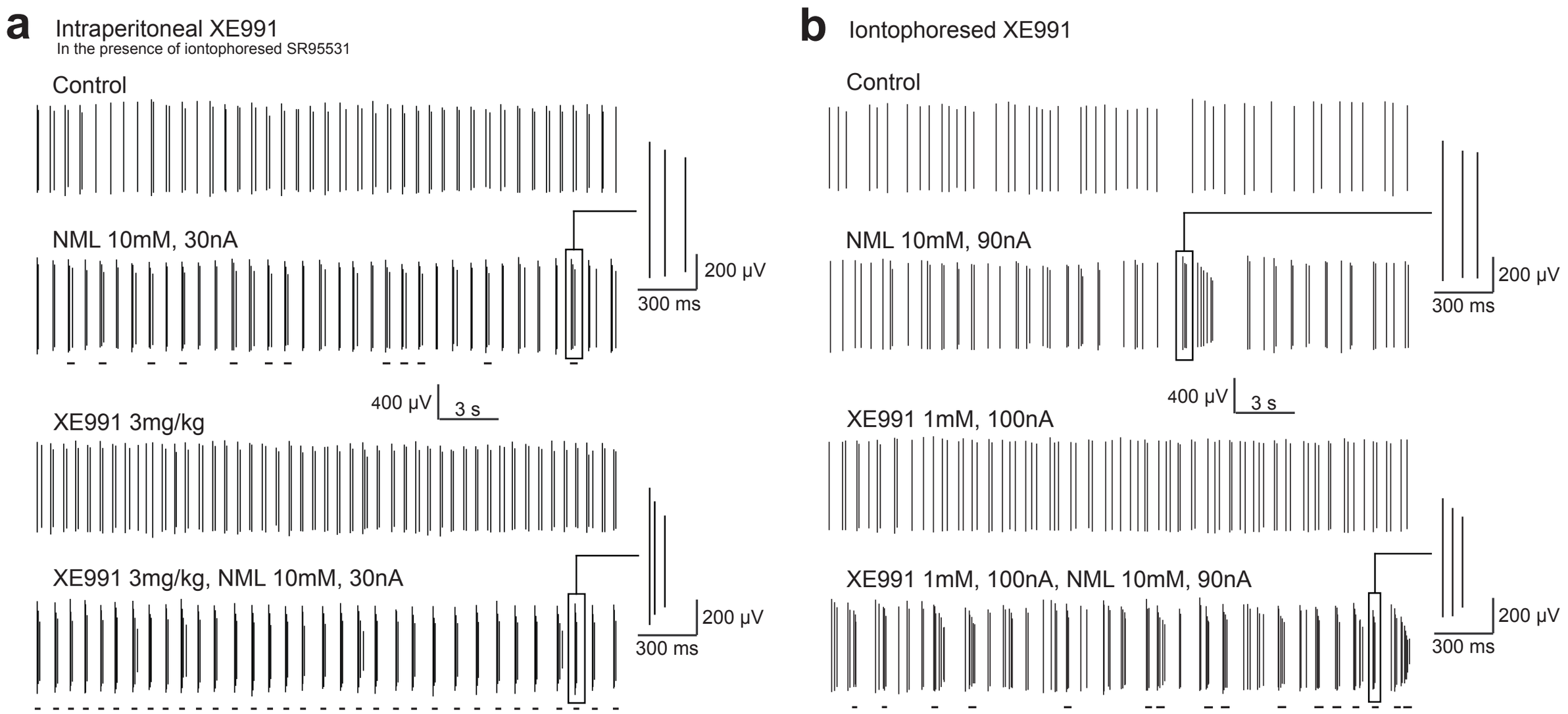




Drion et. al, 2010

Analysis of the Effect of $I_{K,M}$ on the Firing of Dopaminergic Neurons : Experimental Results

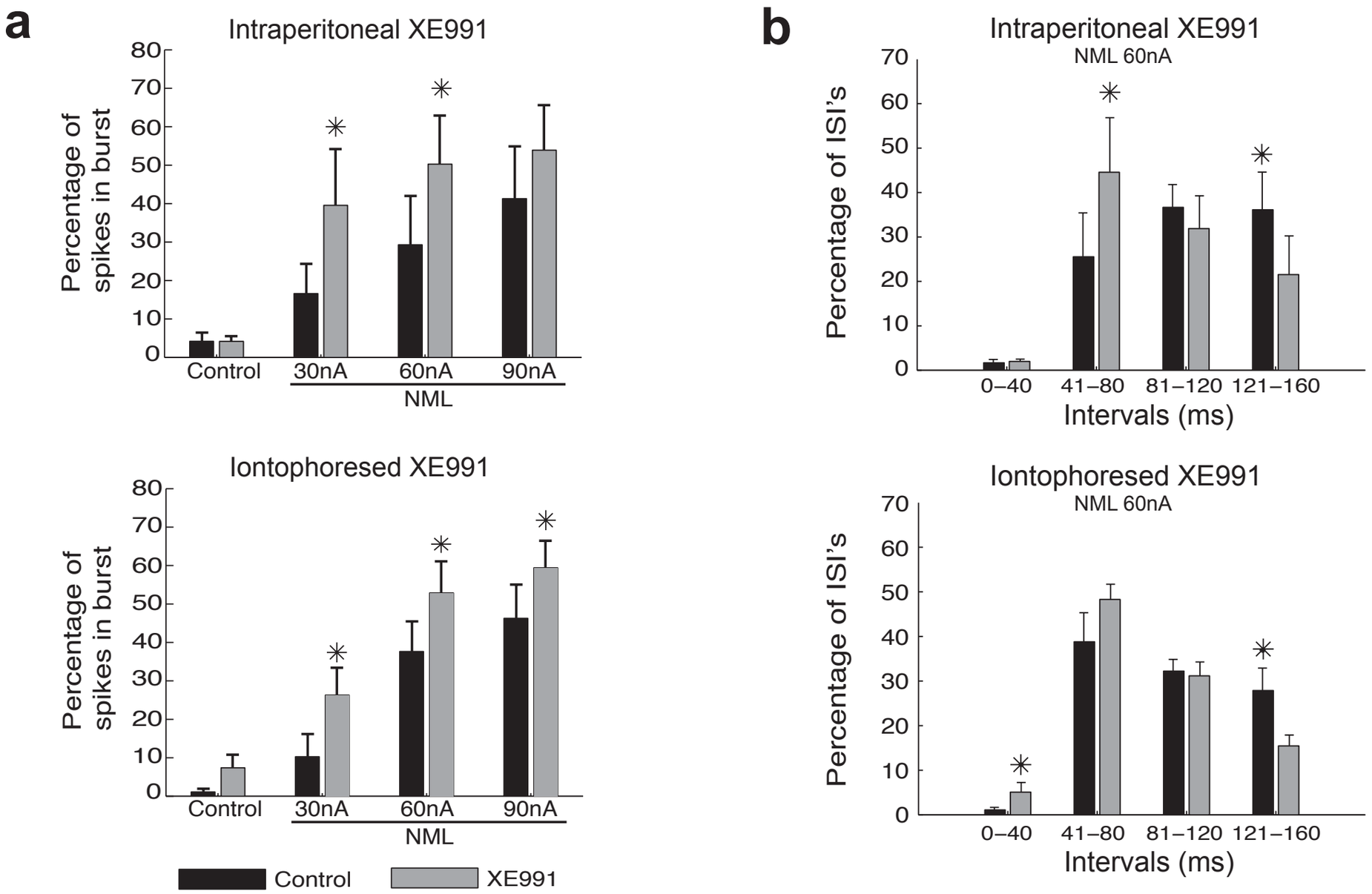
- The M-type channel blocked XE991 increases burst firing of DA neurons while it does not affect tonic firing.



Drion et. al, 2010

Analysis of the Effect of $I_{K,M}$ on the Firing of Dopaminergic Neurons : Analysis of Experimental Results

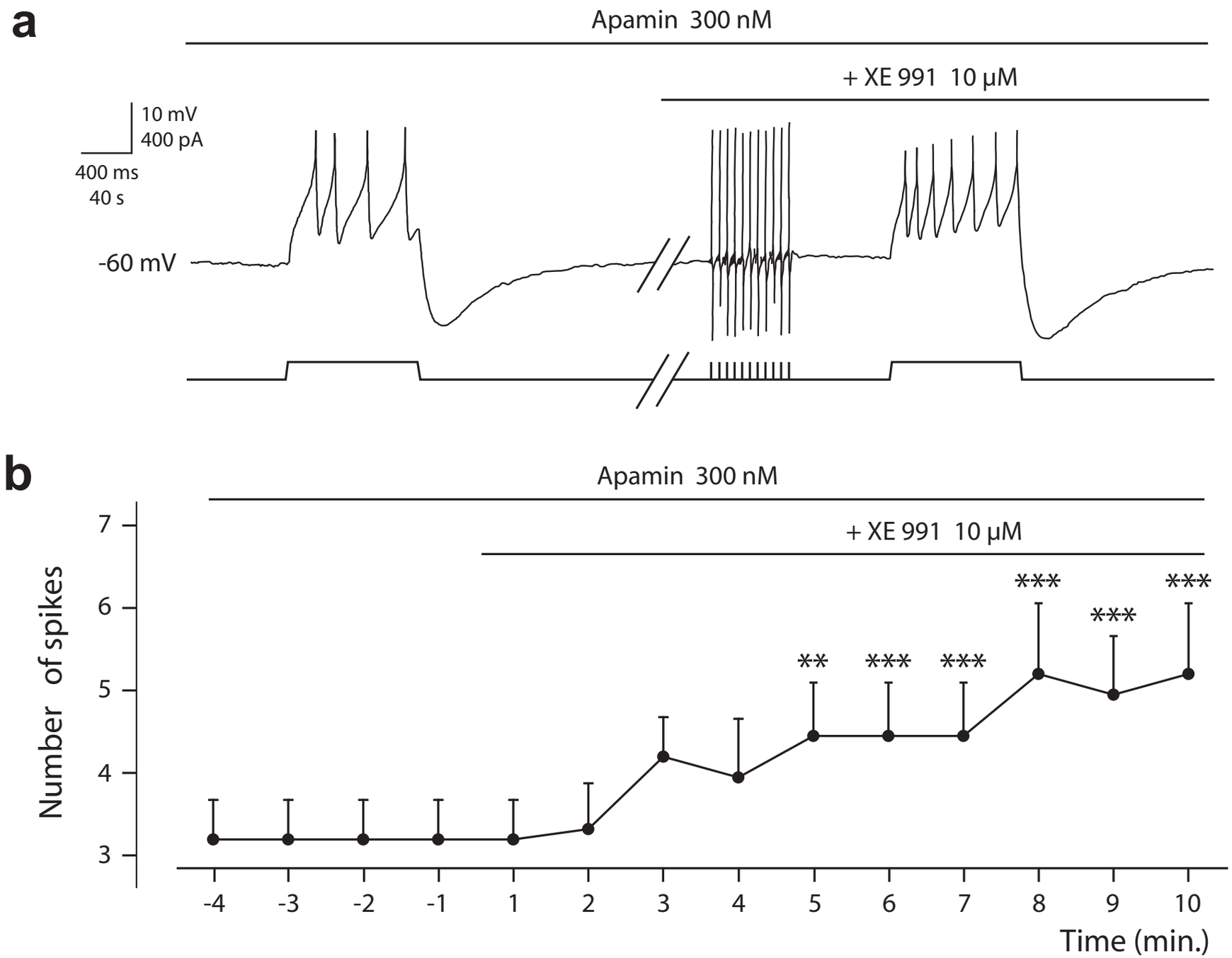
- XE991 increases the proportion of short interspike intervals in bursts.



Drion et. al, 2010

Analysis of the Effect of $I_{K,M}$ on the Firing of Dopaminergic Neurons : *in vitro* Experiments

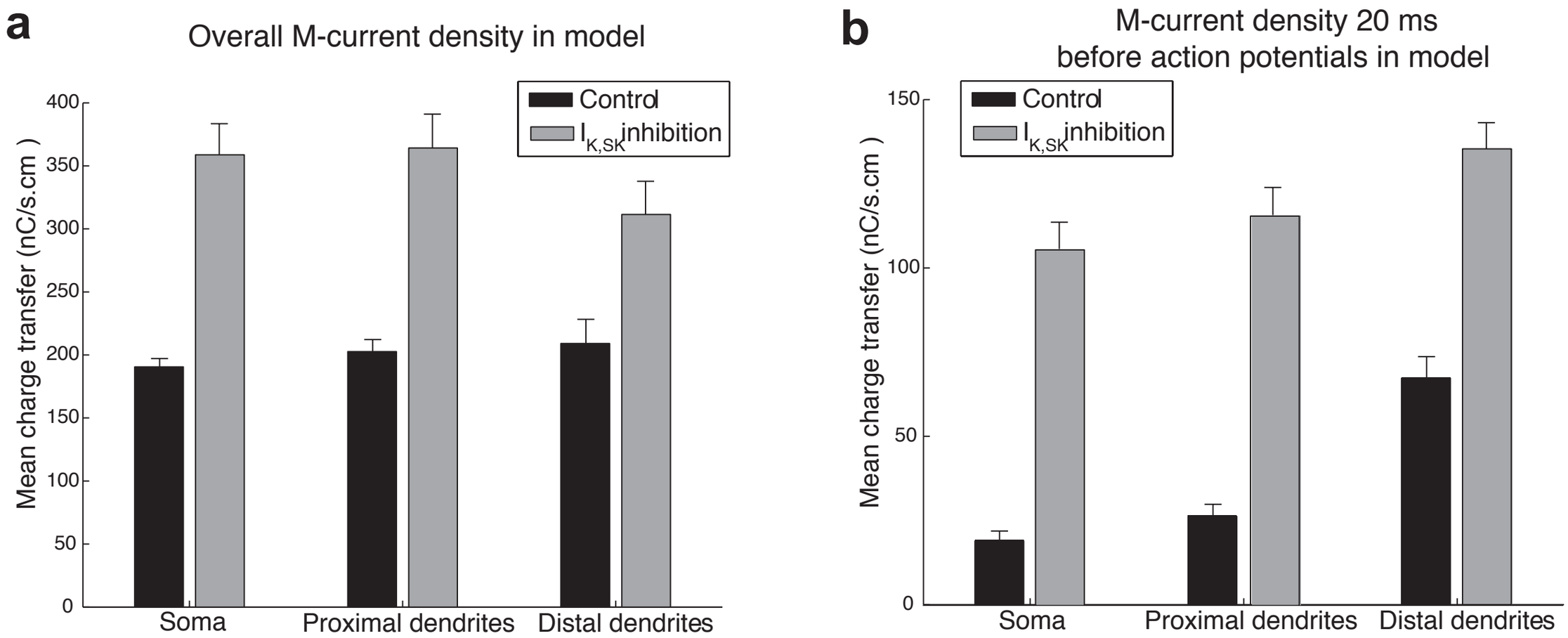
- M-type current inhibition facilitates fast firing during SK blockade *in vitro*.



Drion et. al, 2010

Analysis of the Effect of $I_{K,M}$ on the Firing of Dopaminergic Neurons : Analysis of Model Results

- $I_{K,M}$ solely affects burst firing of DA neurons because it activates in a sustain manner only in this firing mode.



Drion et. al, 2010

Discussion

- M-current selectively gates the NML-induced bursting of DA neurons.
  - XE991 facilitates fast firing by a direct effect.
- Natural and NML-induced bursts have similar characteristics.
  - Our findings can be generalized to the physiological situation.
- $I_{K,M}$ solely affects burst firing of DA neurons because it activates in a sustain manner only in this firing mode.
- Pharmacological modulation of the M-current should have a major impact on DA signaling that could be exploited therapeutically in the future.

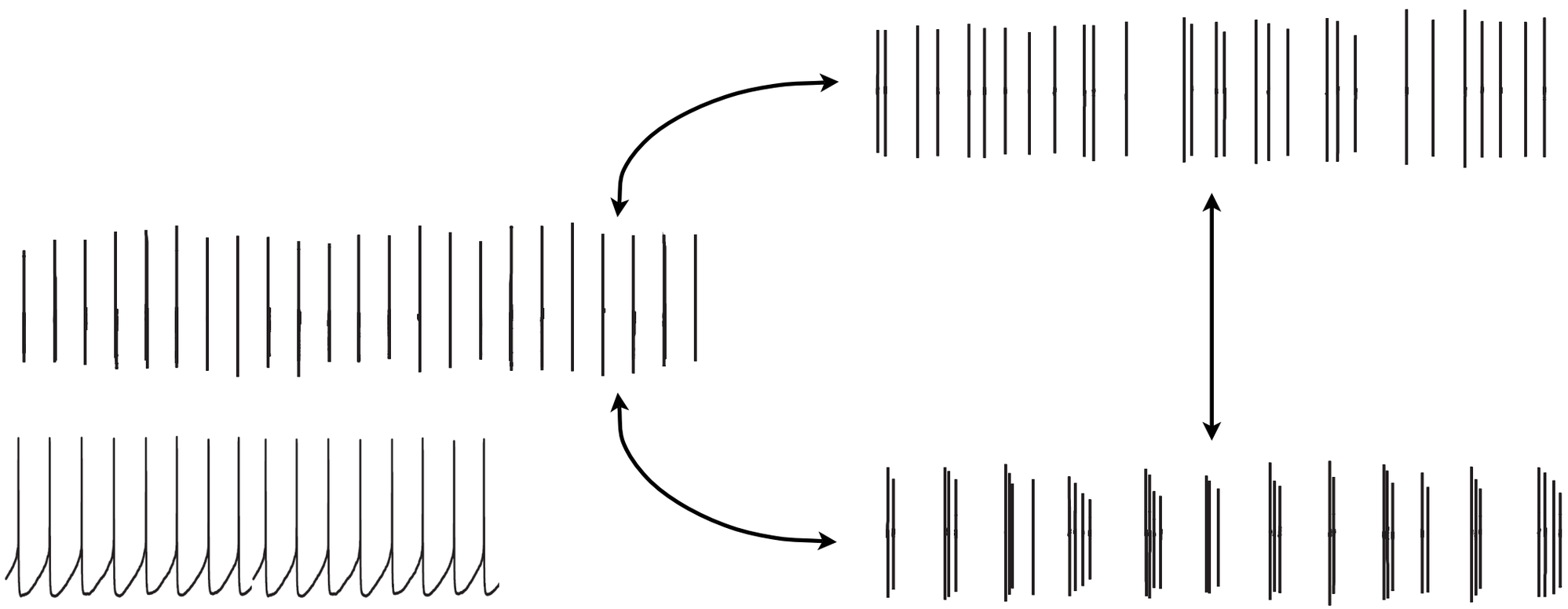
Although Strongly Different Quantitatively as well as in Their Function, Other Pacemaker Neurons Have Interesting Similarities with DA Neurons.

- Pacemaker neurons are excitable cells that exhibit regular single-spike firing in the absence of any external stimulations (i.e. in the absence of synaptic afferents).
- A set of pacemaker neurons of the central nervous system:

Gonadotropin-releasing (GnRH) neurons
Dopaminergic (DA) neurons
Nucleus tractus solitarii neurons
Serotoninergic (5-HT) neurons
Paraventricular nucleus neurons
Deep cerebellar nucleus neurons
Rat subthalamic nucleus neurons
Mitra cells of the olfactory bulb

Although Strongly Different Quantitatively as well as in Their Function, Other Pacemaker Neurons Have Interesting Similarities with DA Neurons.

- Many pacemaker cells can switch between irregular and burst firing *in vivo.*



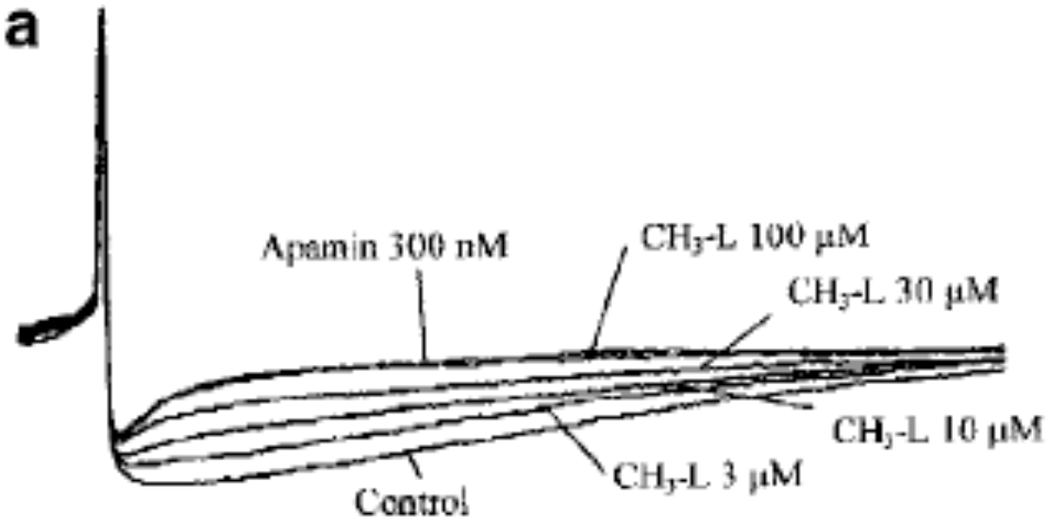
No synaptic afferents (*in vitro*)

Synaptic afferents (*in vivo*)

- Neurotransmitter release critically relies on the firing pattern of the cell.

Moreover, Small Conductance Calcium-Activated (SK) Potassium Channels Regulates a Part of the AHP for Most of These Cells.

- Small-conductance calcium-activated (SK) potassium channels gating is sensitive to the intracellular calcium concentration BUT NOT to the membrane potential.

