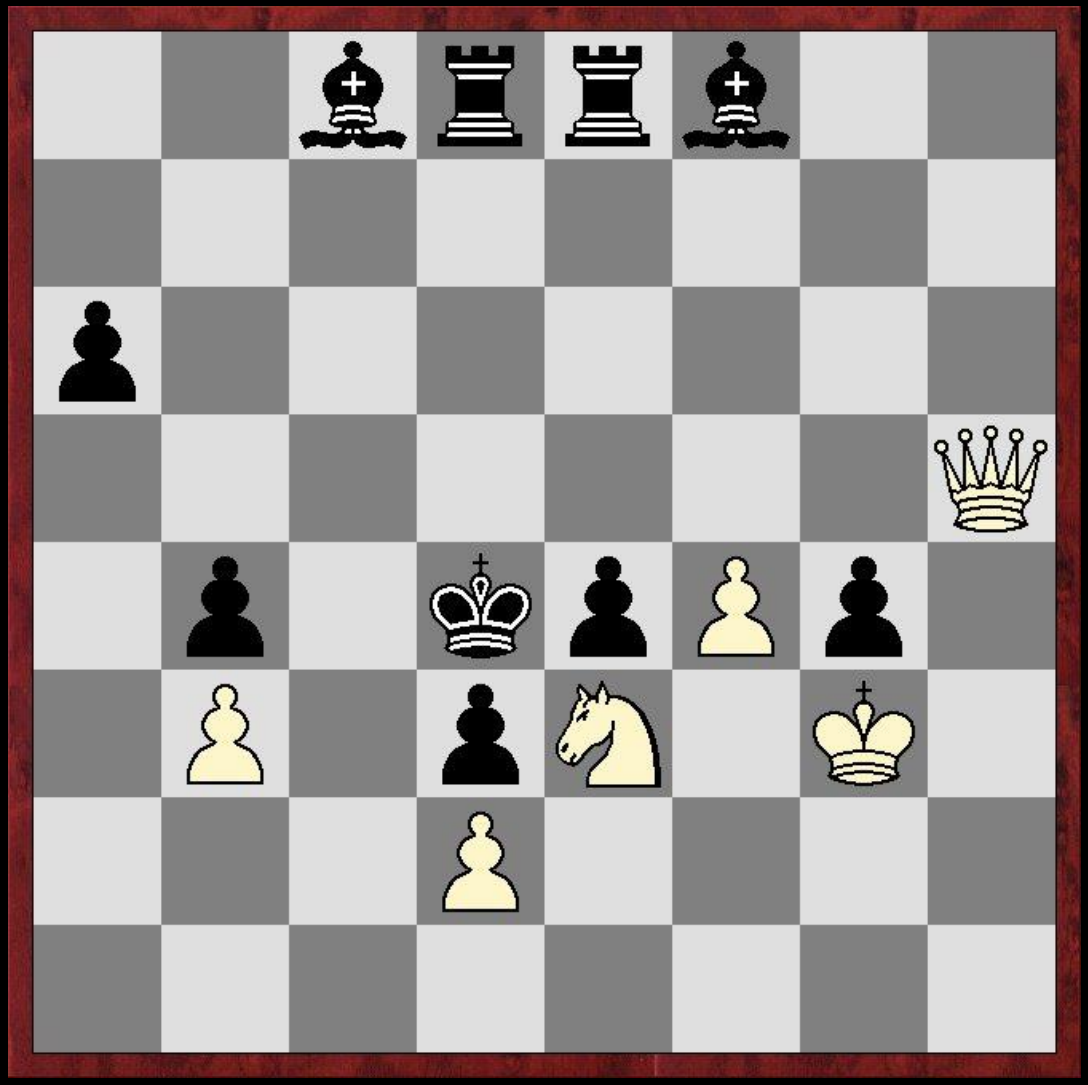
How Neurons Communicate at Synapses

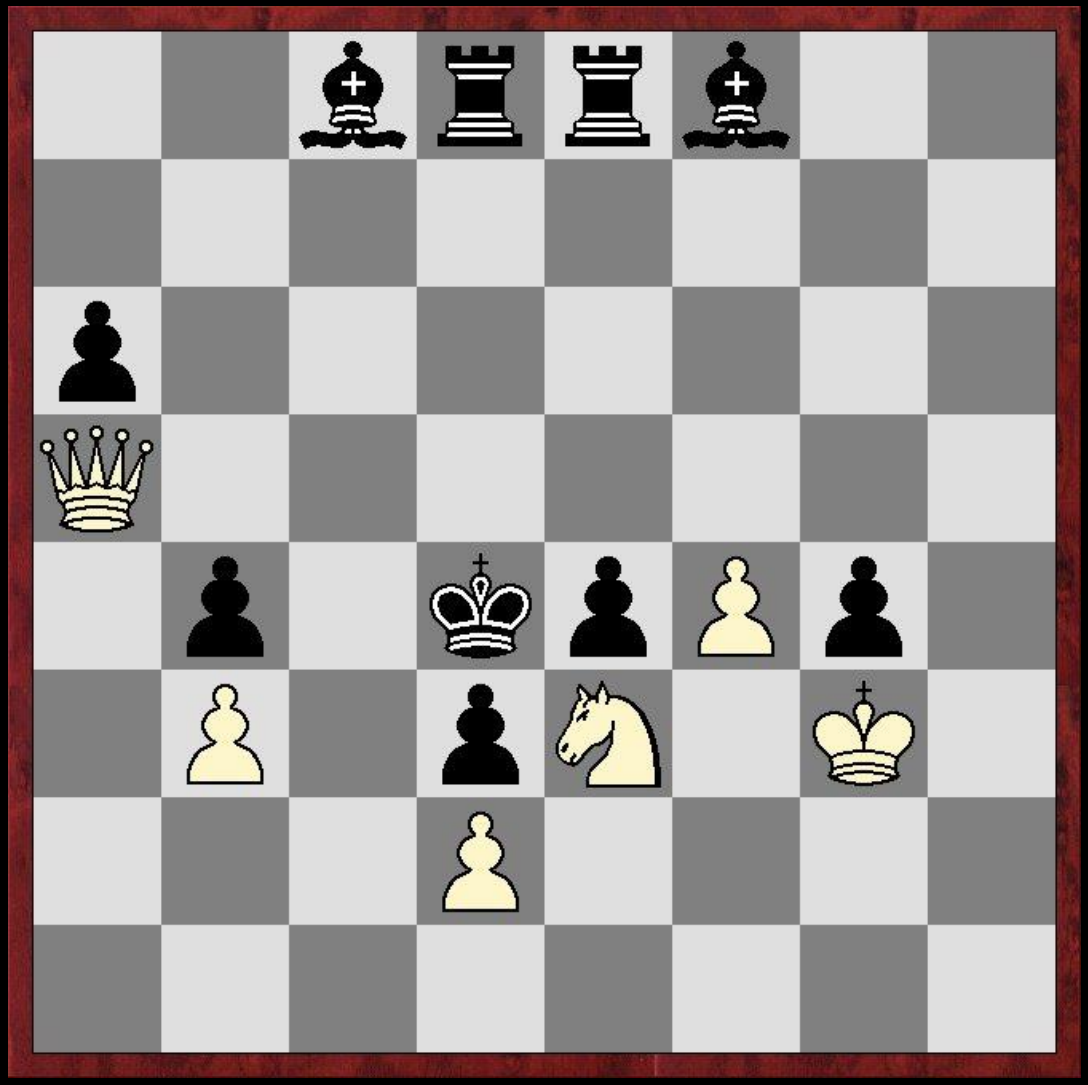
Jose Rizo-Rey

White gives check mate in two moves



Samuel Loyd 1859

So beautiful!