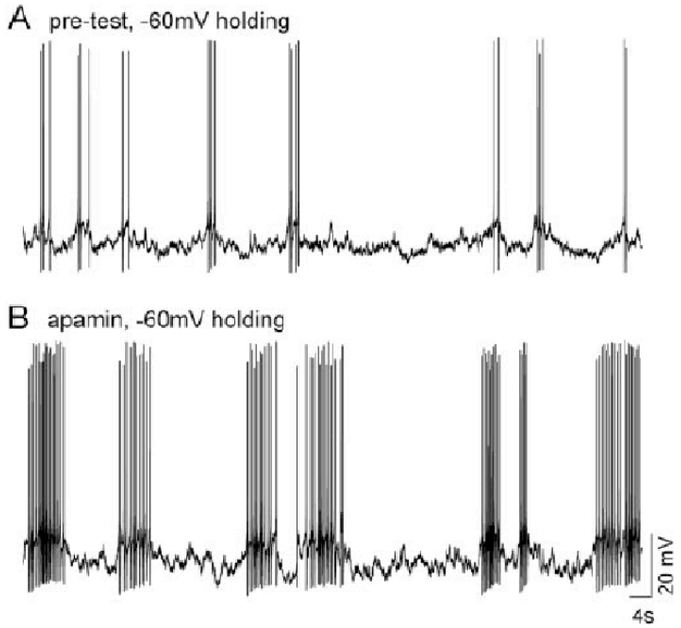


Effect of SK blockade on the AHP of a 5-HT neuron[1]

[1]Scuvée-Moreau et. al, 2004

SK Channels also Strongly Affect the Excitability and/or Firing Pattern of Pacemaker Cells

Gonadrotropin-releasing hormone (GnRH) neurons[1]



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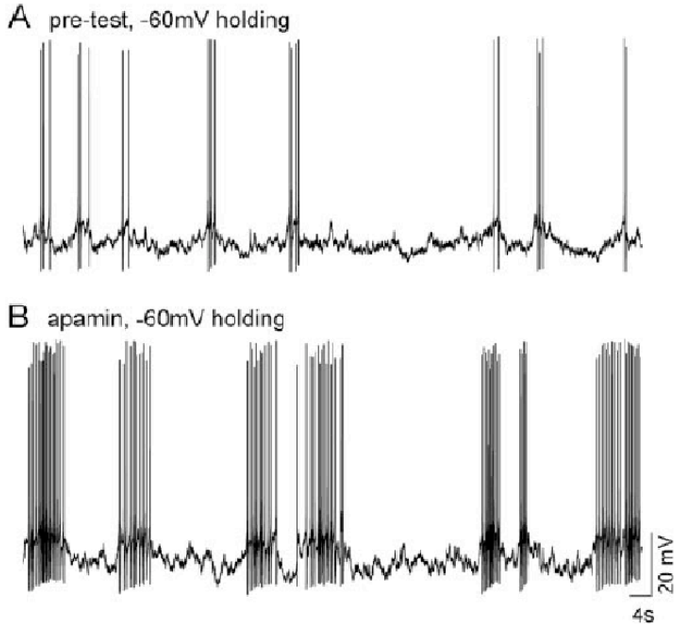
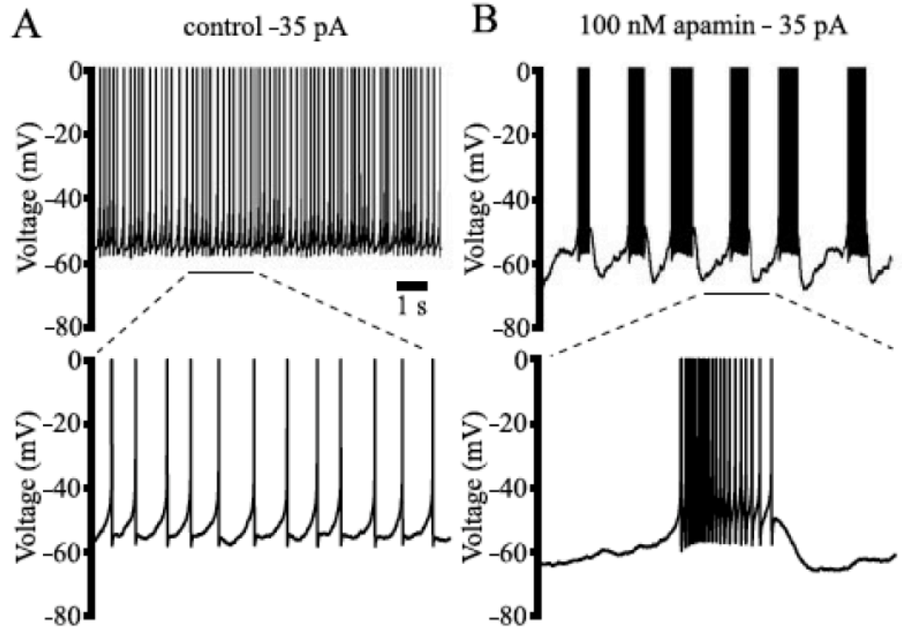


Subthalamic Nucleus (STN) neurons[2]



[1]Liu et. al, 2008 [2]Hallworth et. al, 2003

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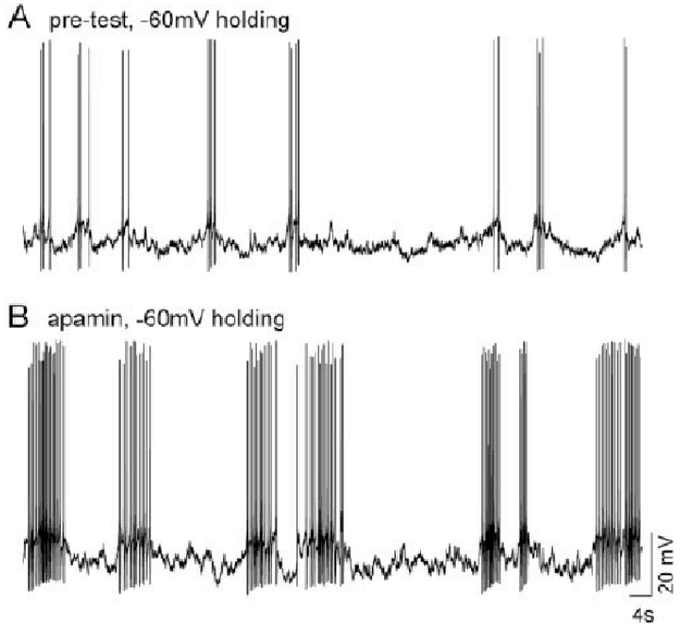

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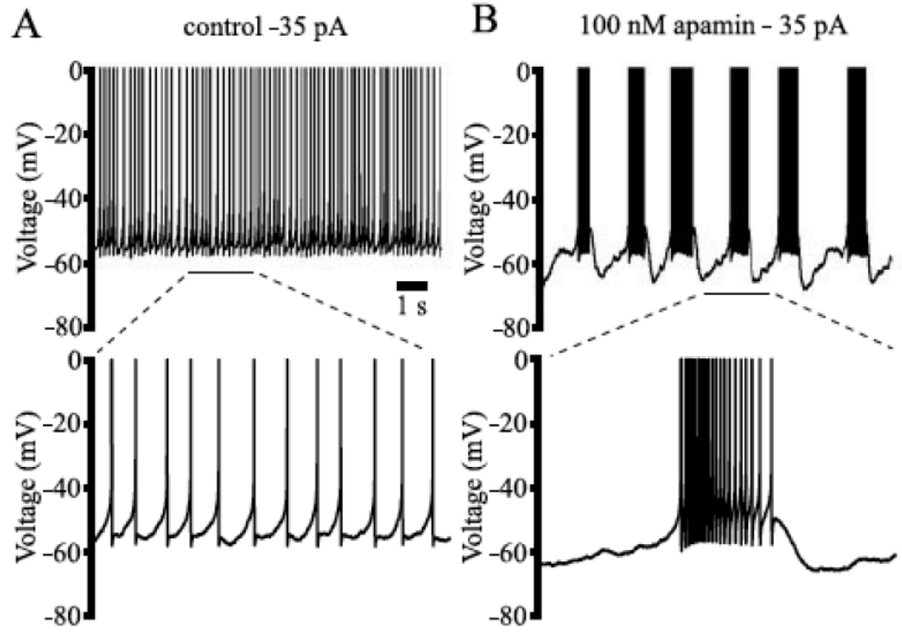
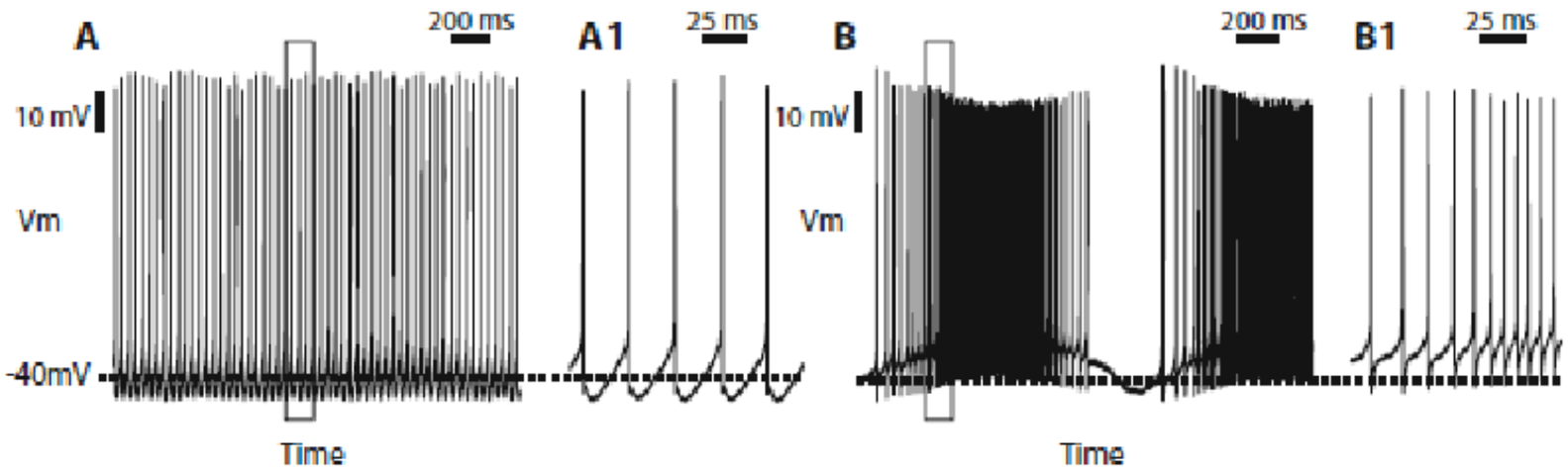
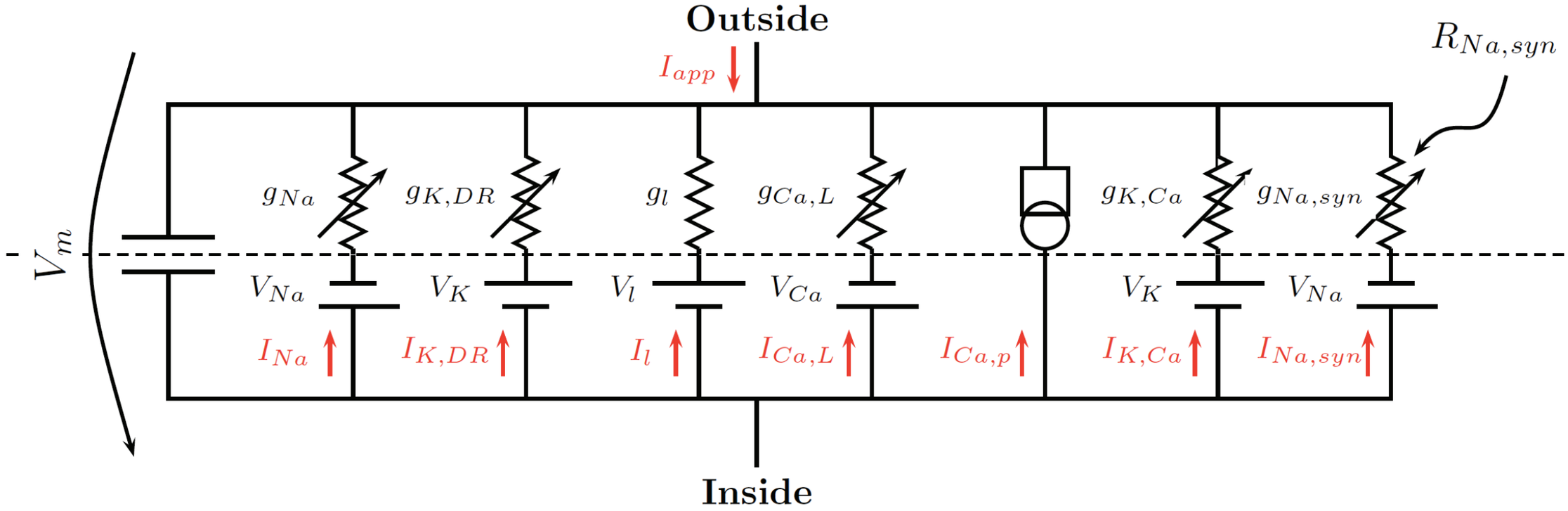


Deep cerebellar nucleus neurons[3]



[1]Liu et. al, 2008 [2]Hallworth et. al, 2003 [3]Feng et. al, 2008

A Qualitative Description of the Mechanisms Underlying Burst Firing in Apamin-Induced Bursting Neurons



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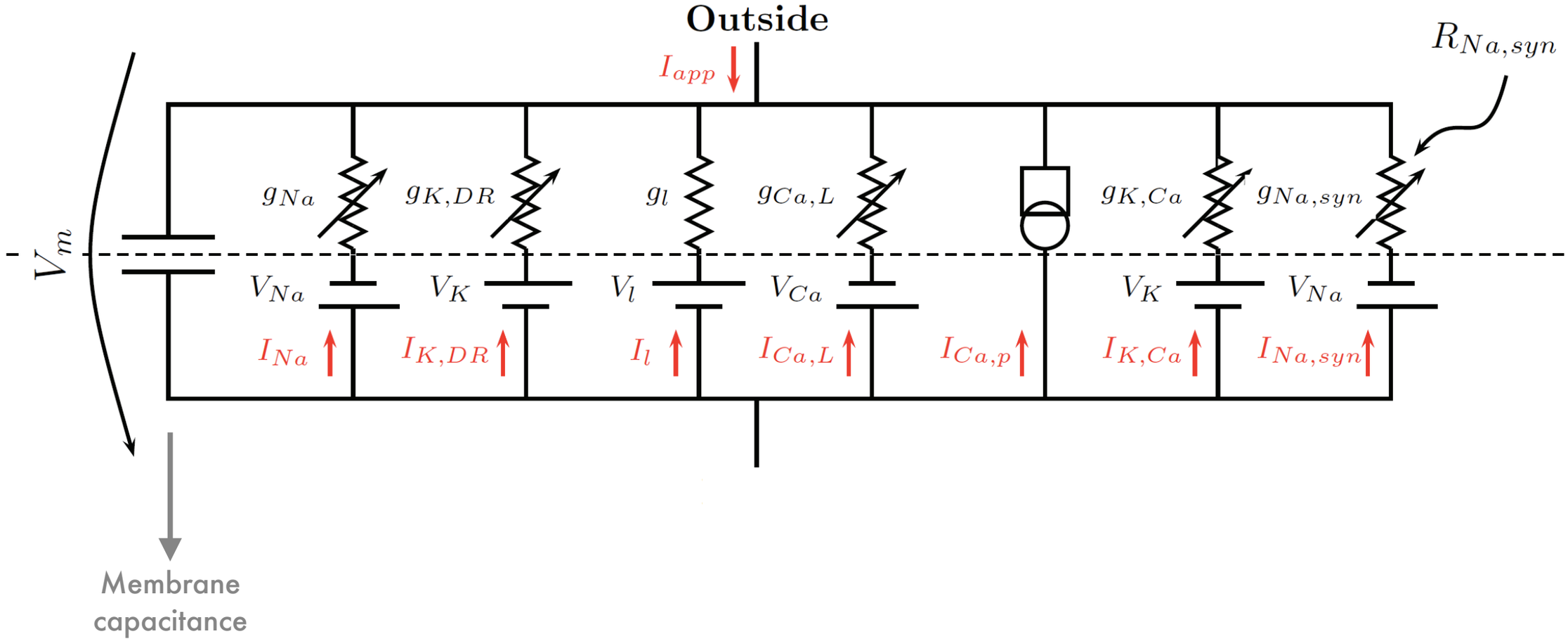

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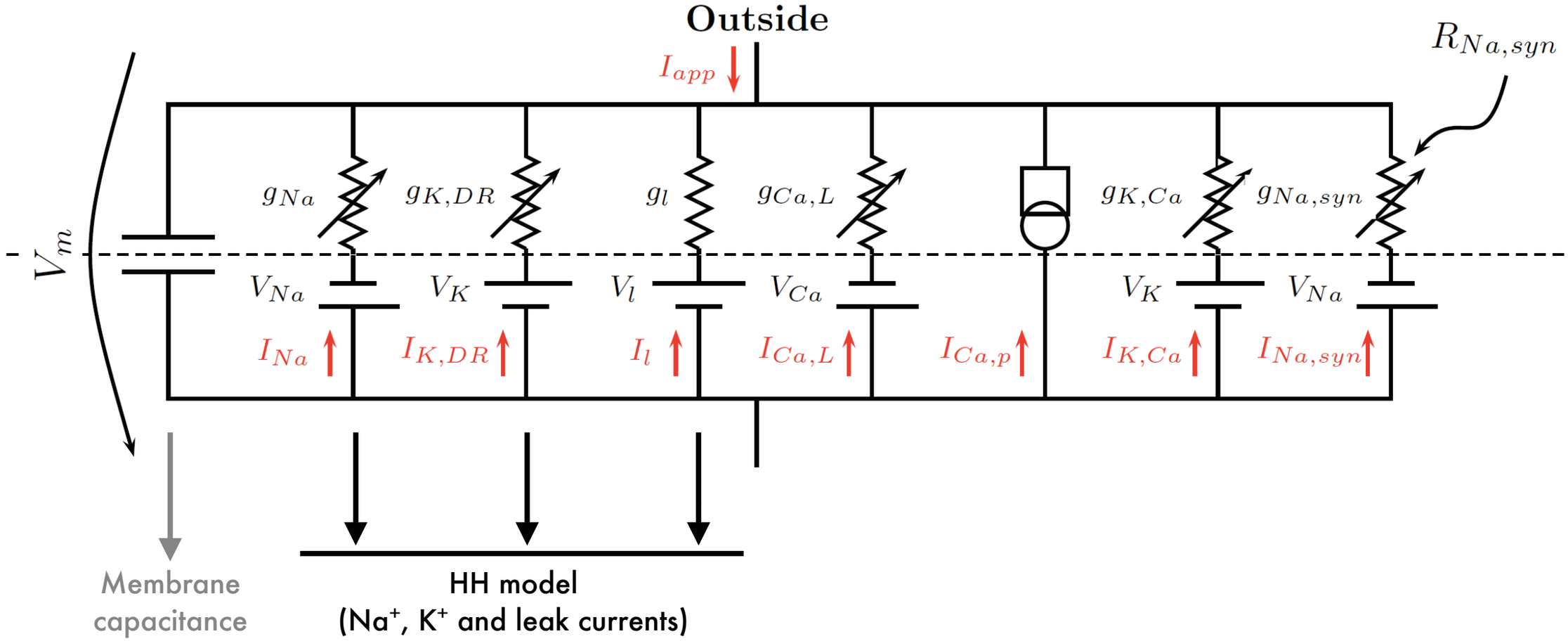

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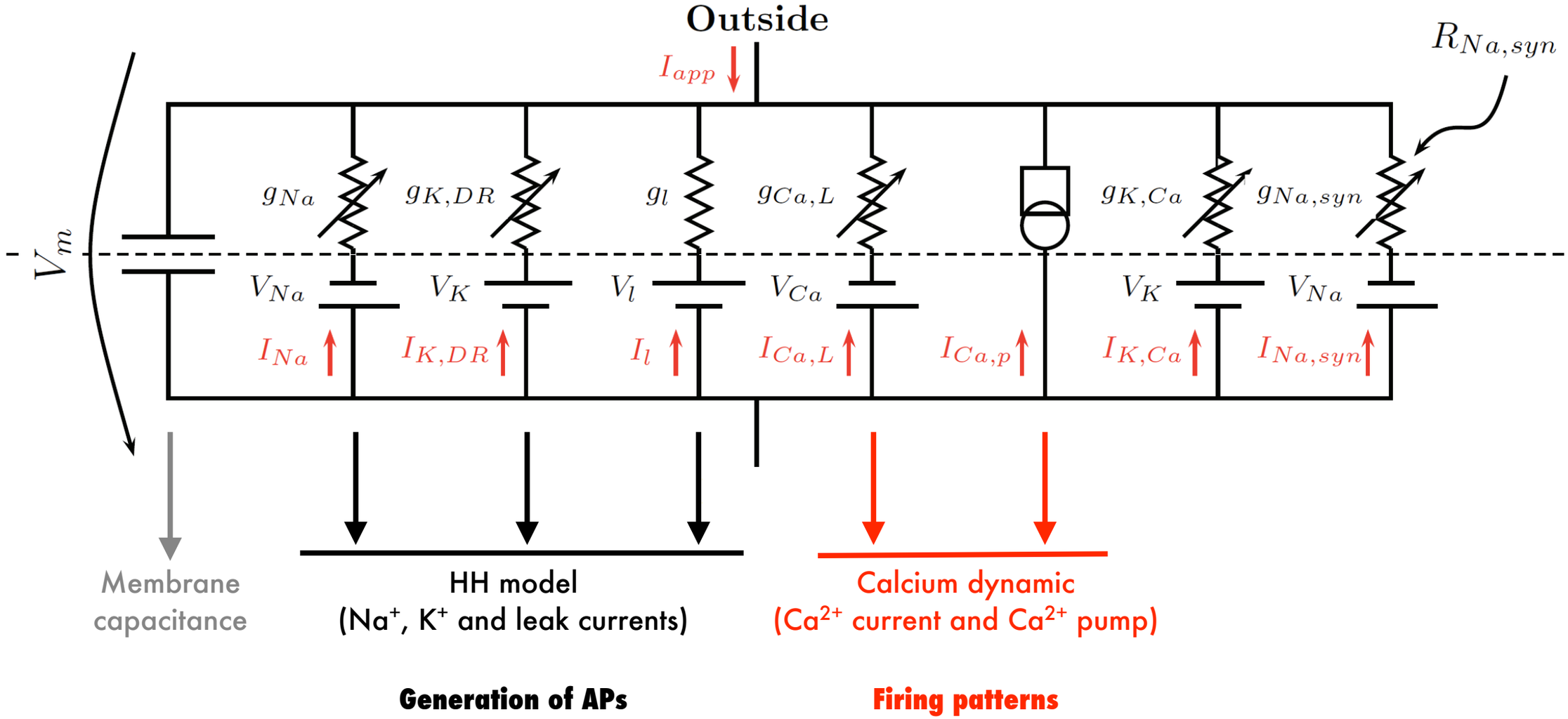

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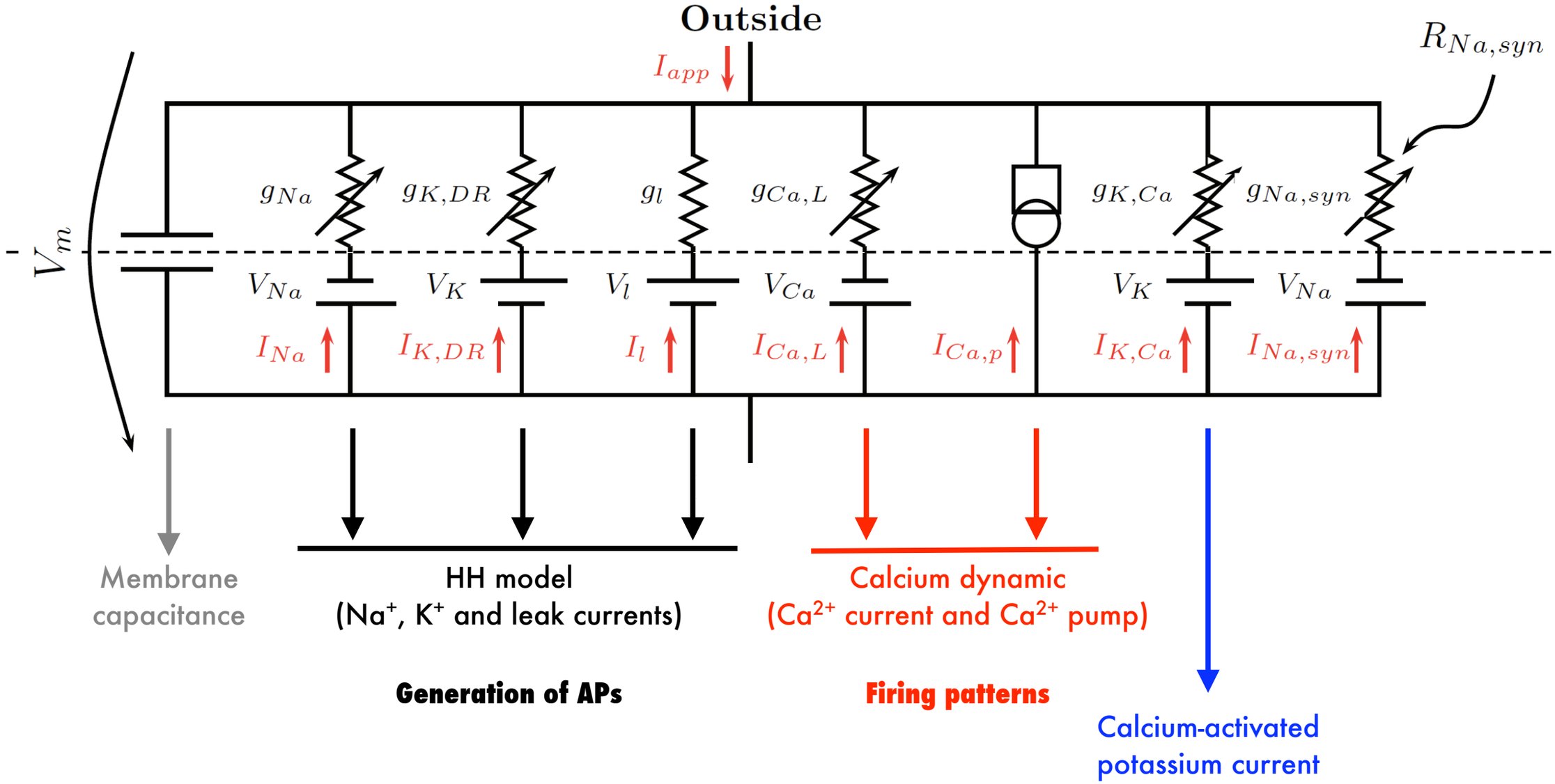

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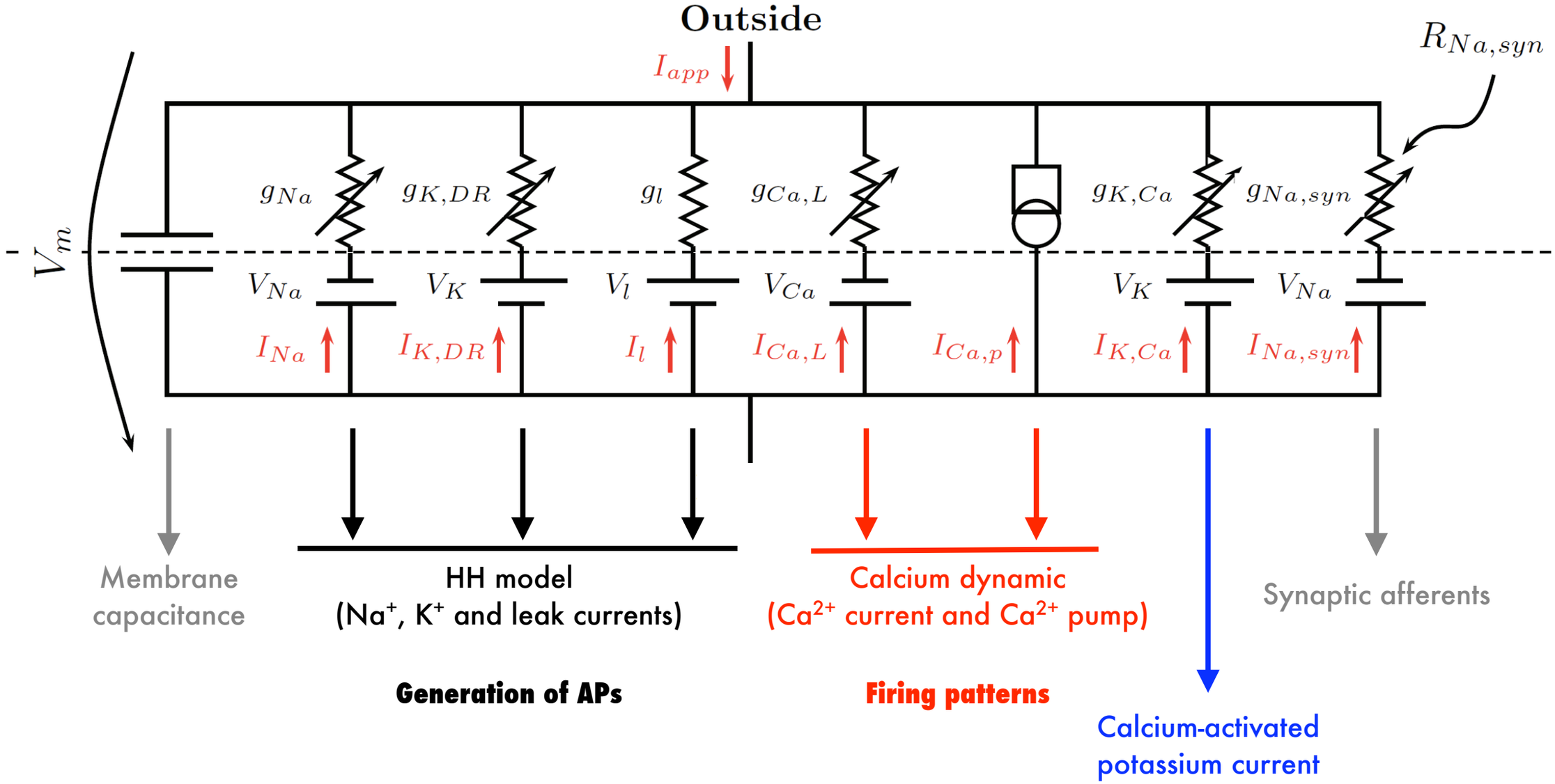
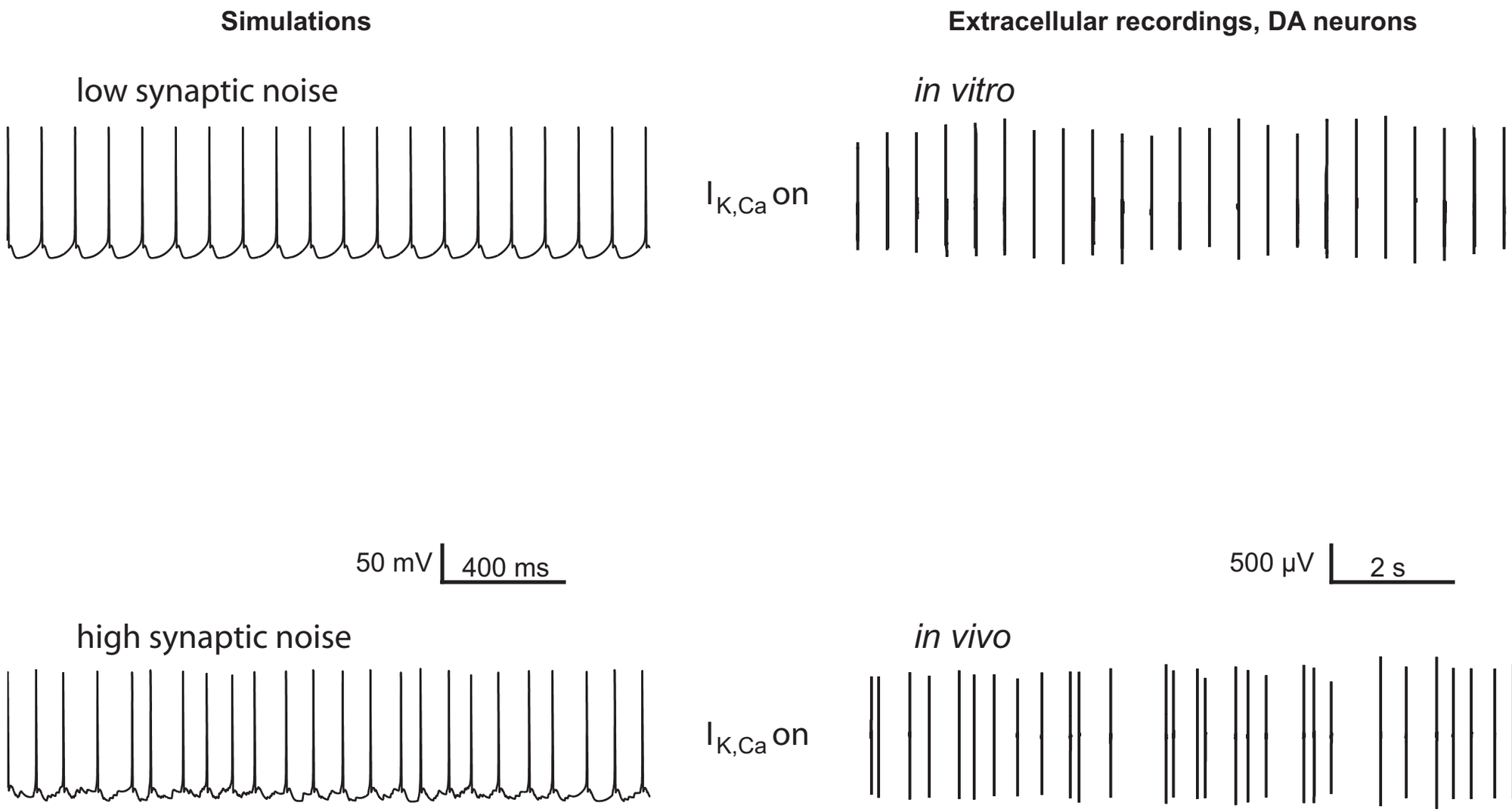


The Model Qualitatively Reproduces Experimental Results



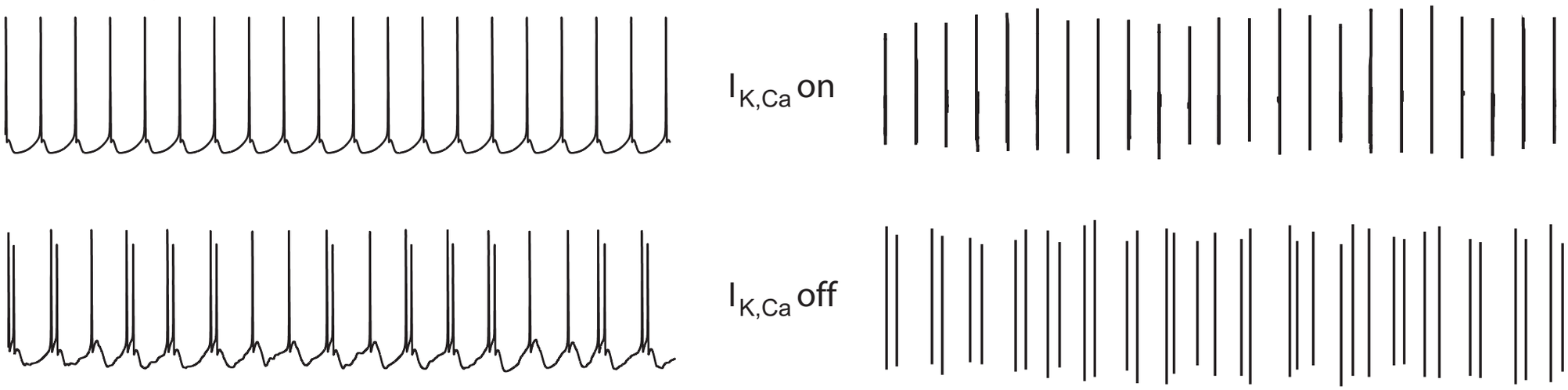
The Model Qualitatively Reproduces Experimental Results

Simulations

Extracellular recordings, DA neurons

low synaptic noise

in vitro

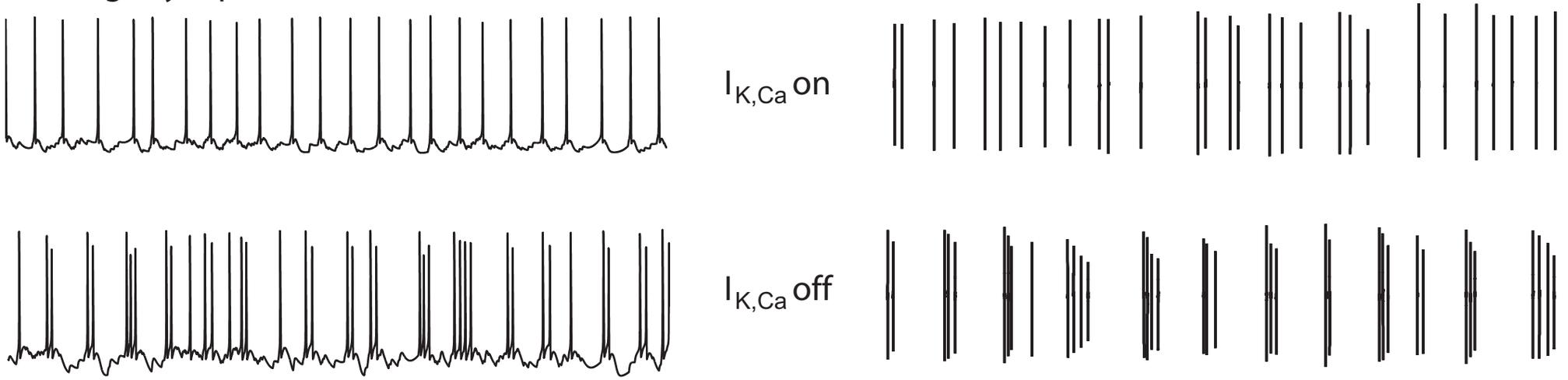


50 mV 400 ms

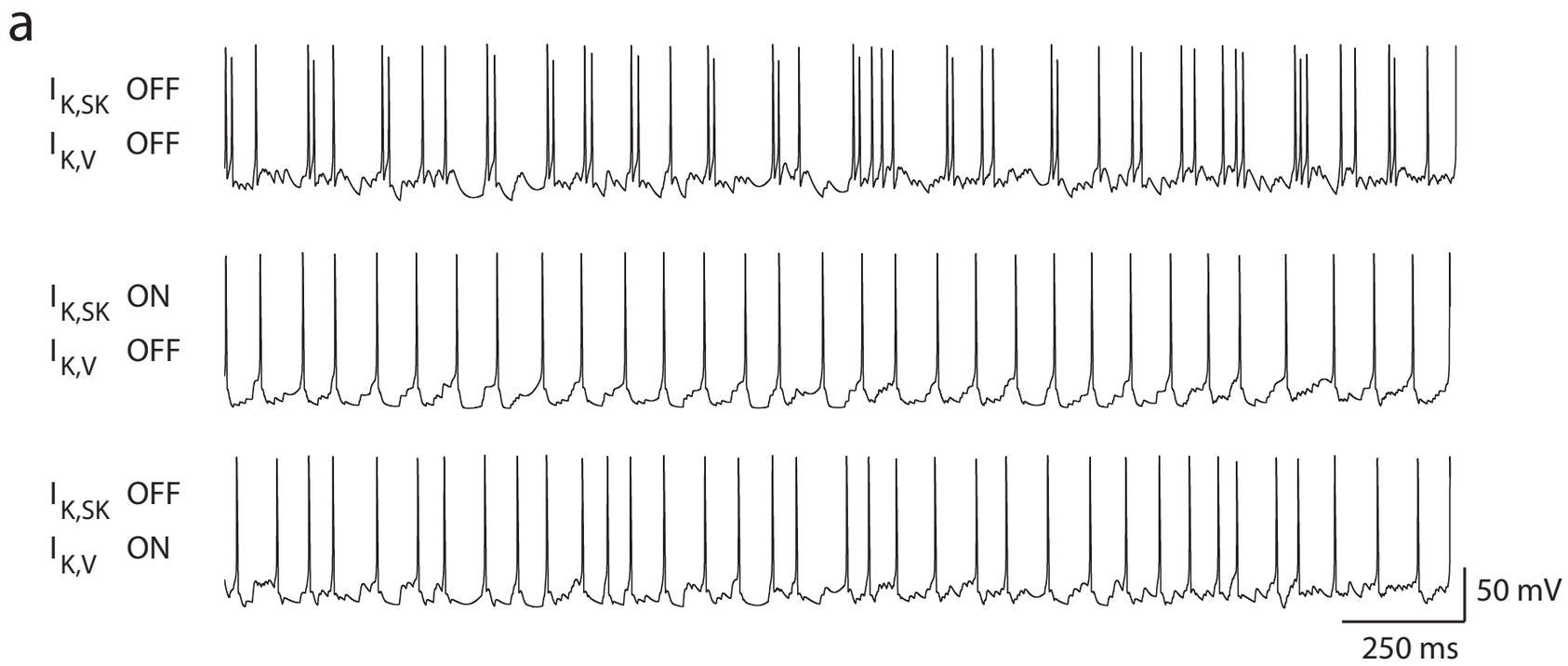
500 µV 2 s

high synaptic noise

in vivo



SK Channels Fully Adapt to The Dynamic of the Neuron, in Contrast to Voltage-Gated Channels



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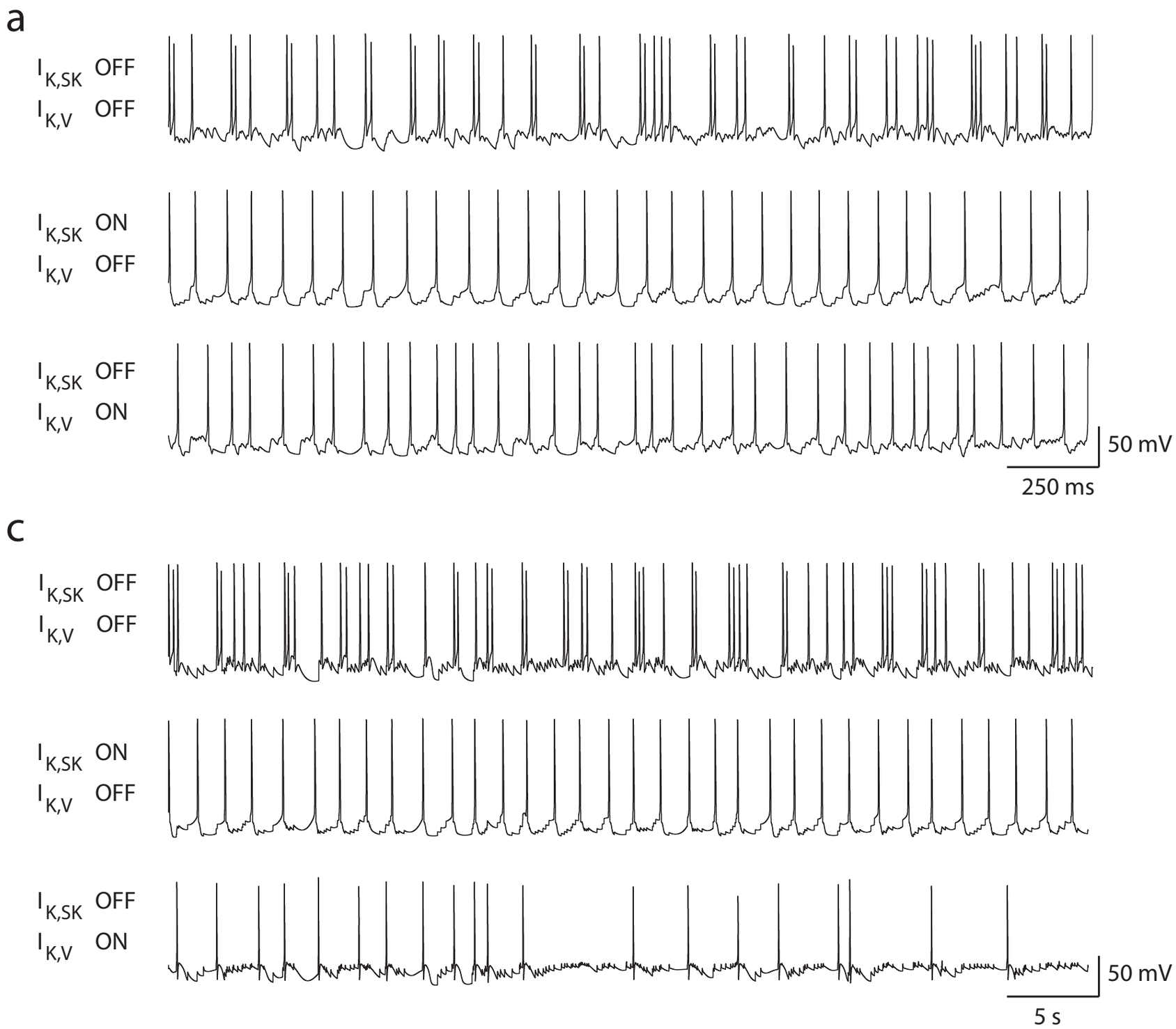
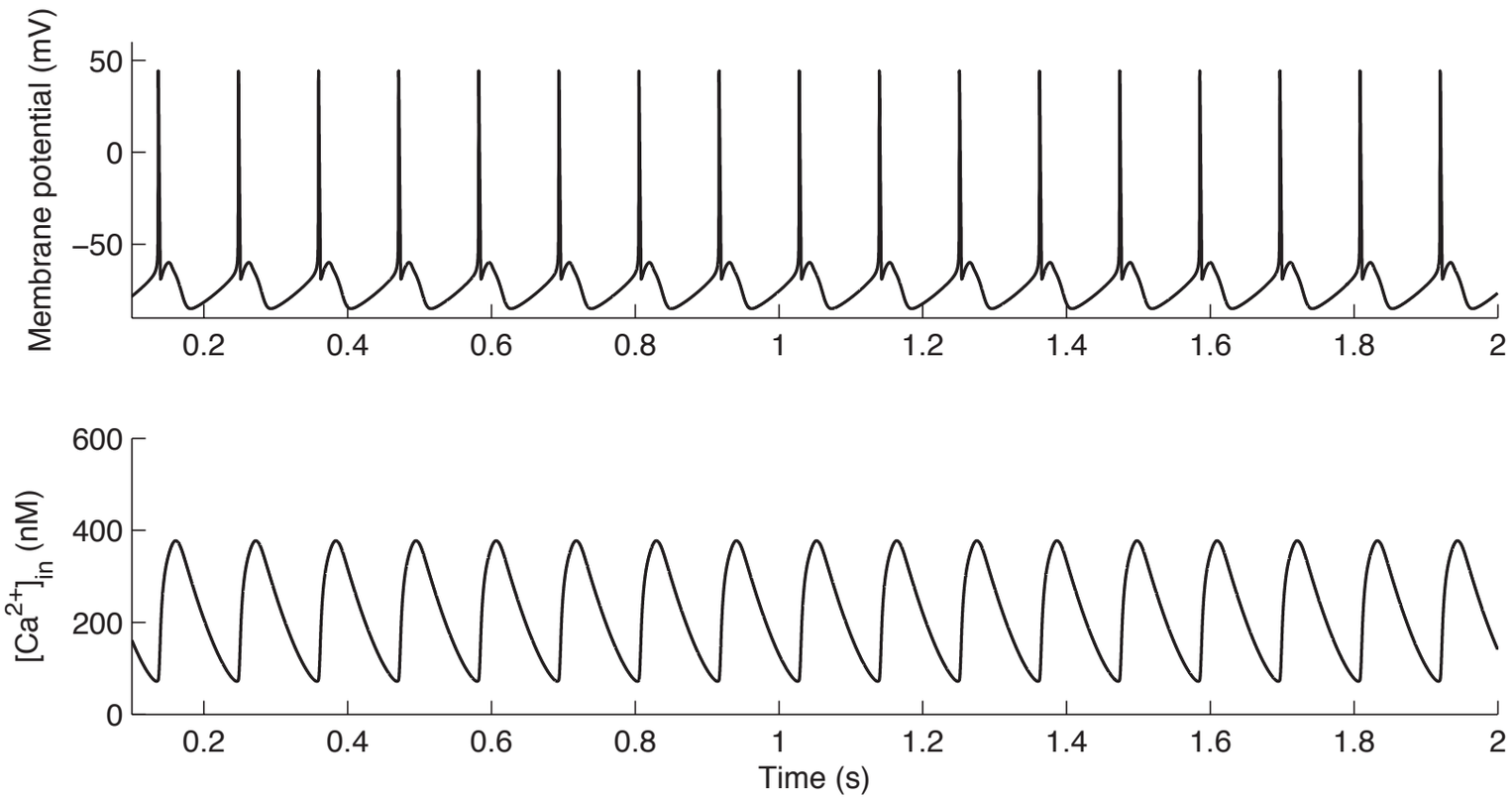


Mechanisms of Pacemaker Firing in the Simple Model.