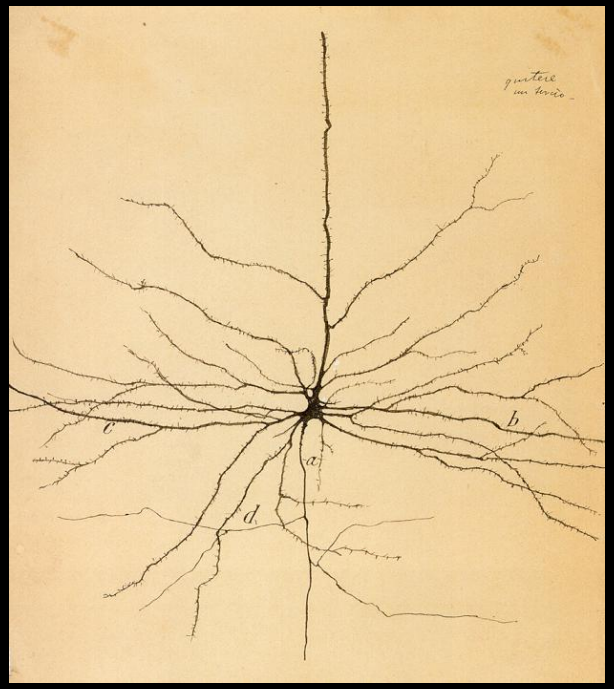


Samuel Loyd 1859

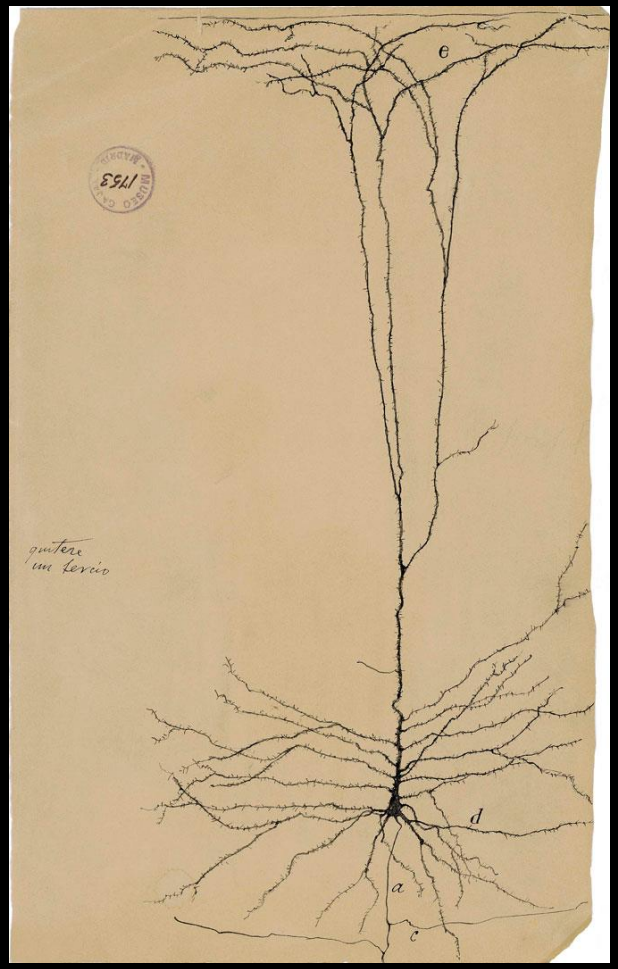
OUR AMAZING BRAIN

http://research.vtc.vt.edu/news/2013/feb/13/brain-awareness-week-designed-highlight-advances-b/