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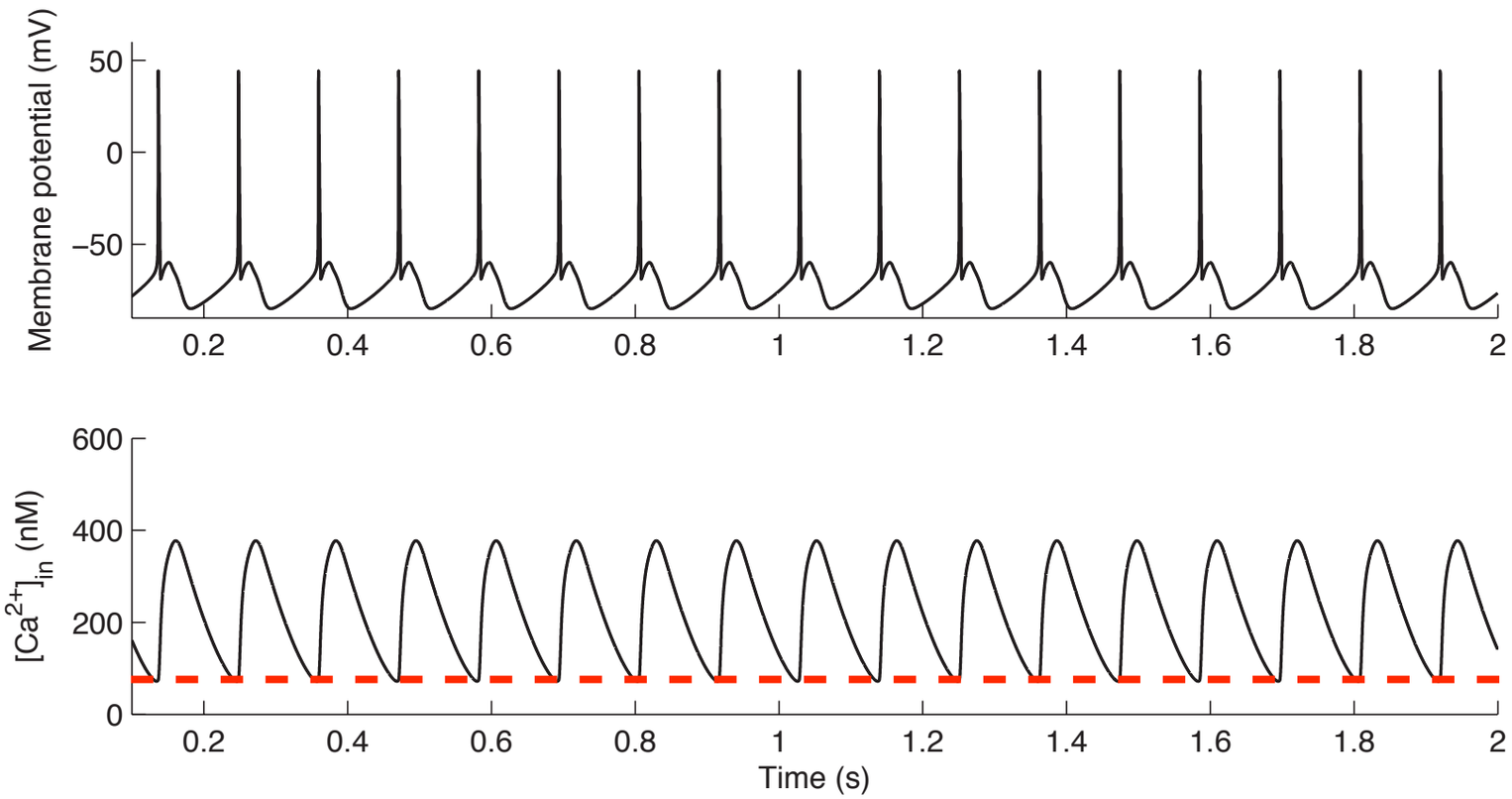

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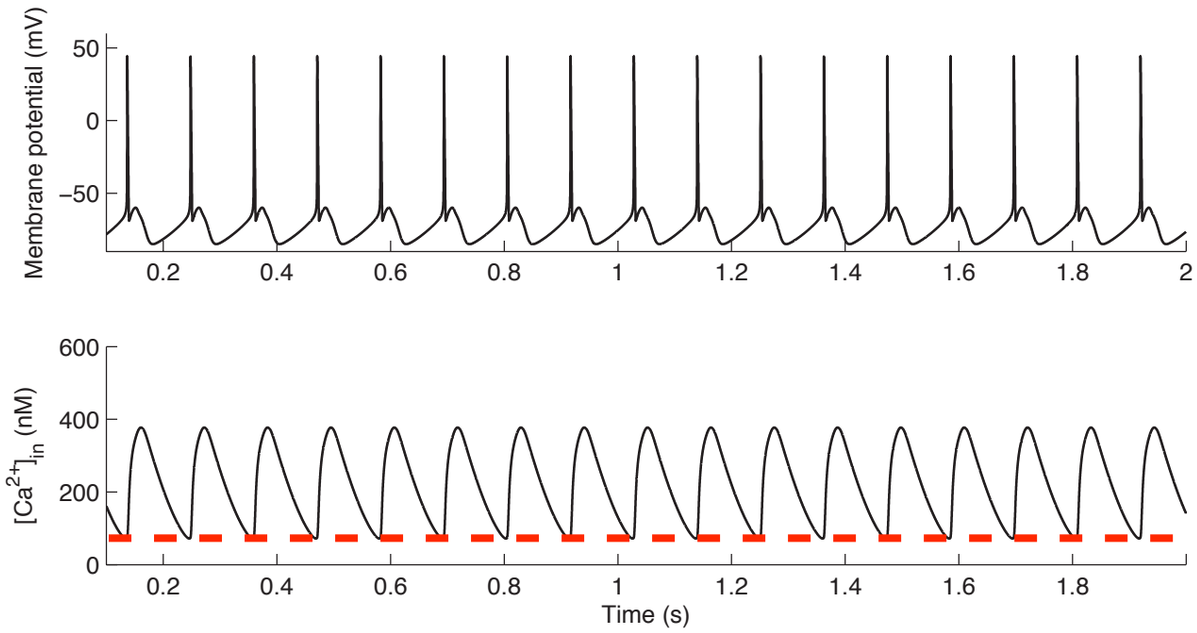

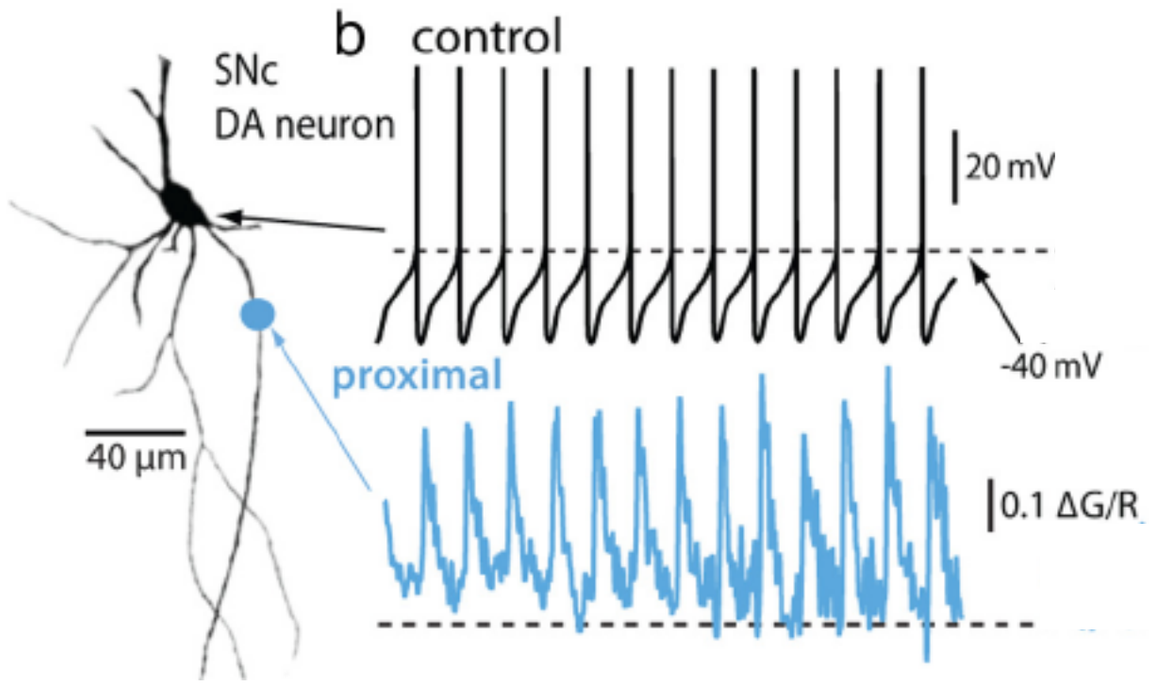

[3]Guzman et. al, 2009

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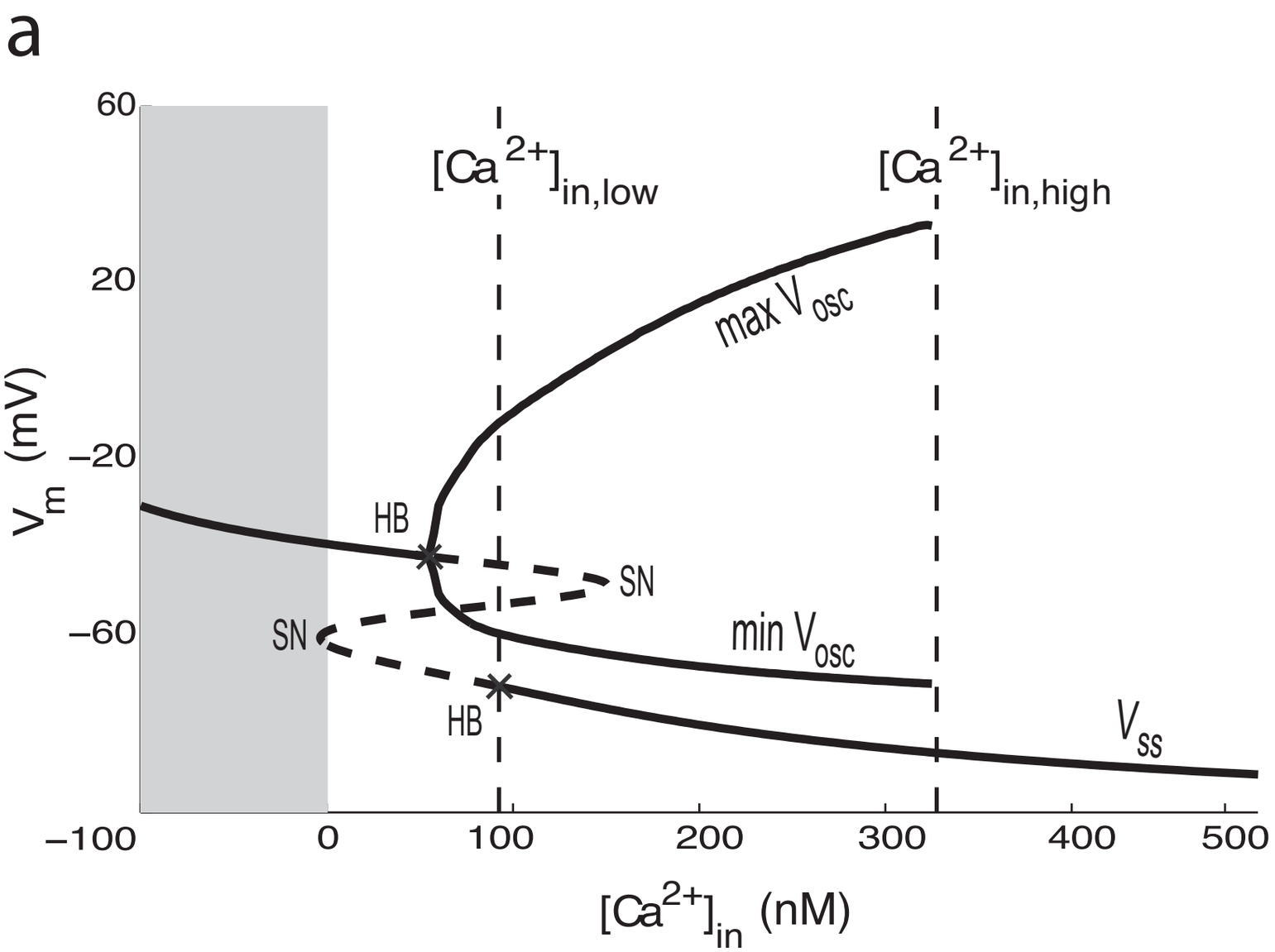

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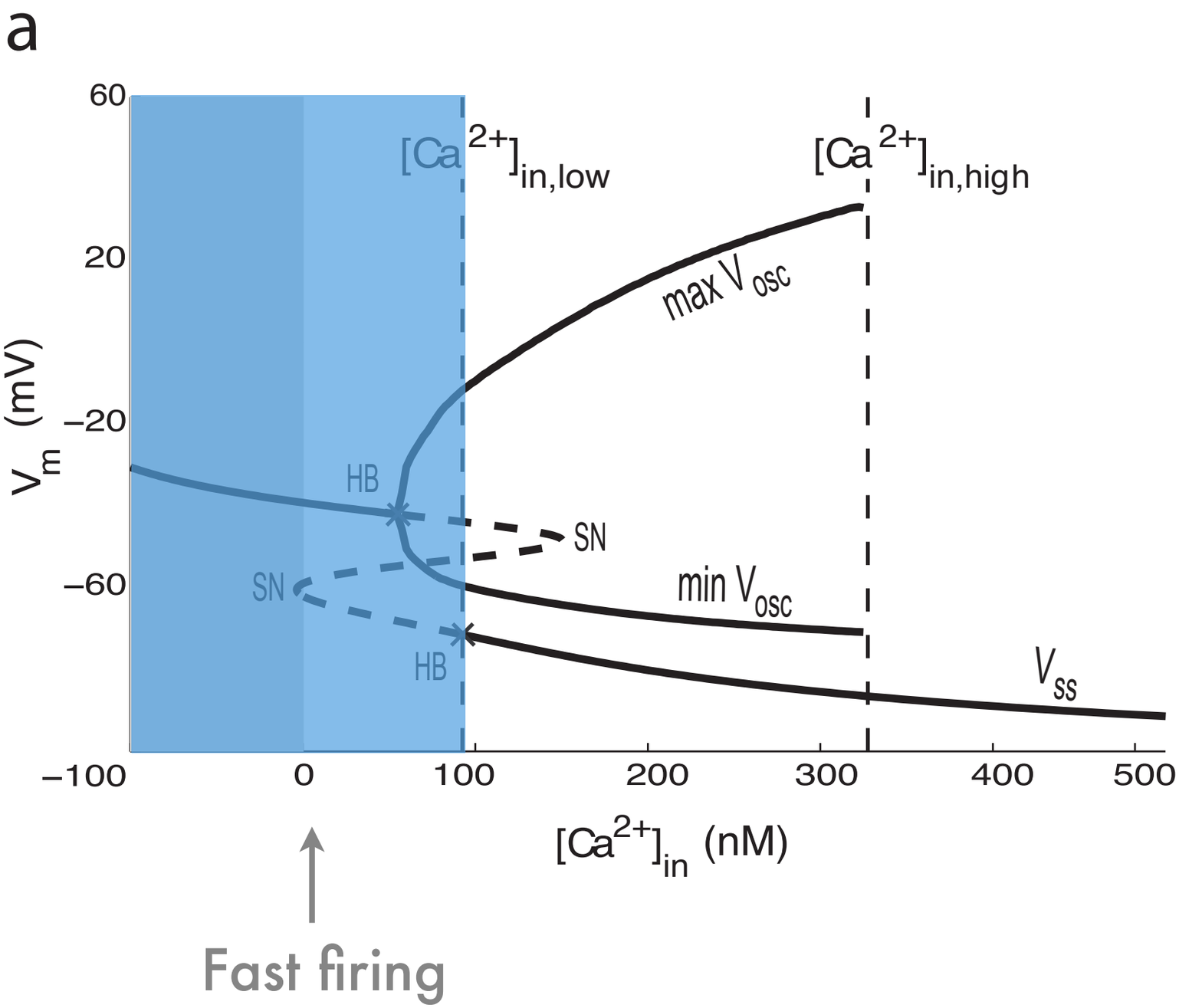

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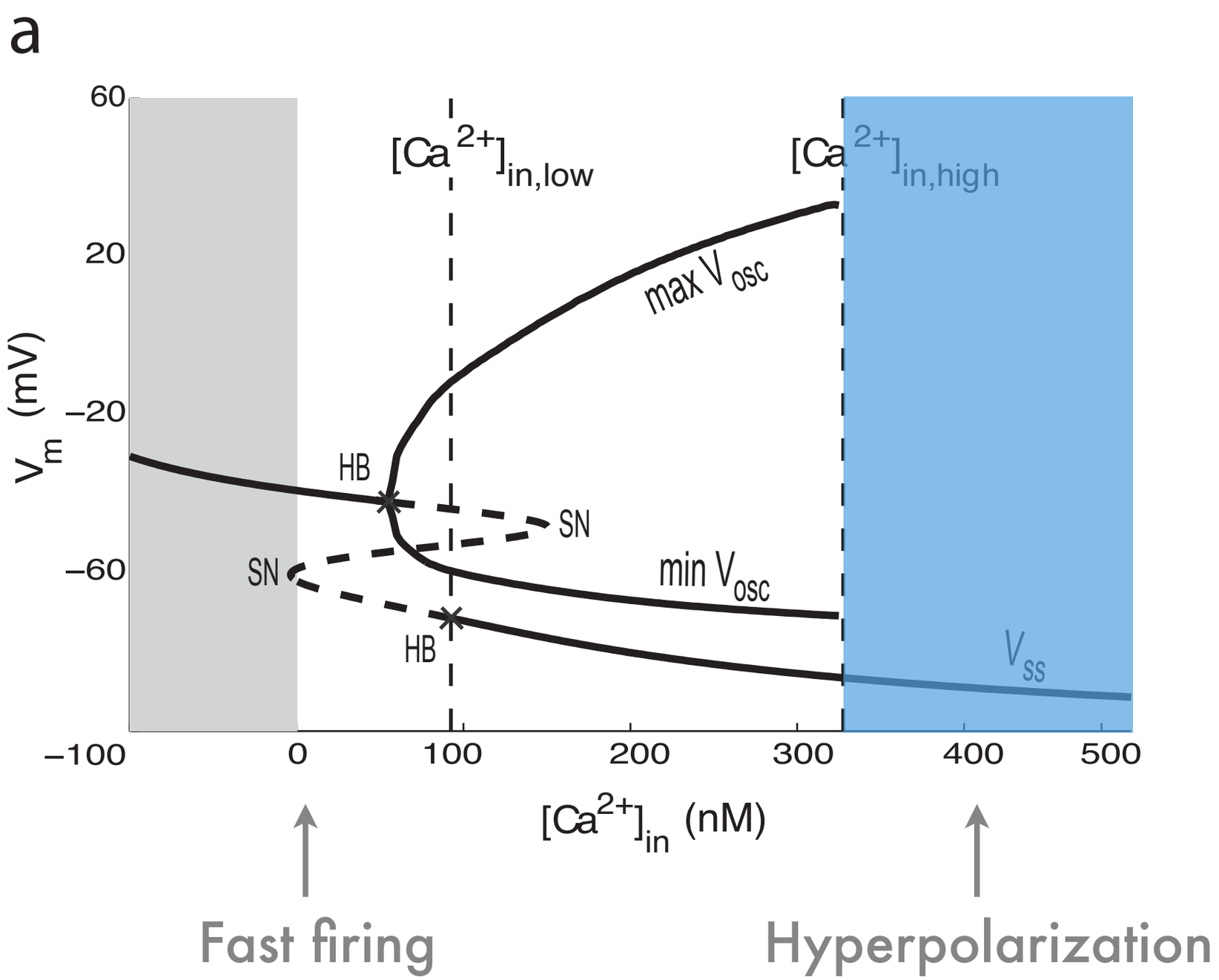

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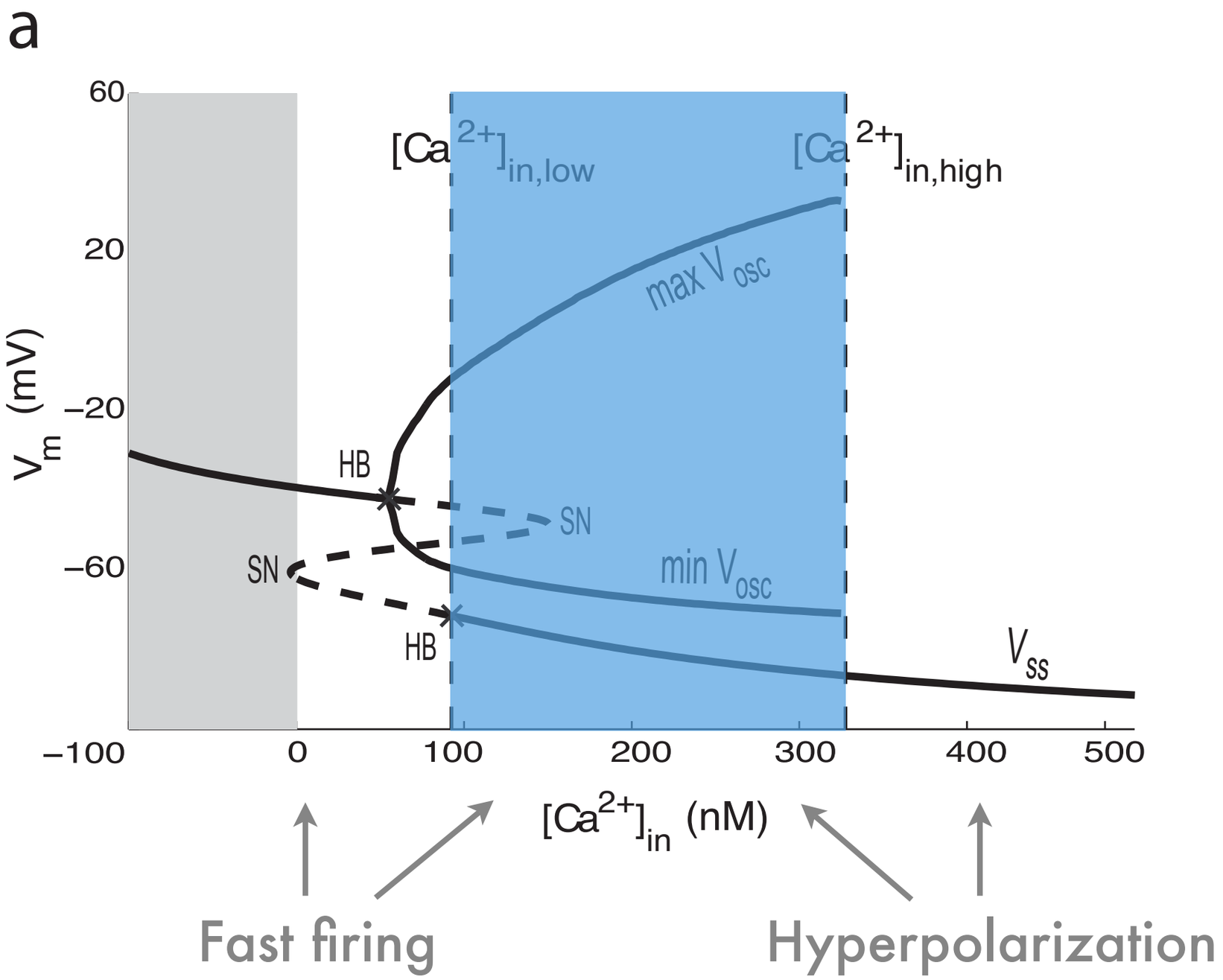

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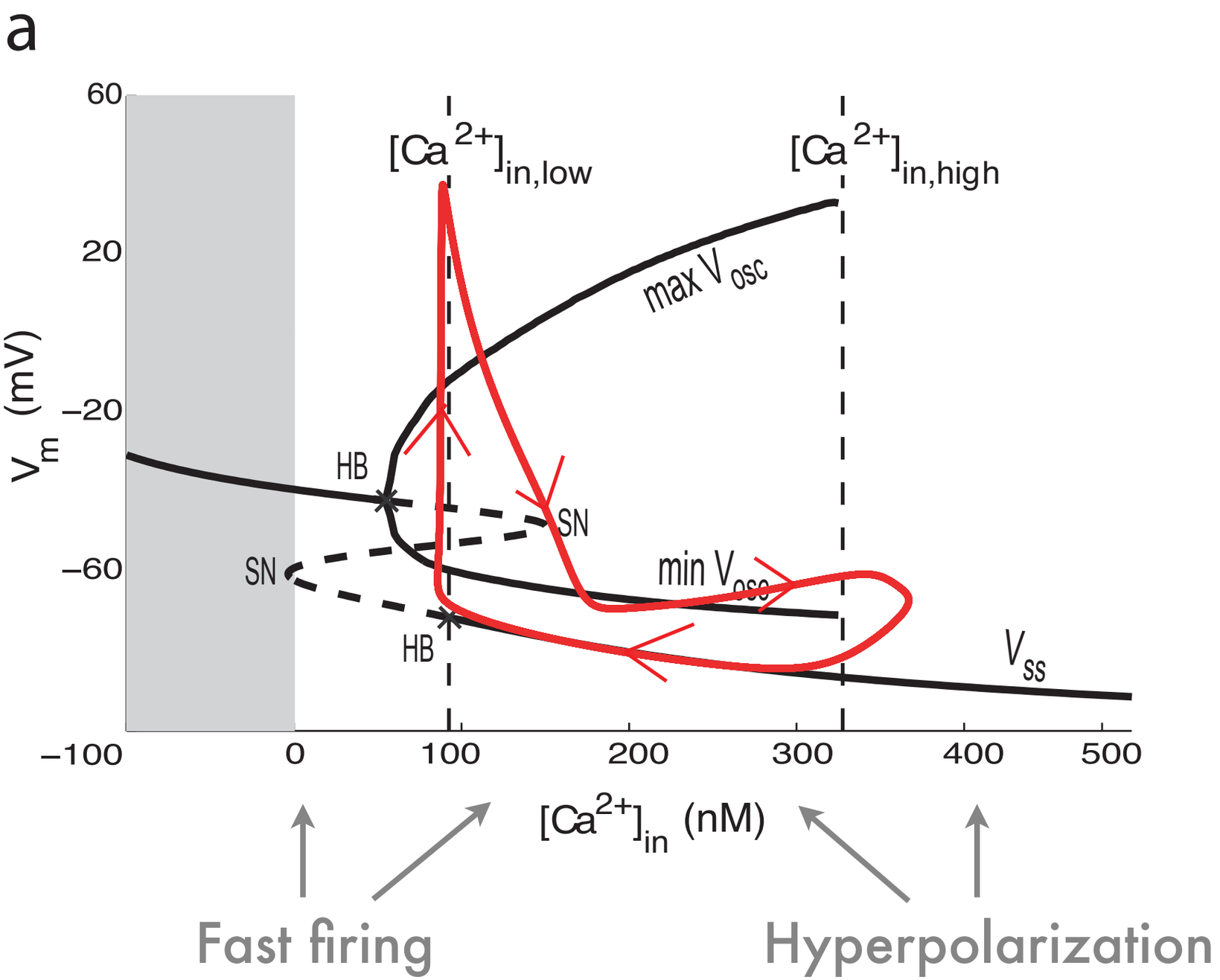
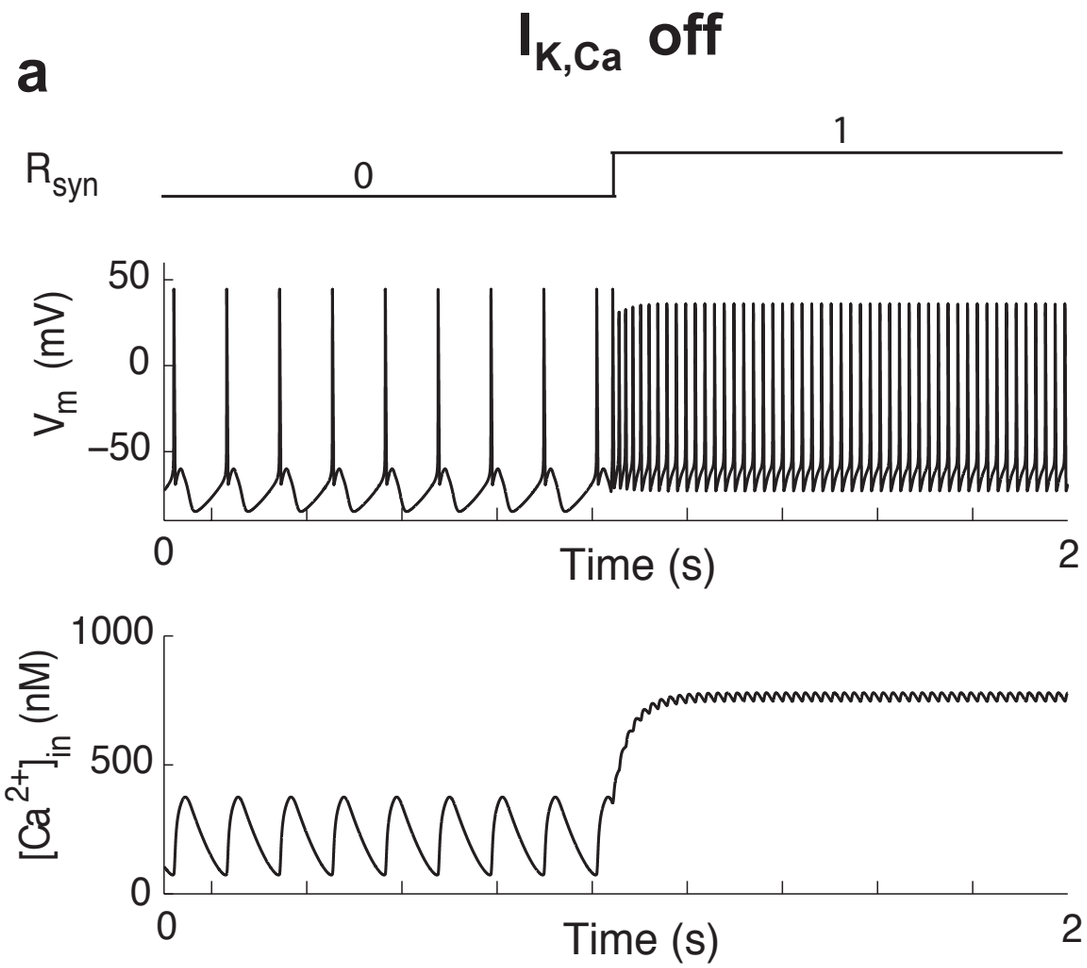


A Step of Synaptic Activation Induces Fast Firing in the Absence of SK Channels



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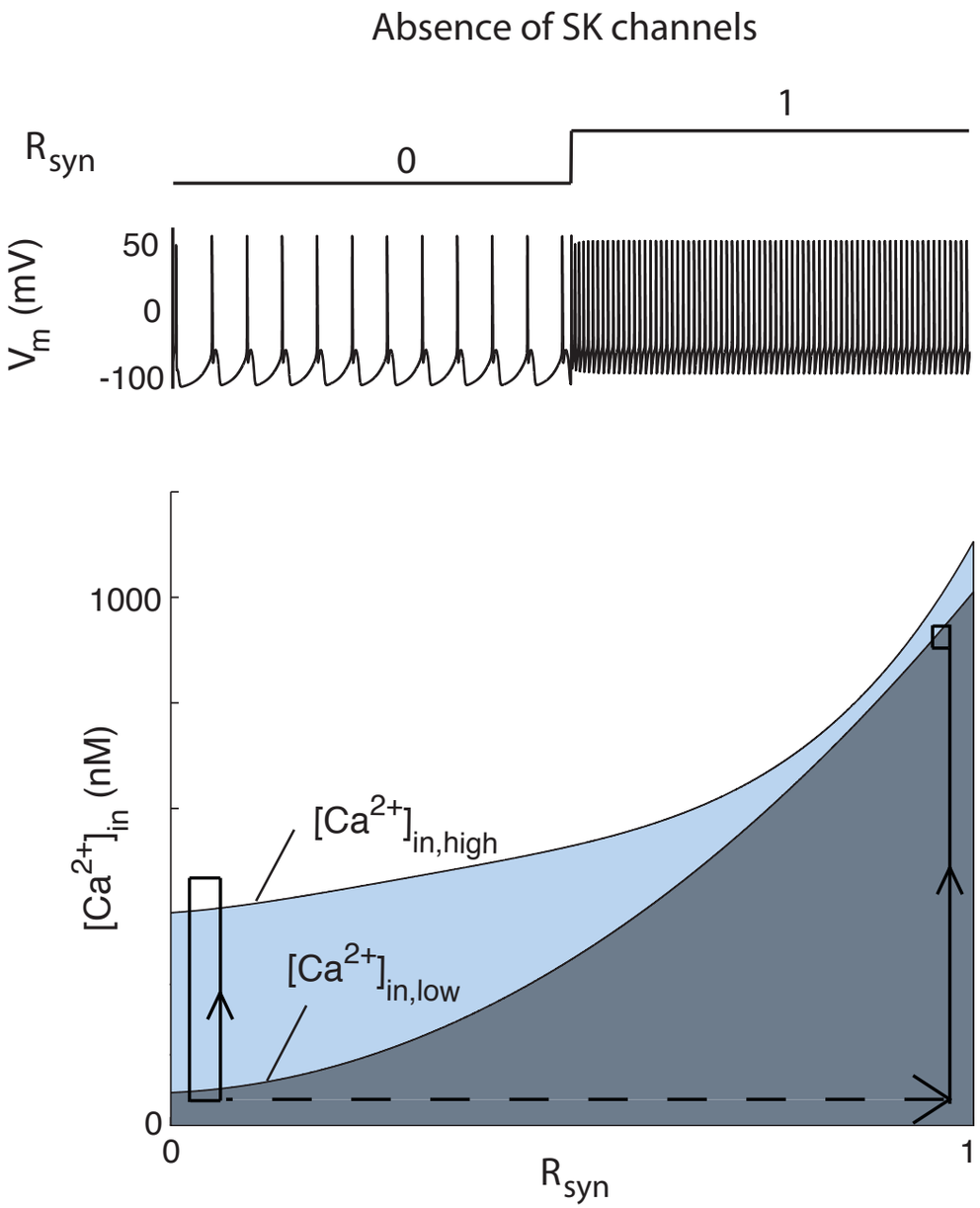
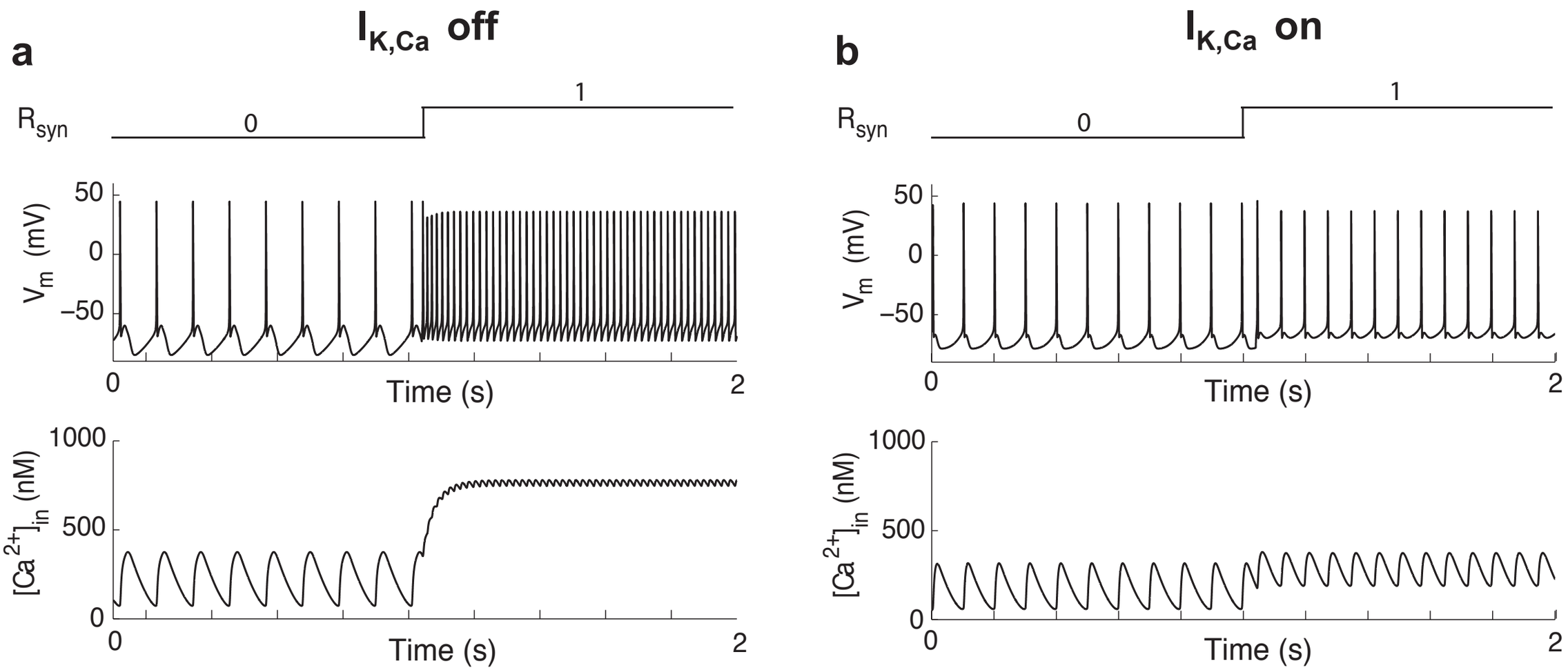


The Presence of SK Channels Counteracts the Induction of Fast Firing by a Step of Synaptic Activation



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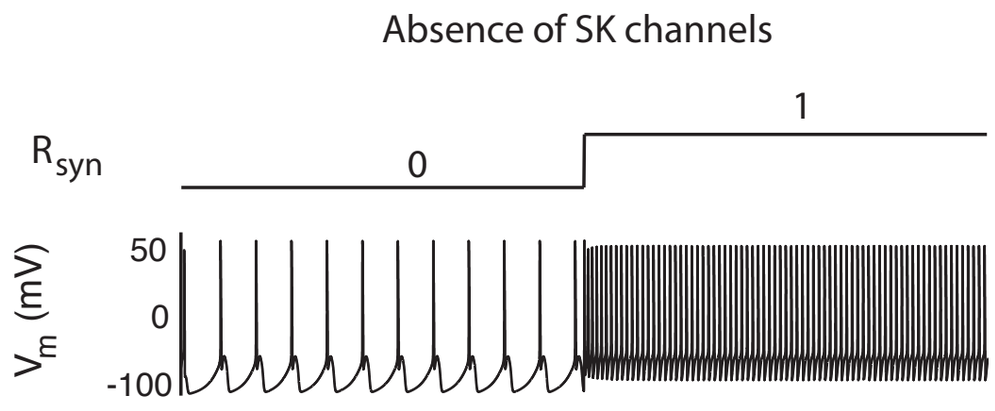
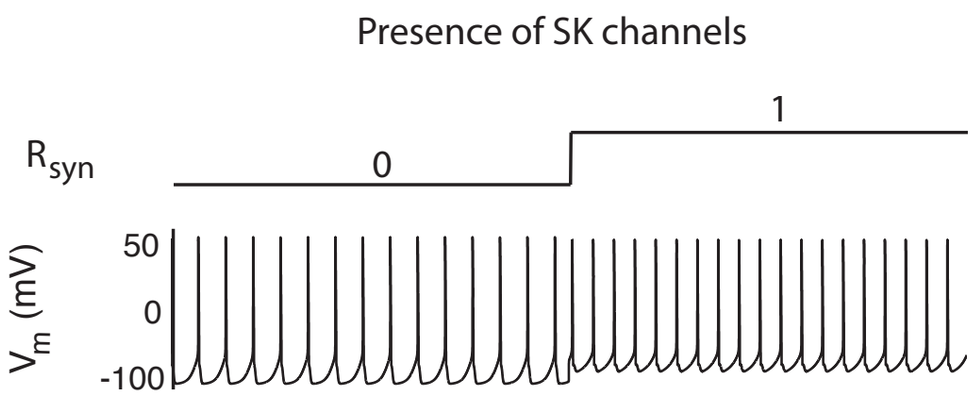
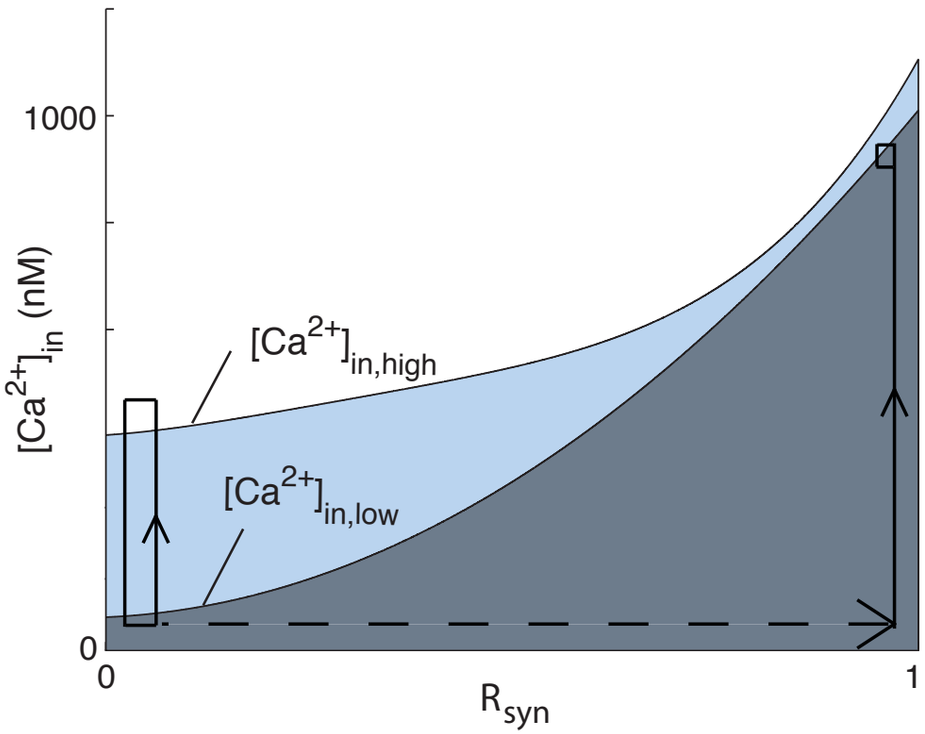
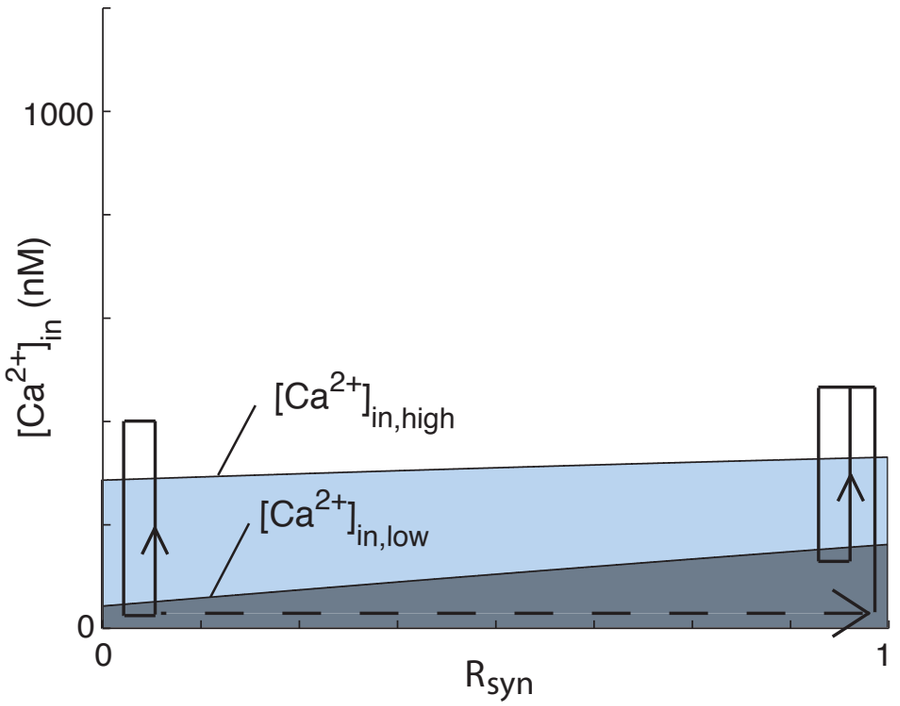


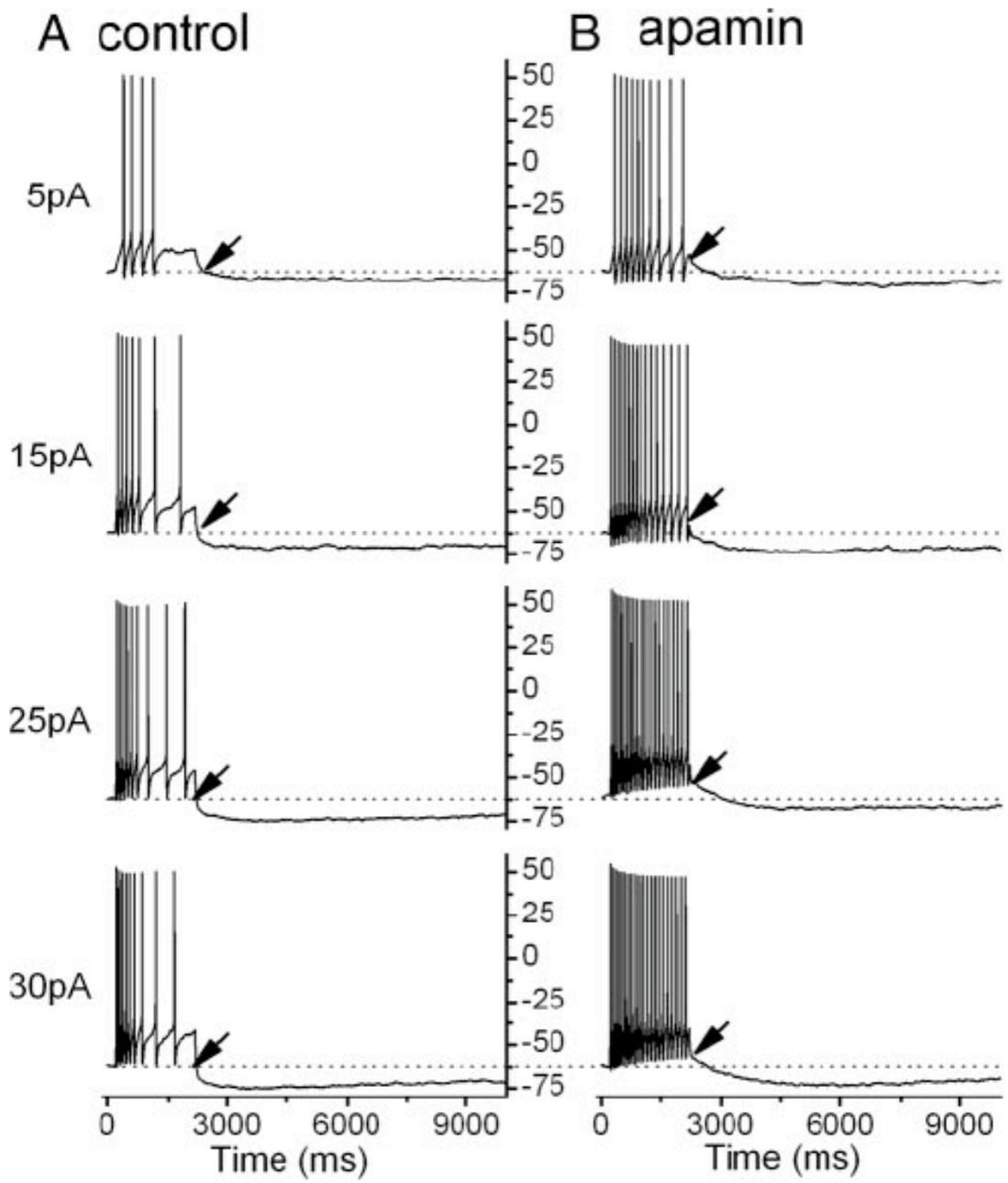






The Presence of SK Channels Counteracts the Induction of Fast Firing by a Step of Synaptic Activation

GnRH Neurons[1]



[1]Liu et. al, 2008

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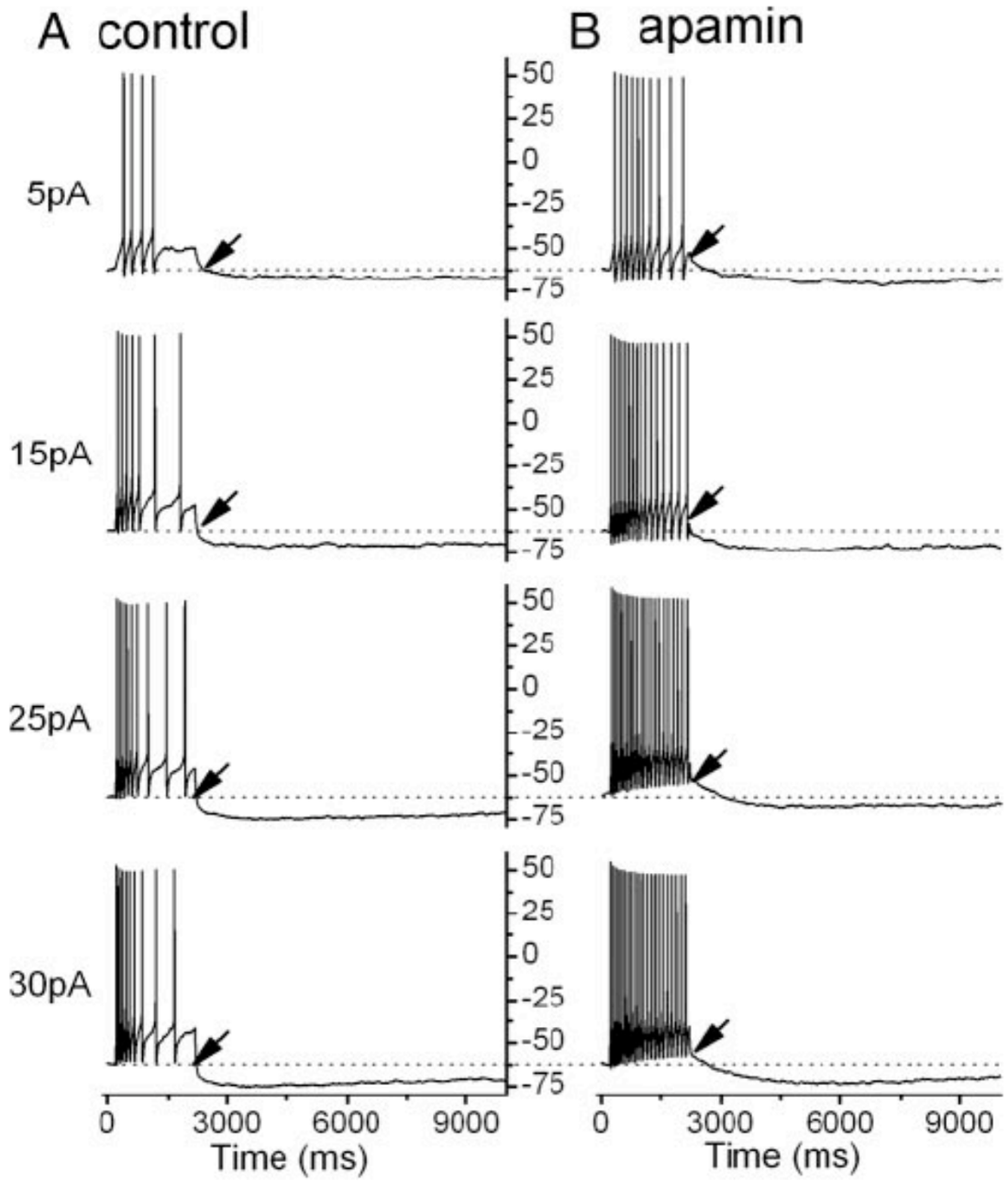
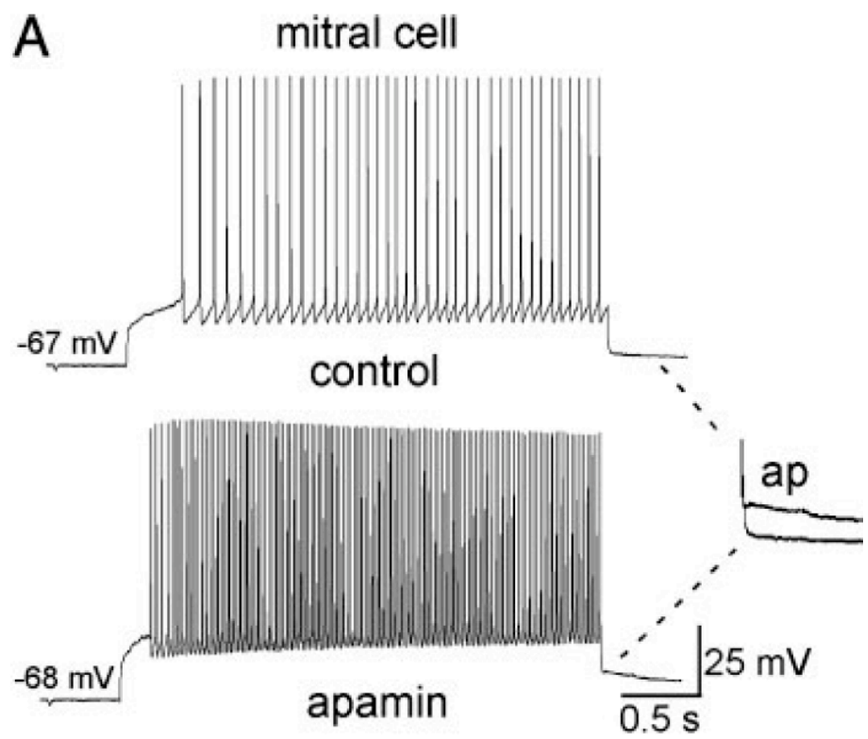