Neurons are the key cells that make the brain so unique



trauma.blog.yorku.ca

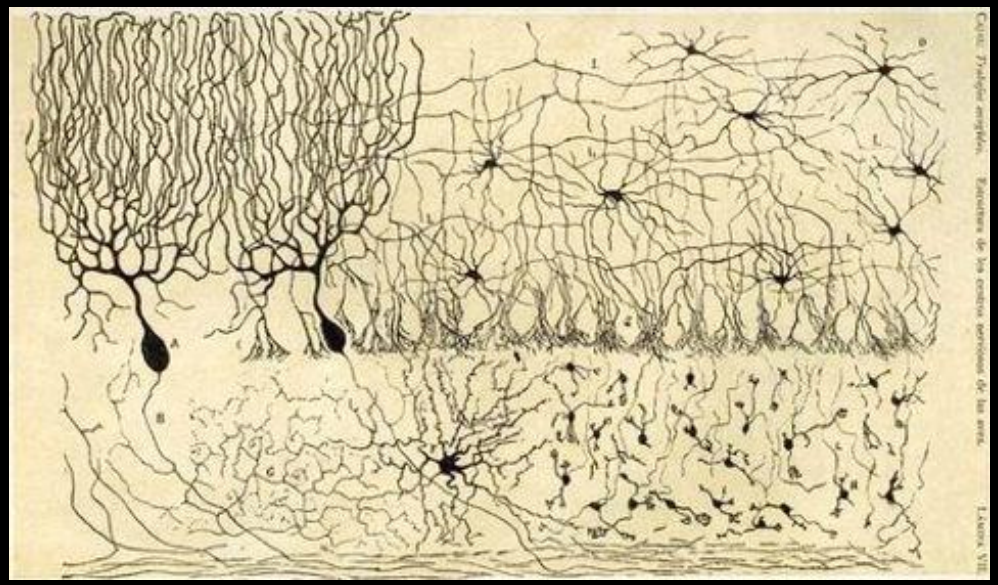


arttattler.com

(drawings by Santiago Ramon y Cajal)