Mitral Cells[2]



[1]Liu et. al, 2008 [2]Maher et. al, 2005

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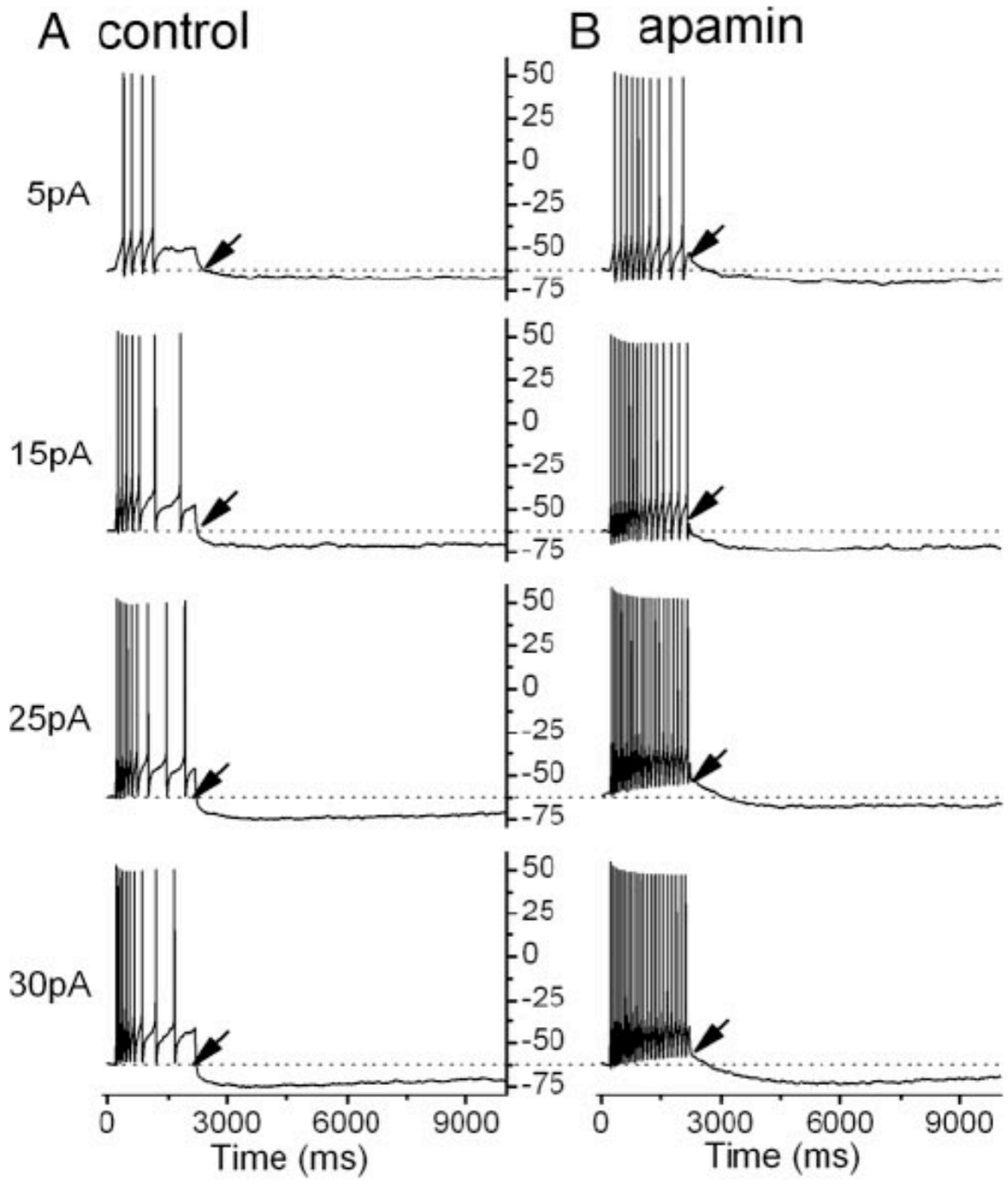

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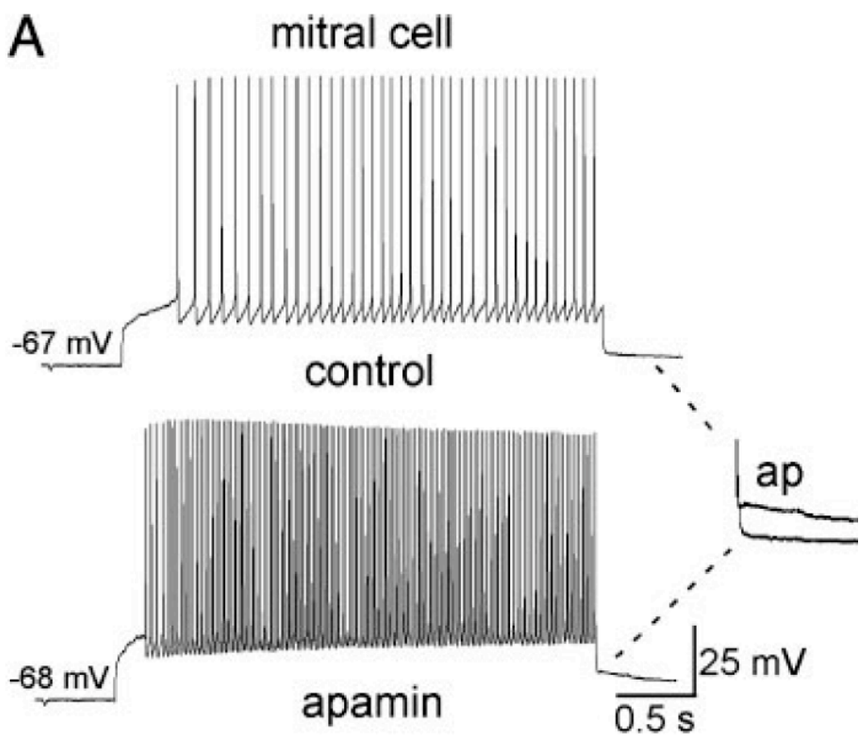
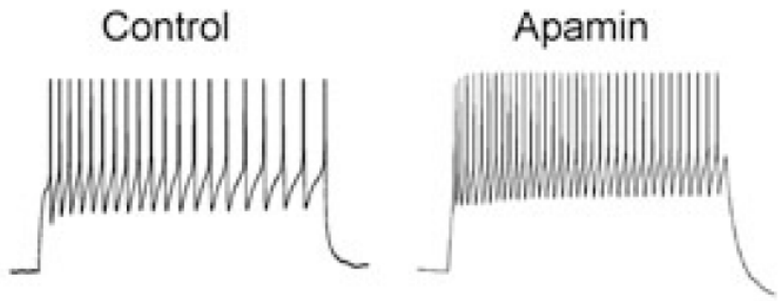
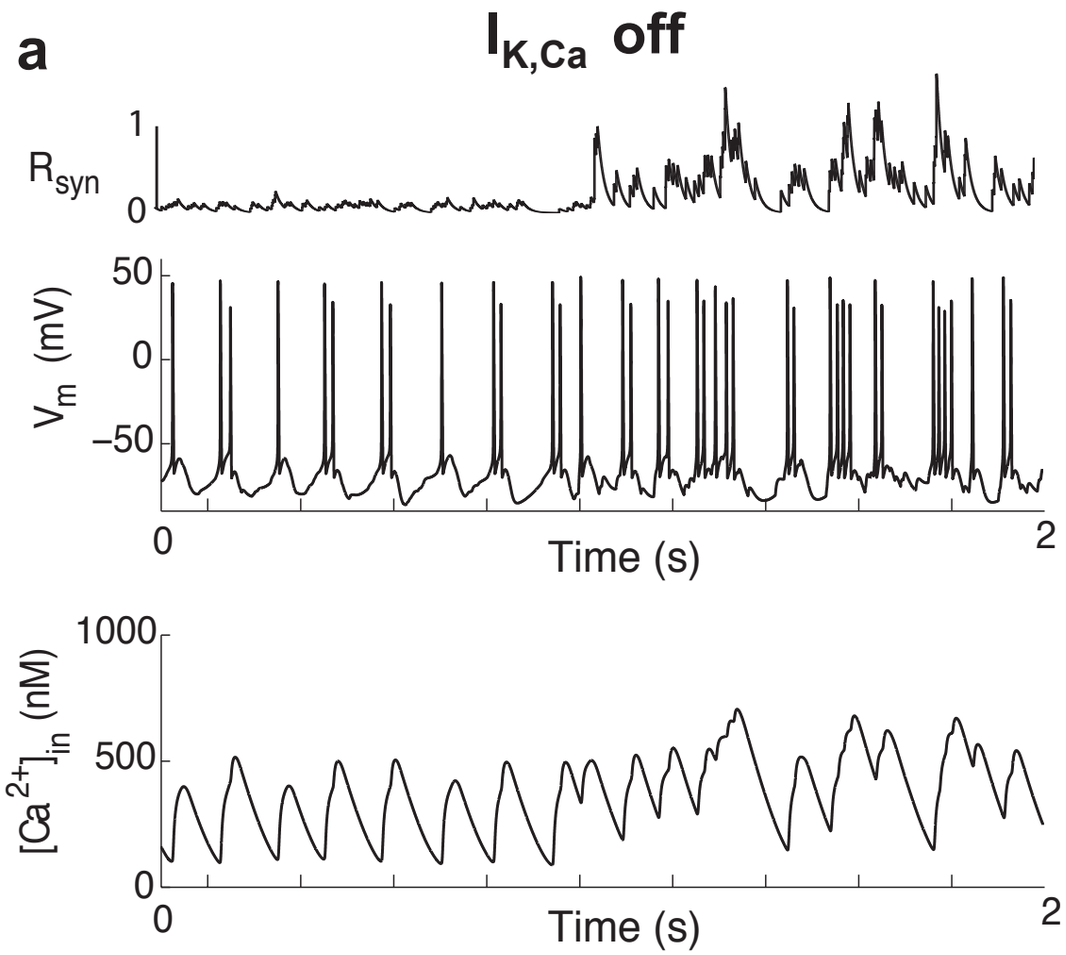


Paraventricular Nucleus Neurons[3]

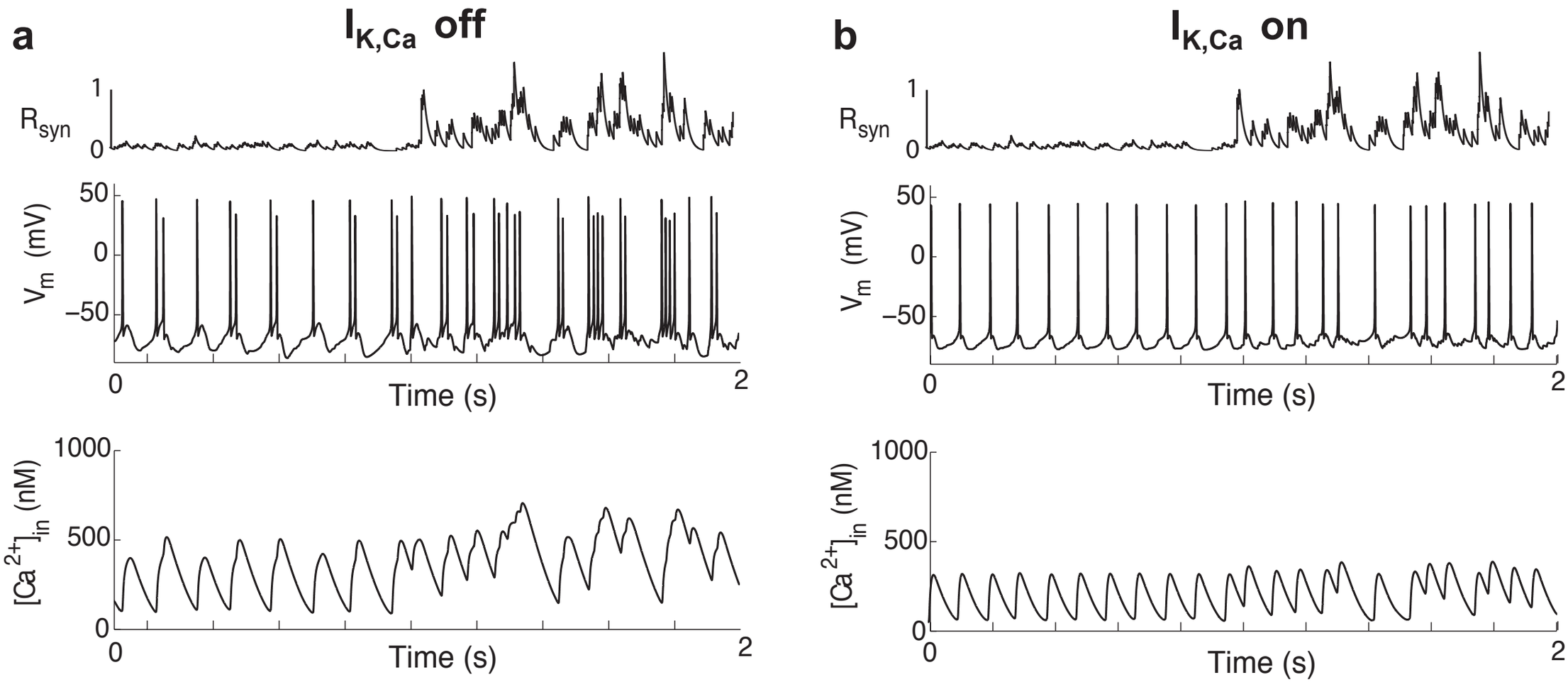


[1]Liu et. al, 2008 [2]Maher et. al, 2005 [3]Chen et. al, 2009

Excitatory Noise Induces Irregularities or Burst Firing in the Absence of SK Channels



SK Channels Act as Filters Against This Excitatory Noise



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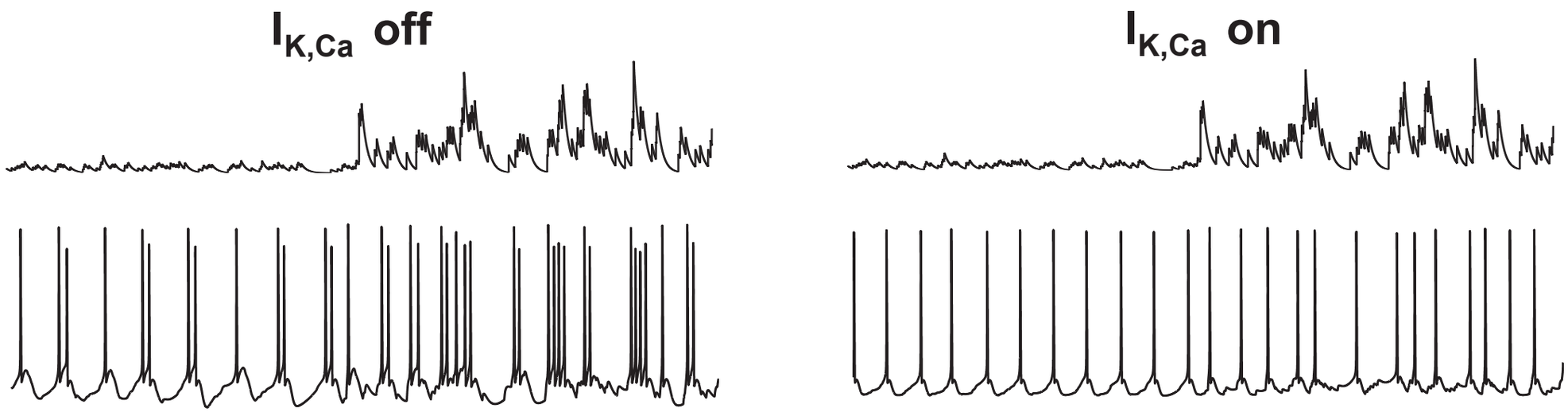

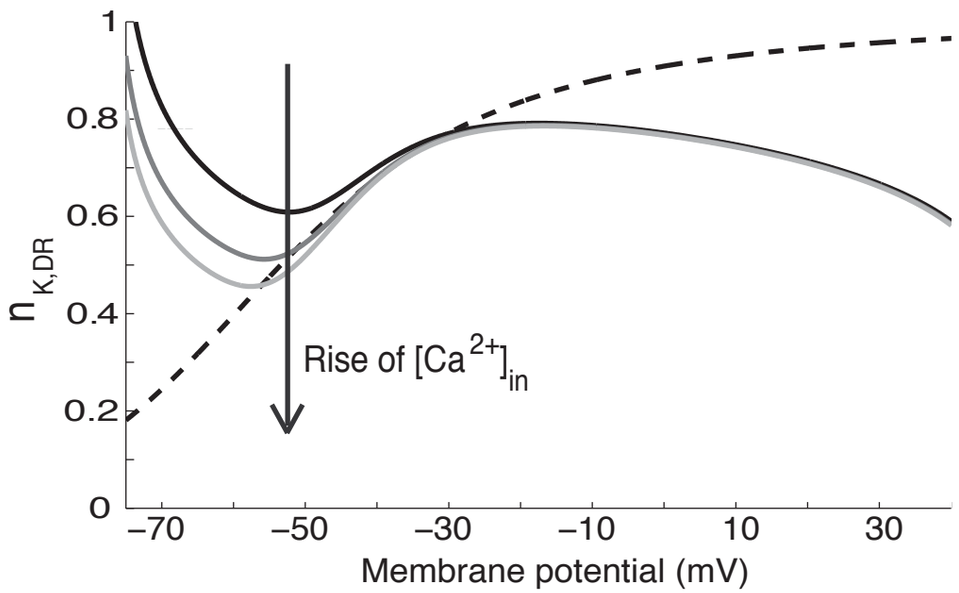

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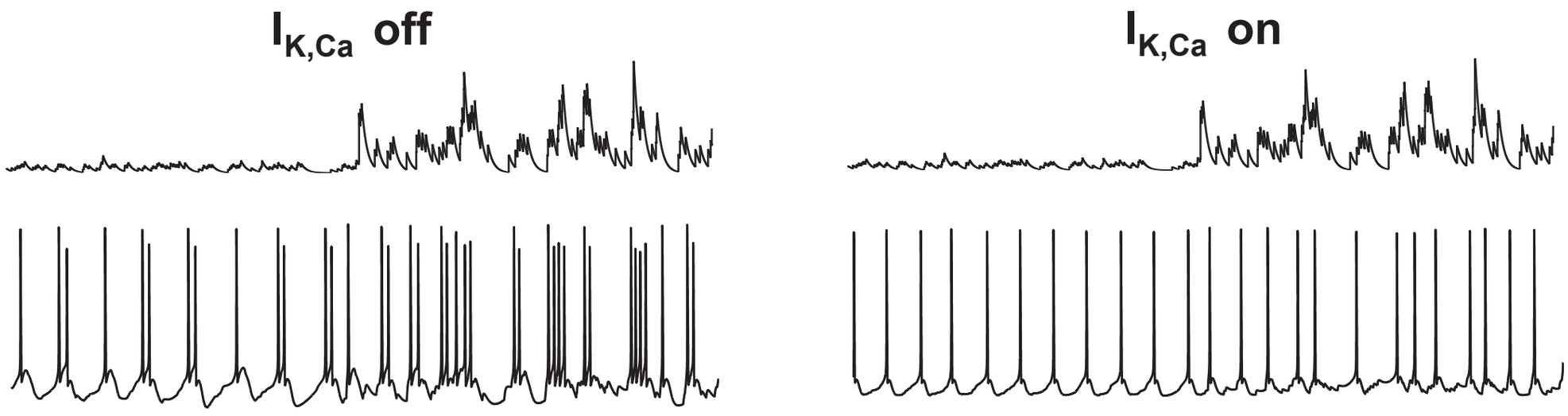