Neurons form amazing networks

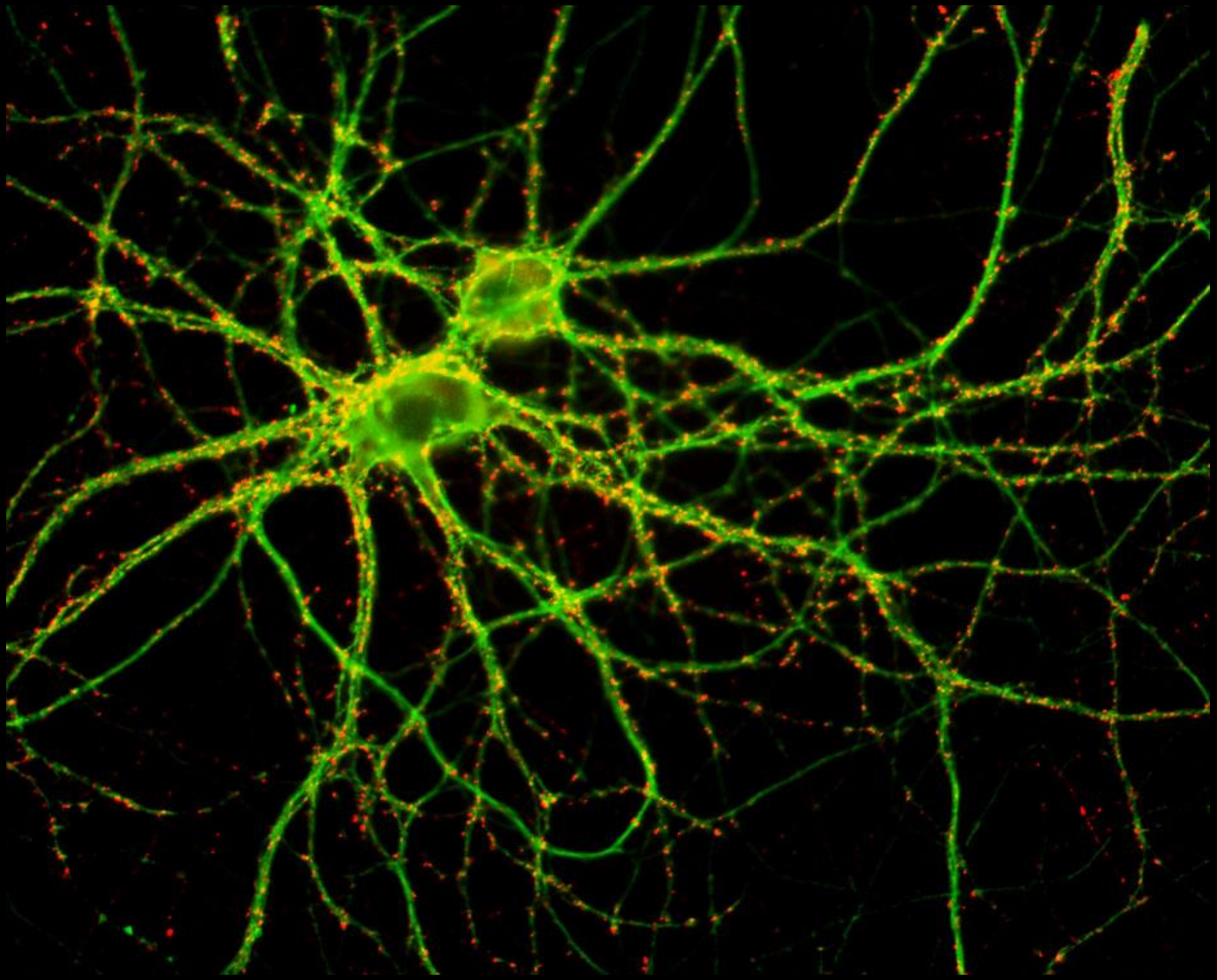
www.the-scientist.com