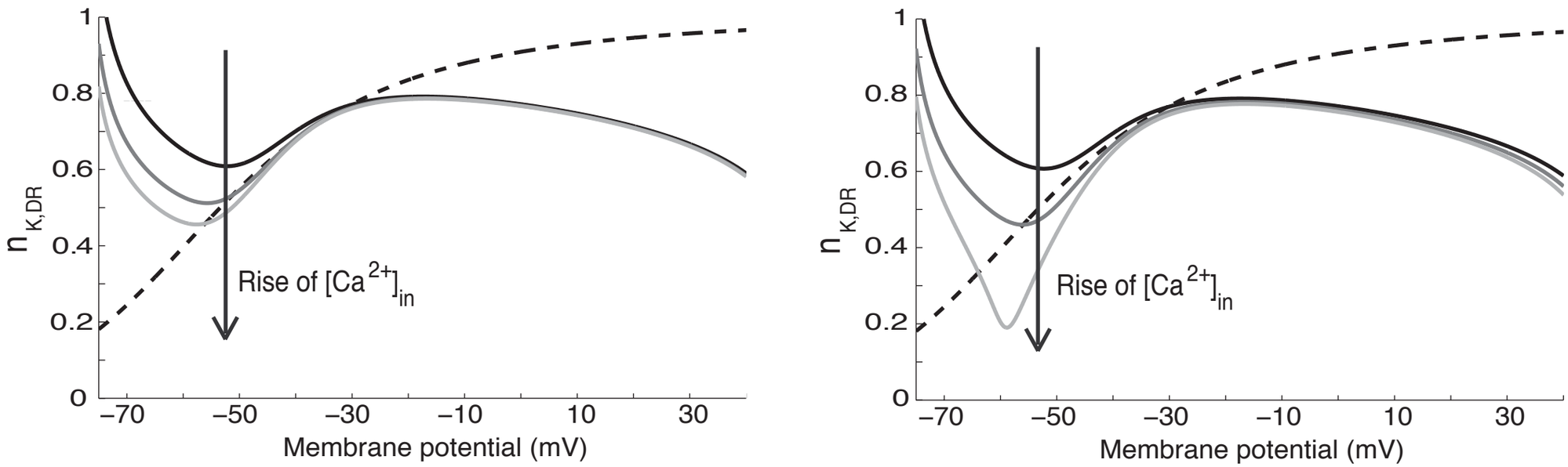

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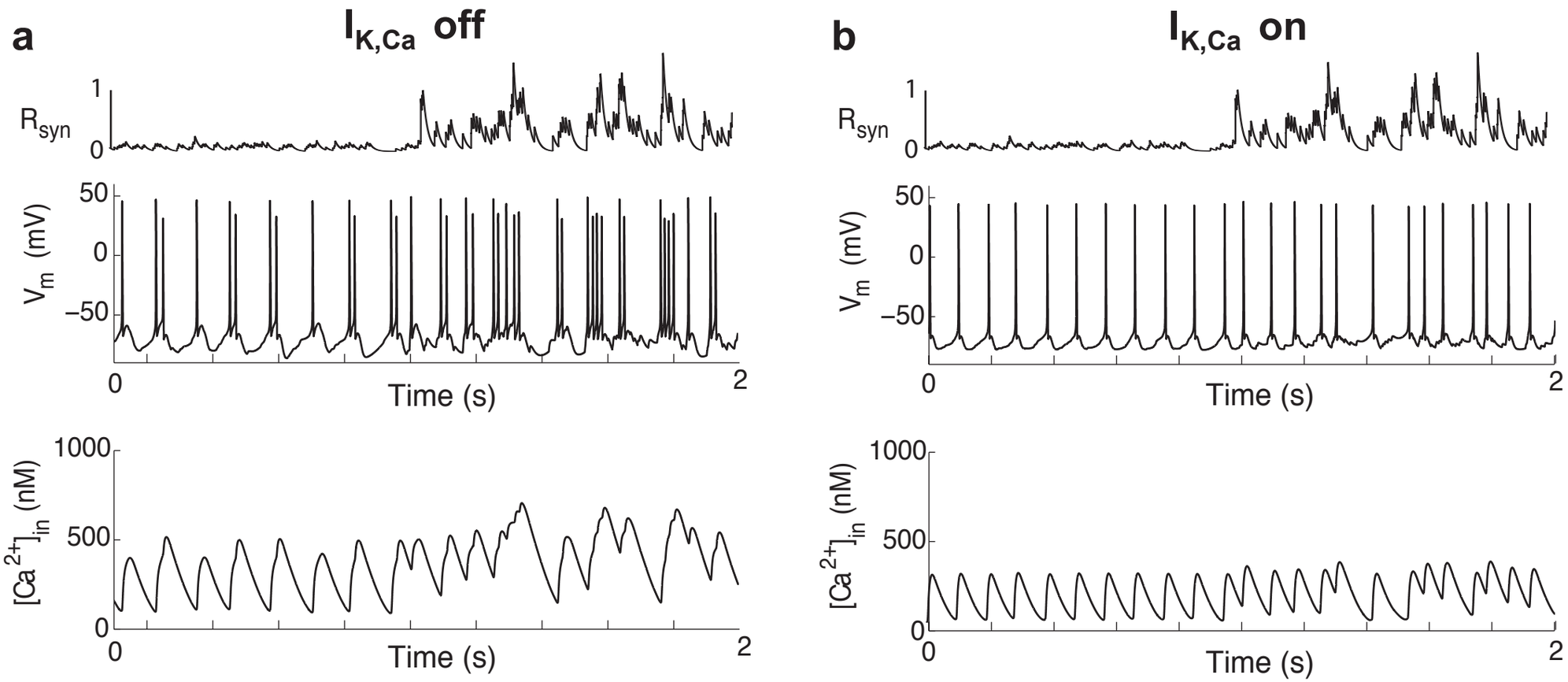
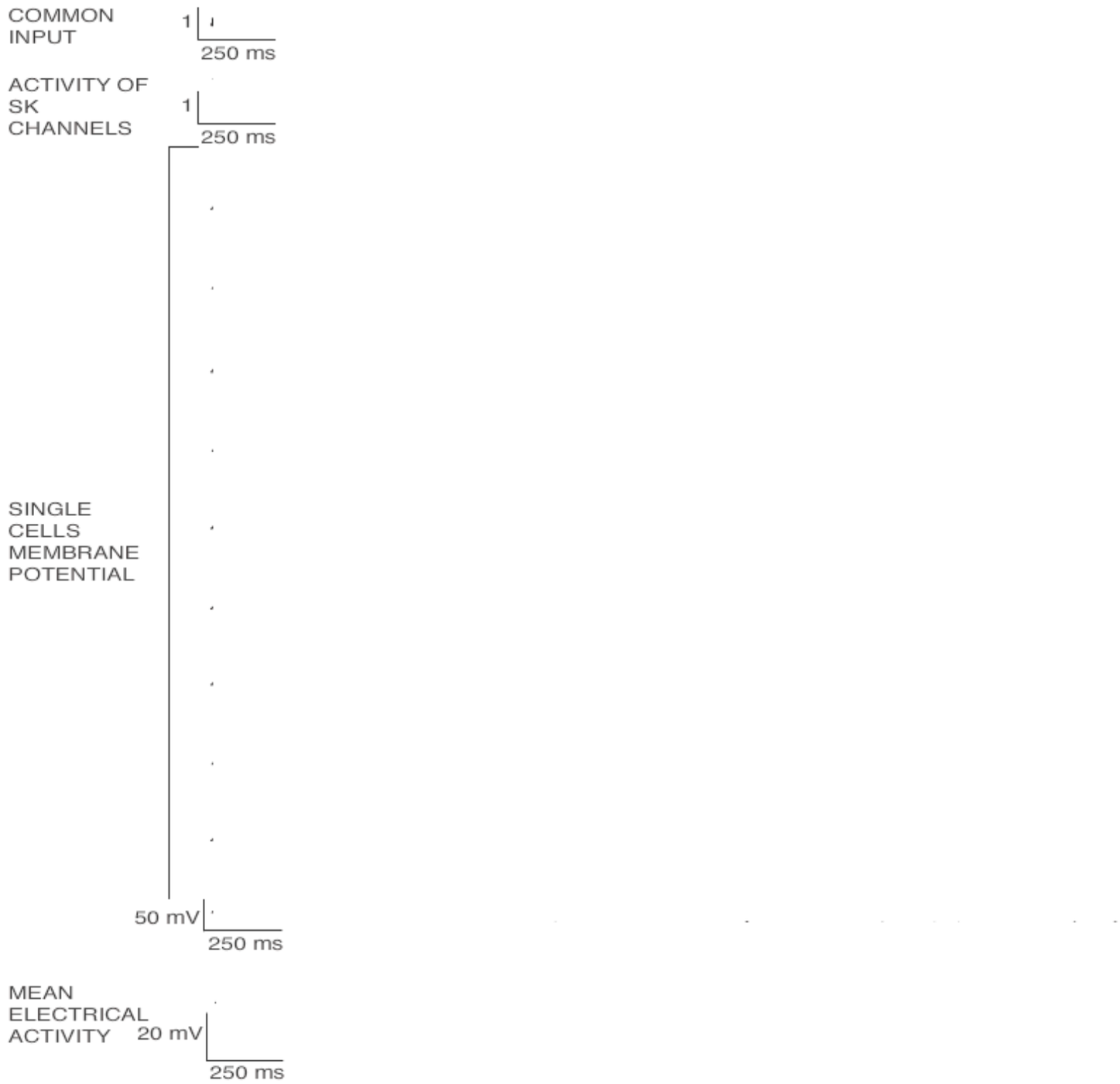


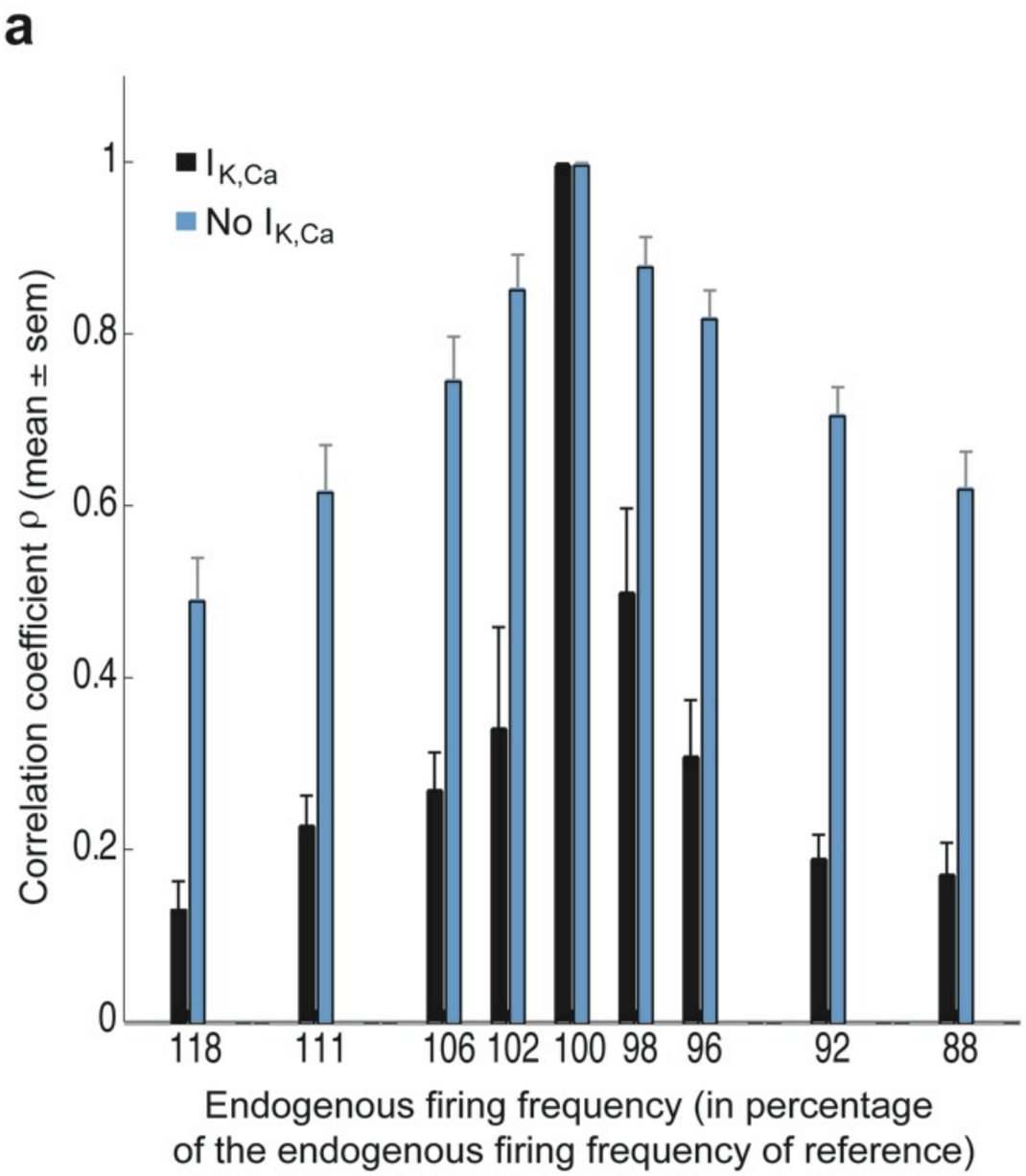
- Firing of a dopaminergic neuron in the anesthetized rat

How SK Channels Could Affect the Synchrony of Neurons Having a Common Excitatory Input?

Neurons Having a Common Input are Much Better Synchronized When SK Channels are Blocked



A Small Difference of Endogenous Rhythm is Critical for the Synchronization of Neurons Only in the Presence of SK Channels



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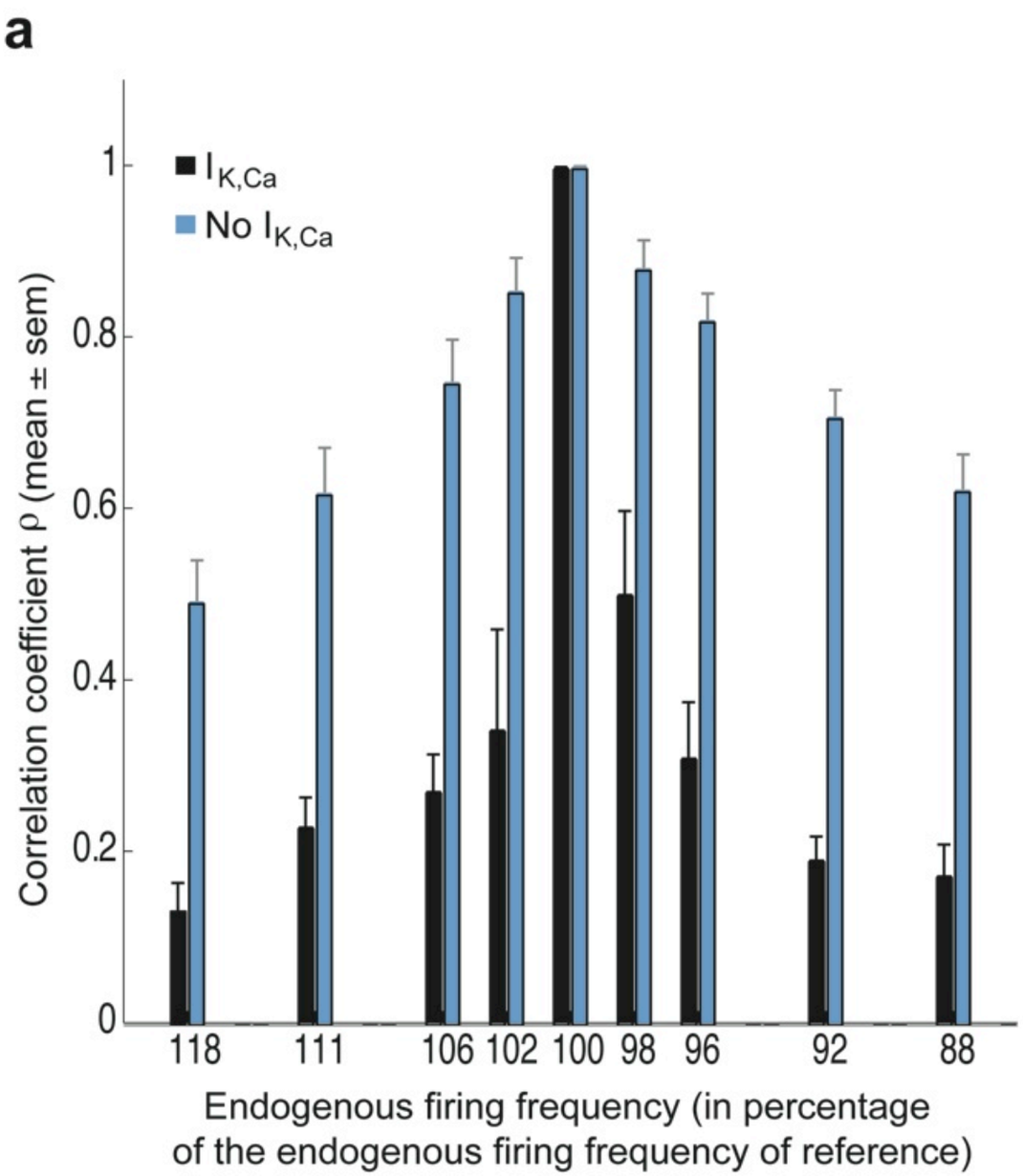
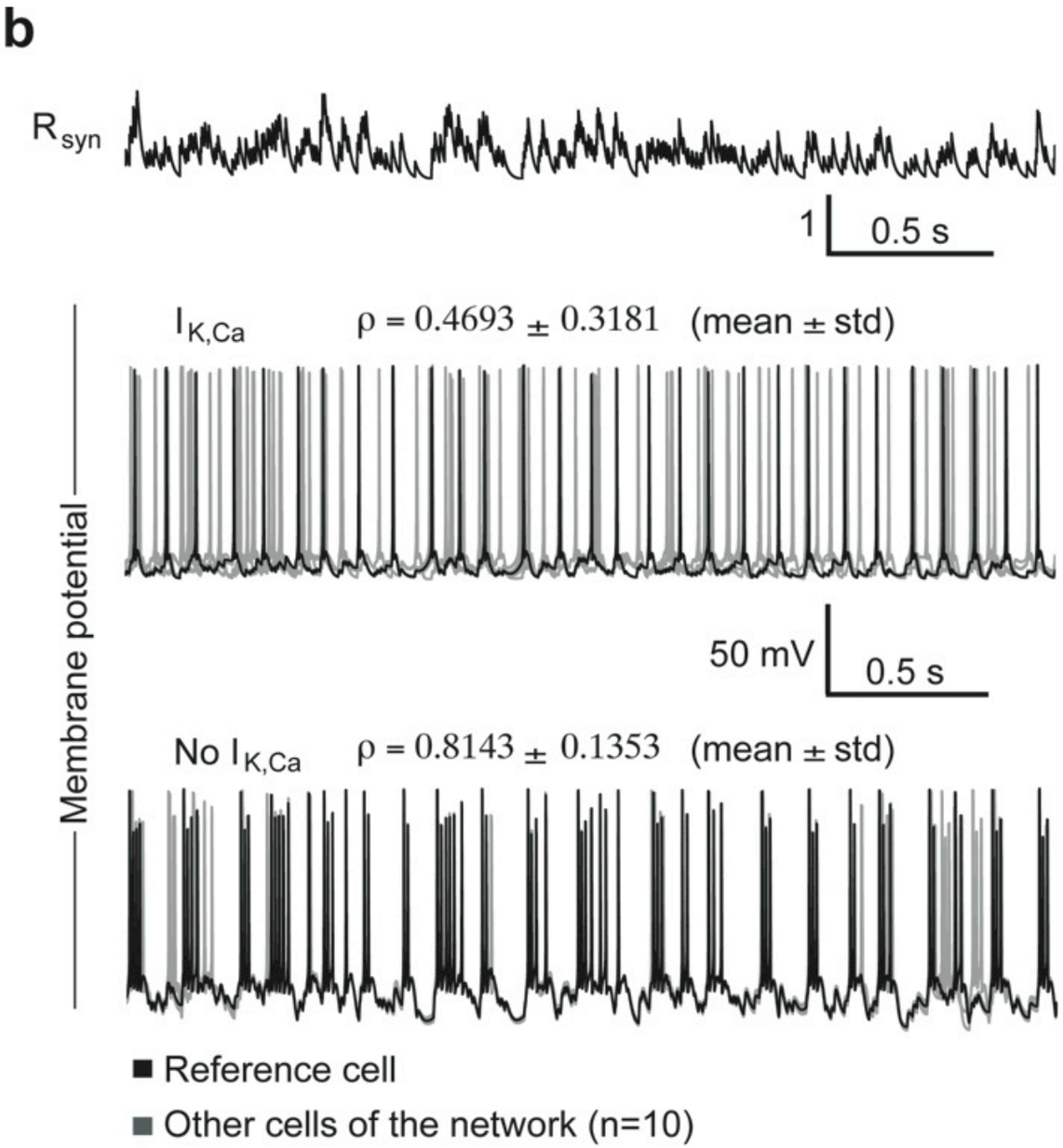
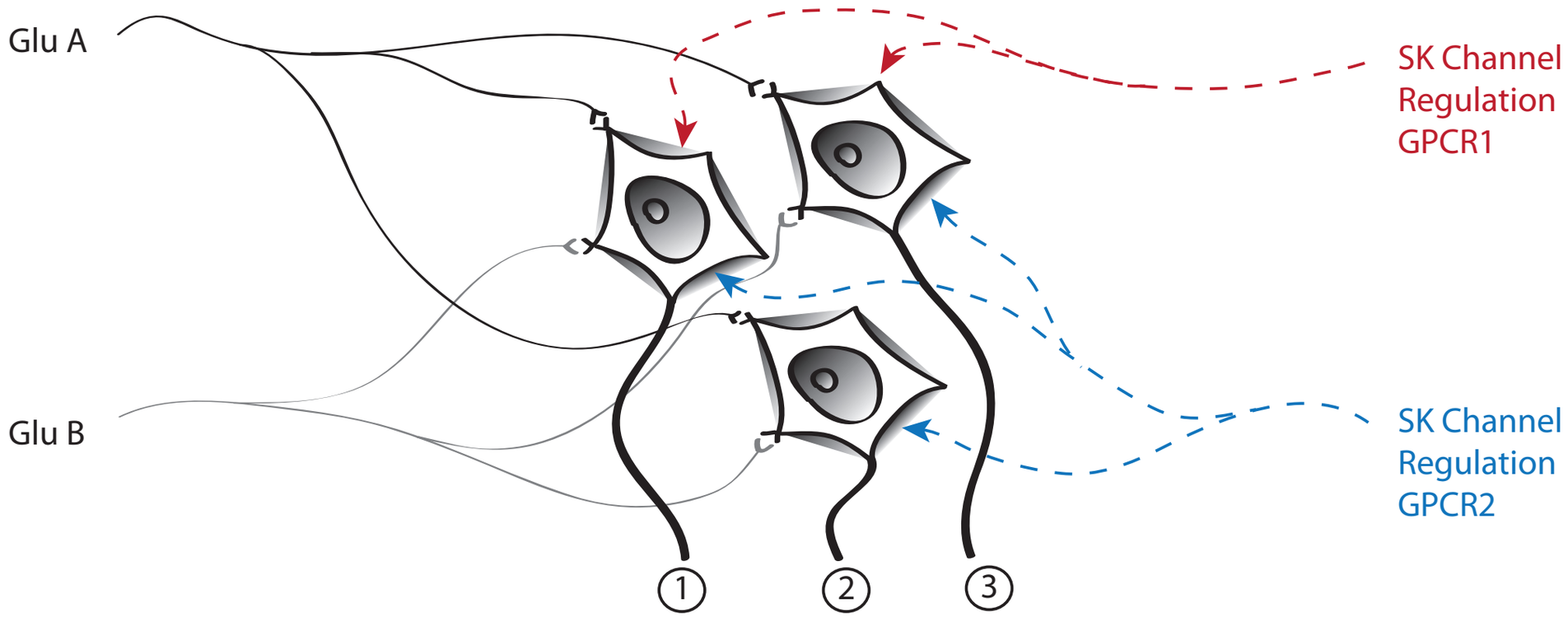




Summary: A Common Mechanism for the Regulation of Firing and Synchrony of a Category of Pacemaker Neurons



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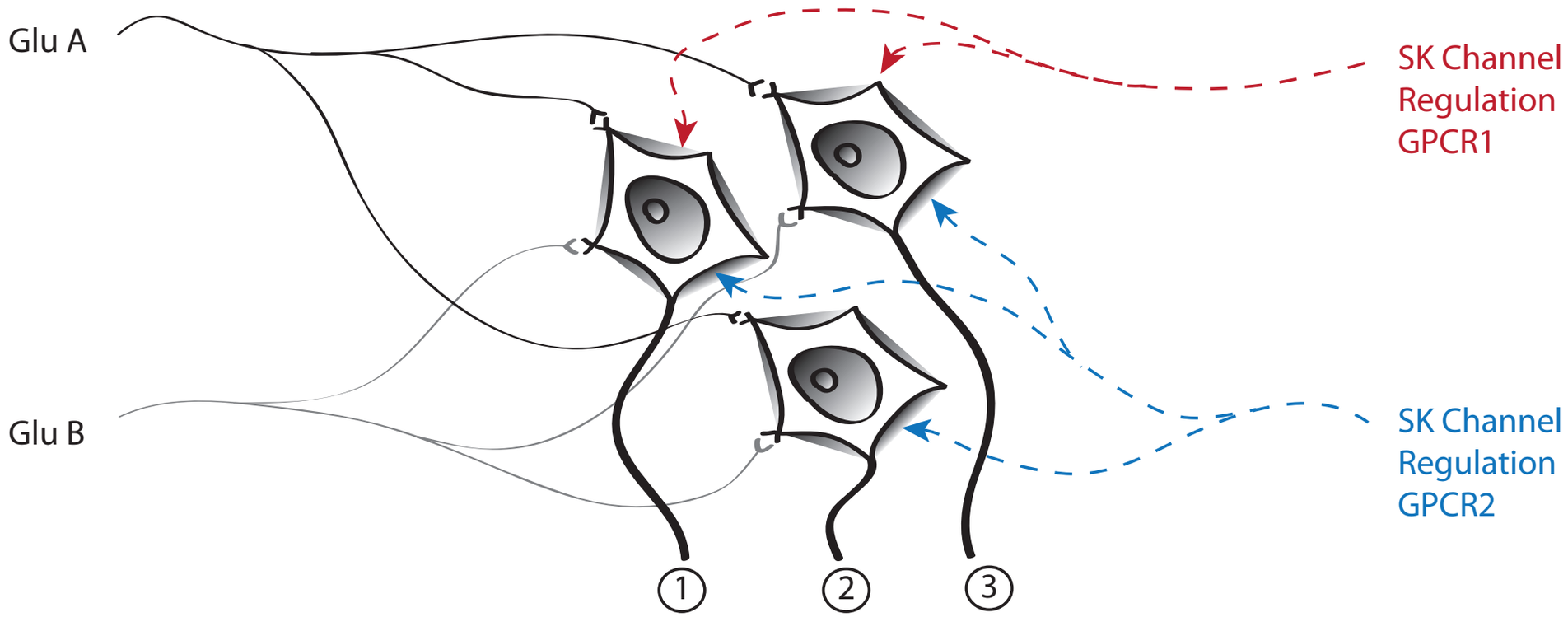