neuronico.net

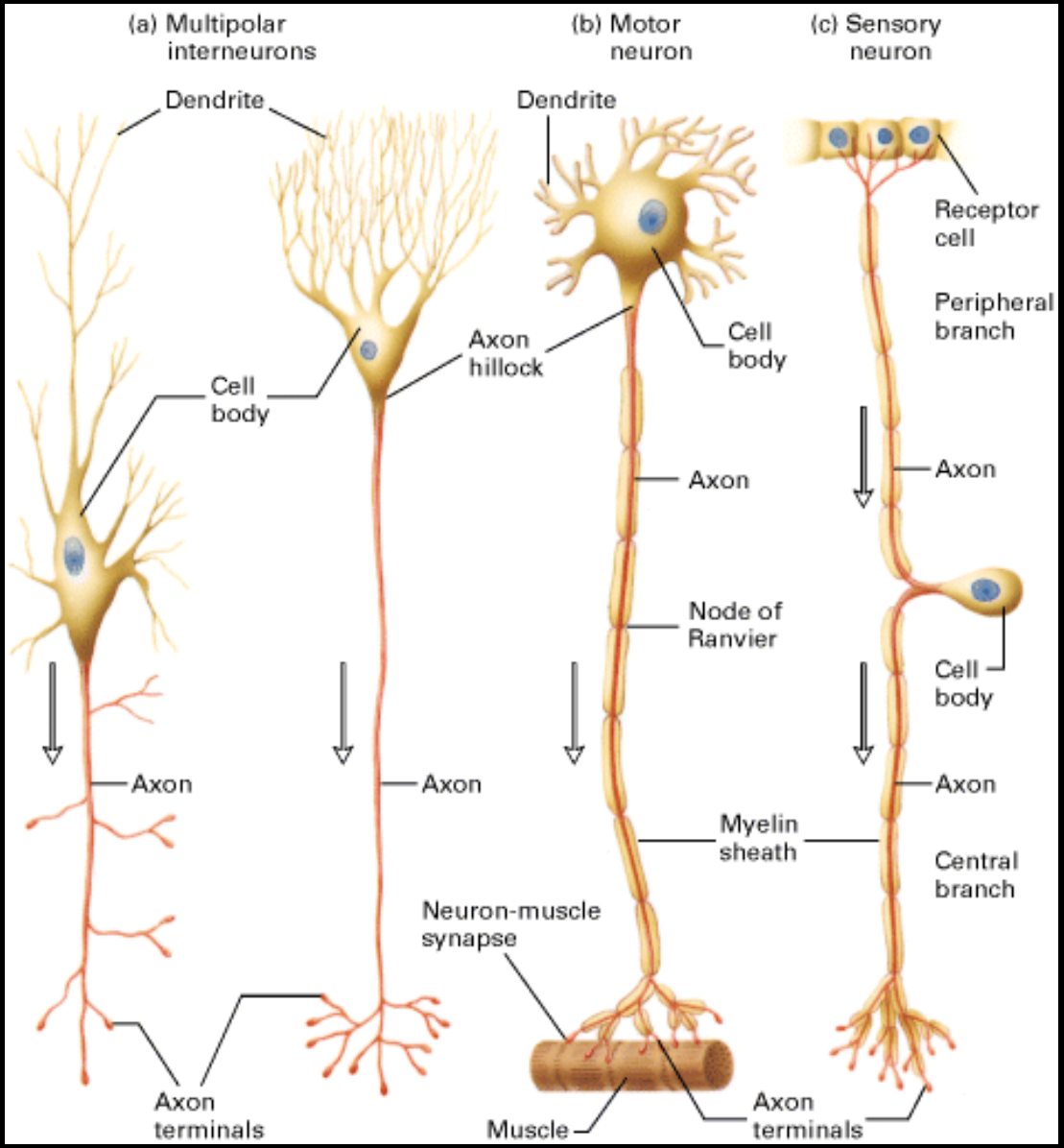
(drawings by Santiago Ramon y Cajal)