	Synaptic Inputs Inactive (a)
Neuron 1	
Neuron 2	
Neuron 3	

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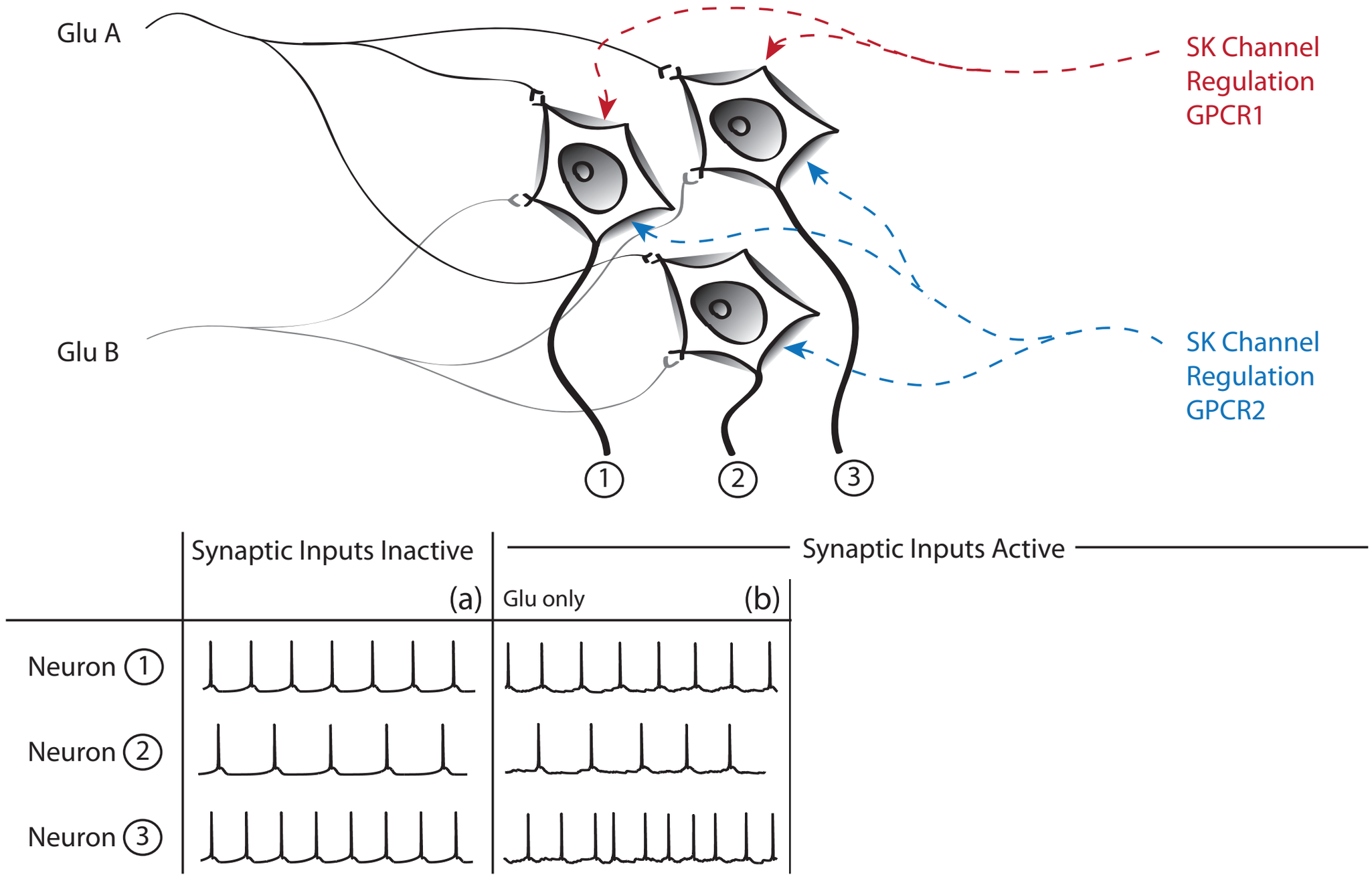

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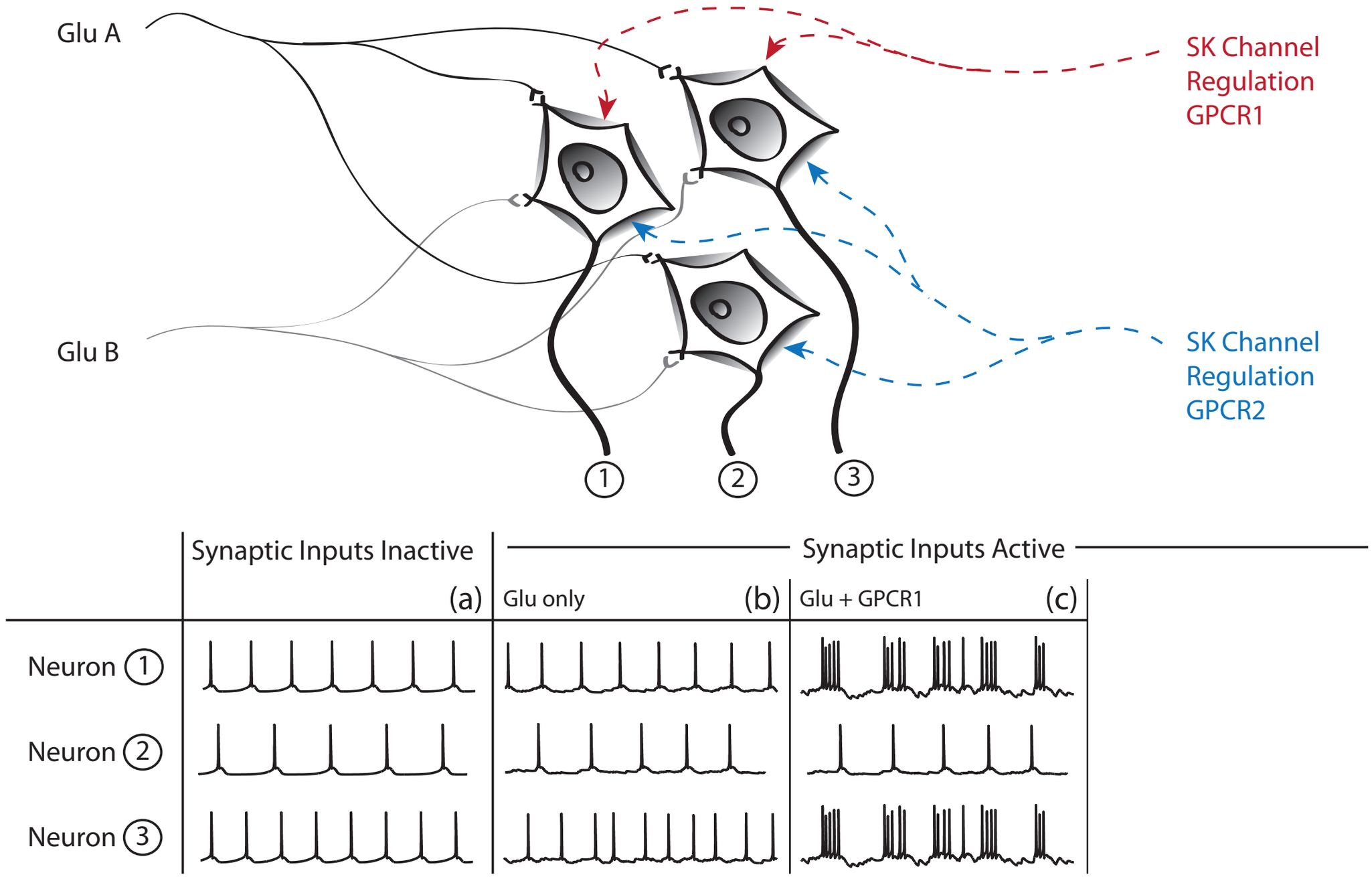

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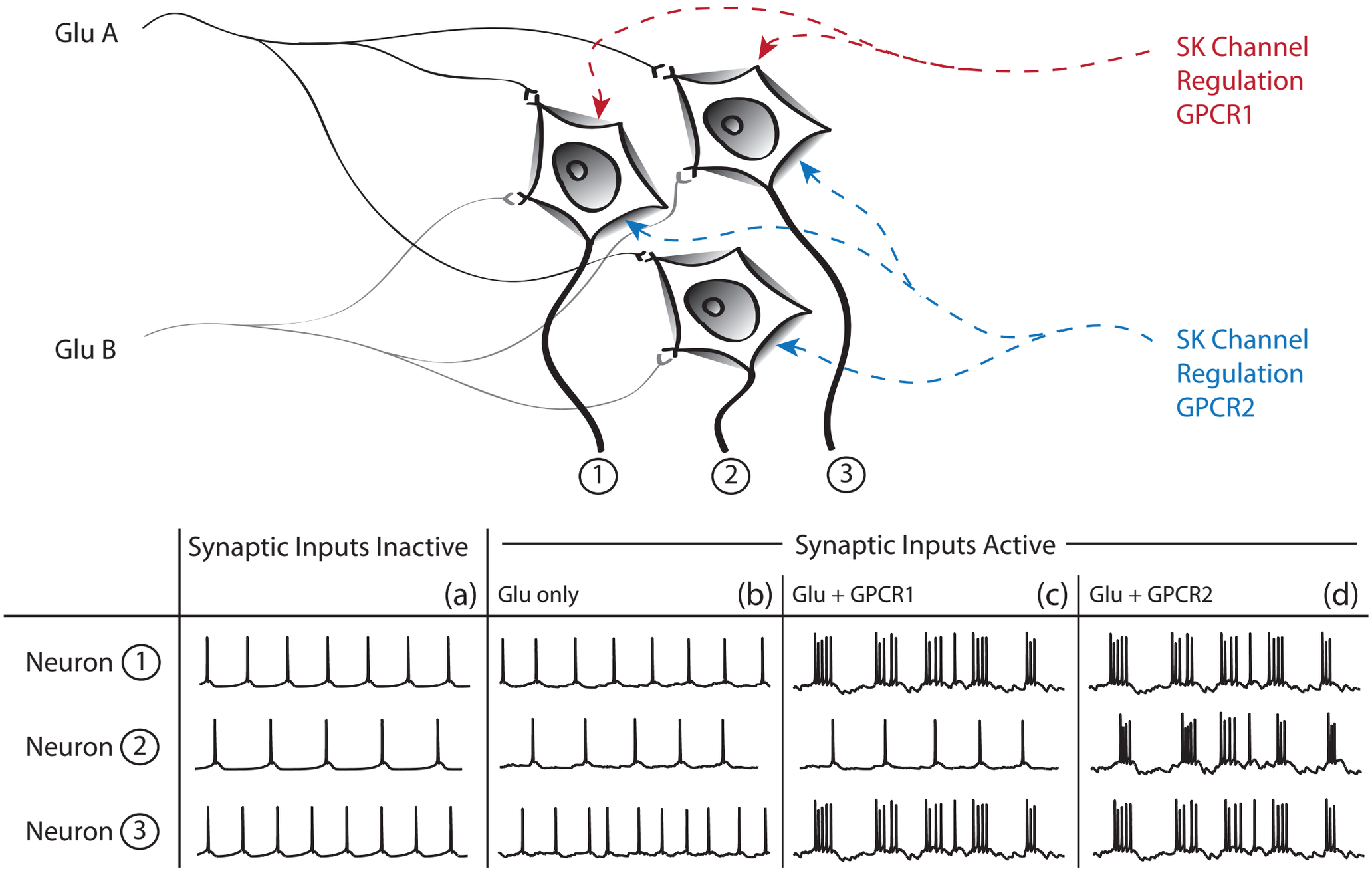


Pathological (Progressive?) Downregulation of SK Channels: A Potential Starting Point for Parkinson's Disease.

SK Channel downregulation

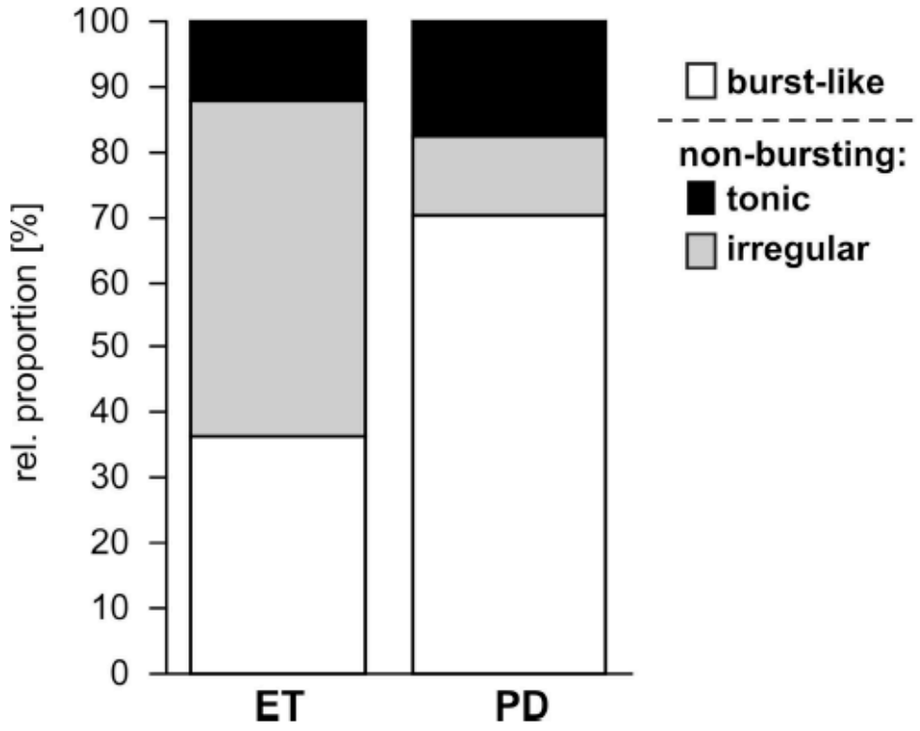
↓

Affected neurons become highly sensitive to external excitatory stimulations (synaptic afferents)

↓

Increase in the proportion of synchronously bursting neurons

- Subthalamic nucleus neurons



Steigerwald et. al, 2008

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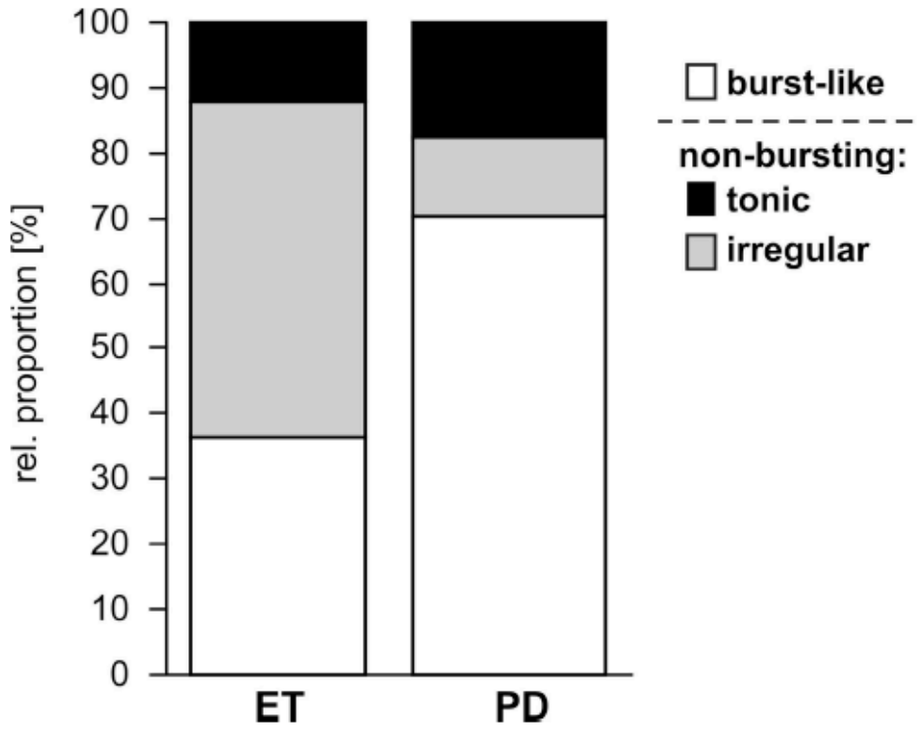

Excitotoxicity and neurodegeneration

- Dopaminergic neurons
- Serotoninergic neurons
- Mitral cells of the olfactory bulb
- Interstitial cells of Cajal (intestine)
- ...

Steigerwald et. al, 2008

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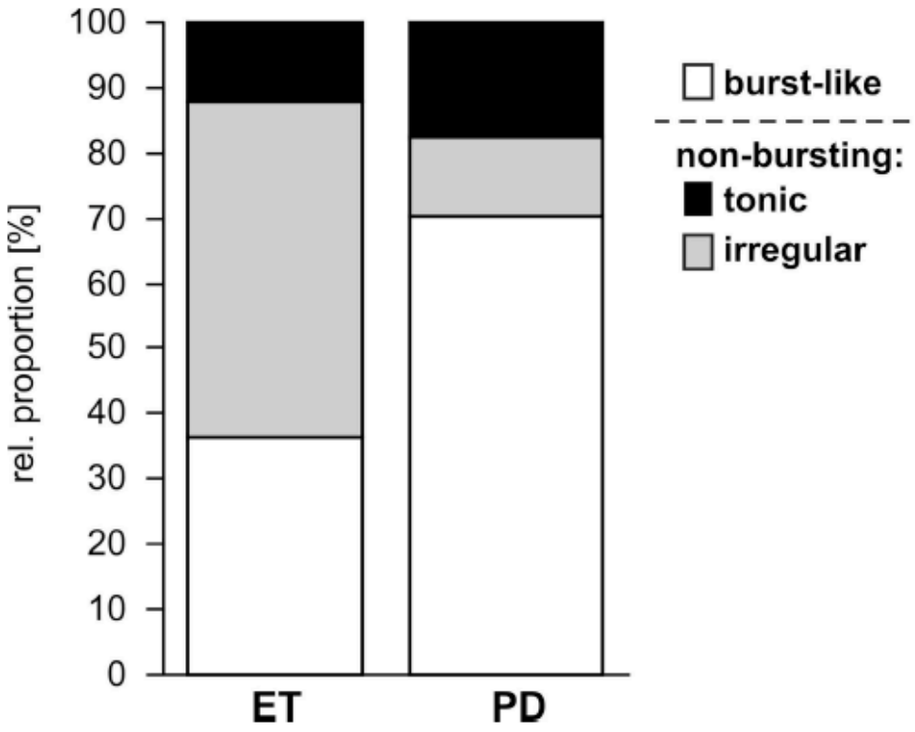

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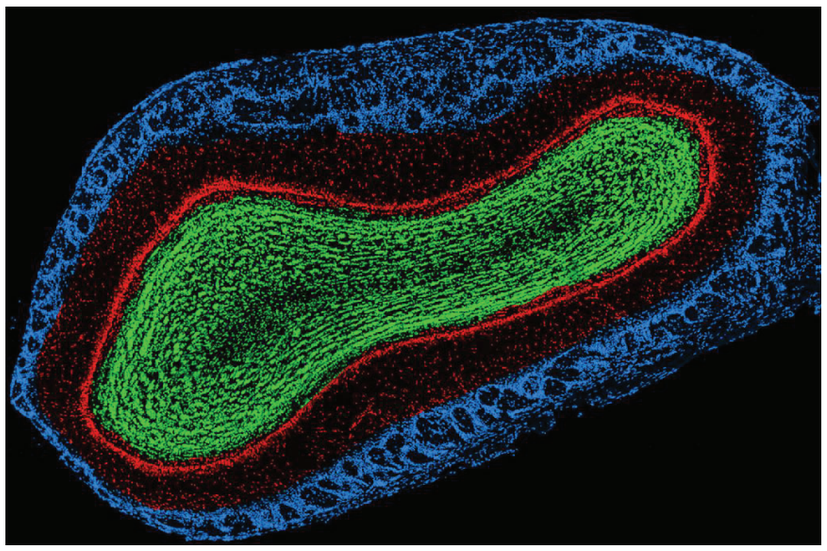

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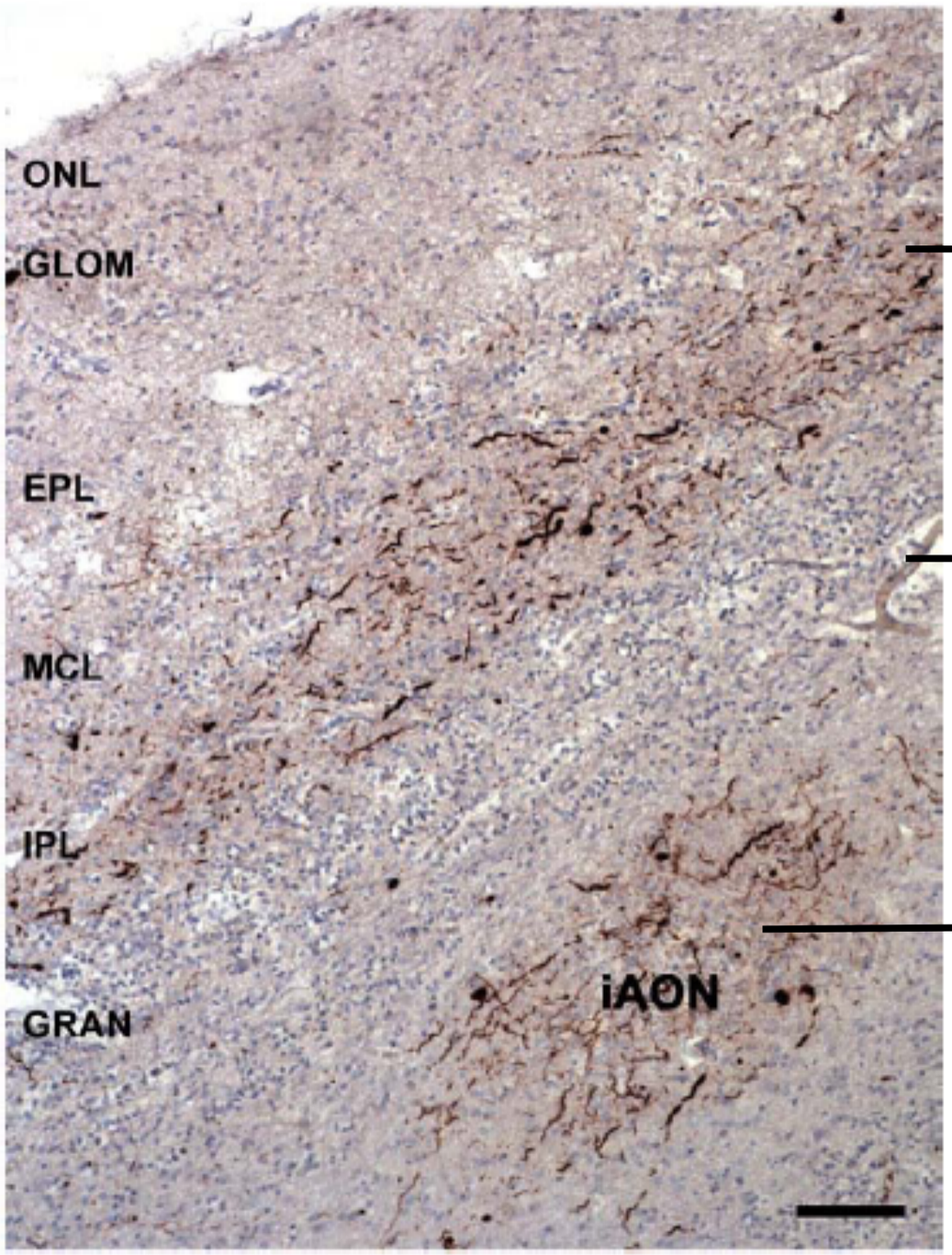
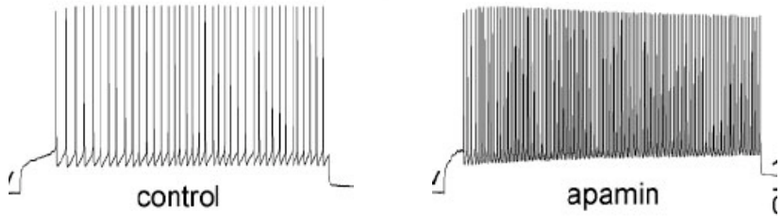
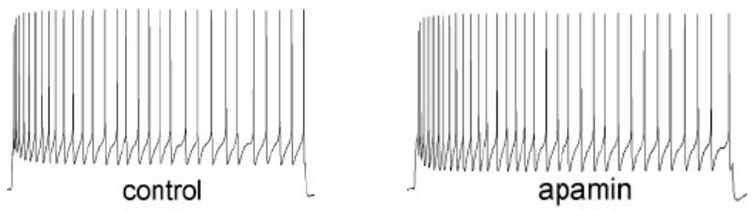


Lewy bodies in the mitral cell layer and the external plexiform layer.



No lewy bodies in the granule cell layer.



Lewy bodies in the anterior olfactory nucleus (where the excitatory afferents come from mitral cells).

[1]Duda, 2009 [2]Maher et al, 2005

Acknowledgments

Supervision

Vincent Seutin

Rodolphe Sepulchre

Modeling

Maxime Bonjean

Anne Collard

Experiments

Olivier Waroux

Jacqueline Scuvée-Moreau

Medicinal Chemistry

Jean-François Liégeois

Modeling and Measurements of Cerebral Signaling Circuits

Guillaume Drion[1,2], Vincent Seutin[2] and Rodolphe Sepulchre[1]

[1]Department of Electrical Engineering and Computer Science
[2]Laboratory of Pharmacology and GIGA neurosciences
University of Liège, Belgium