The brain is an extremely complex communications network
Interneuronal communication occurs at synapses



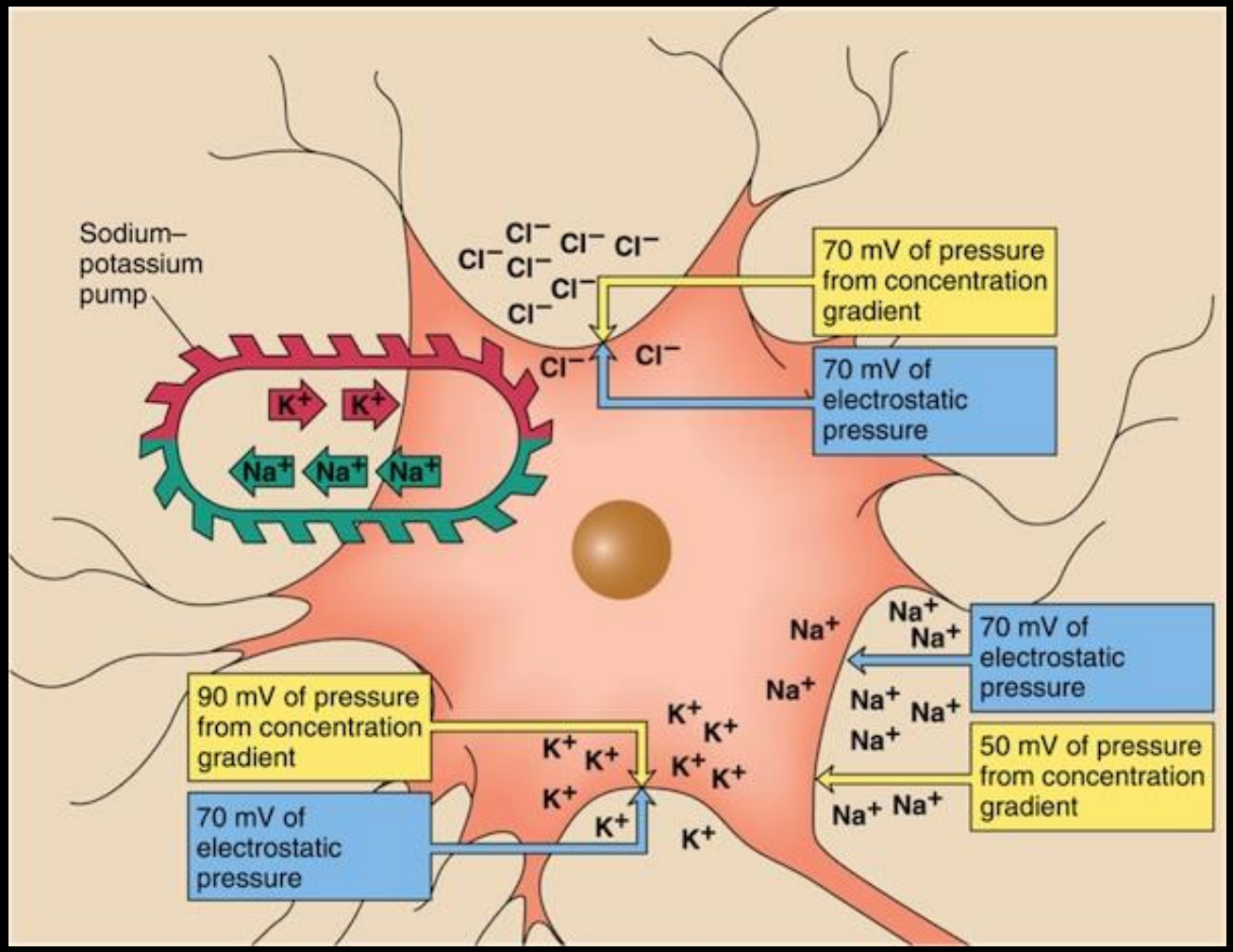
Xinran Liu

There are many types of neurons
A common feature is their polarity



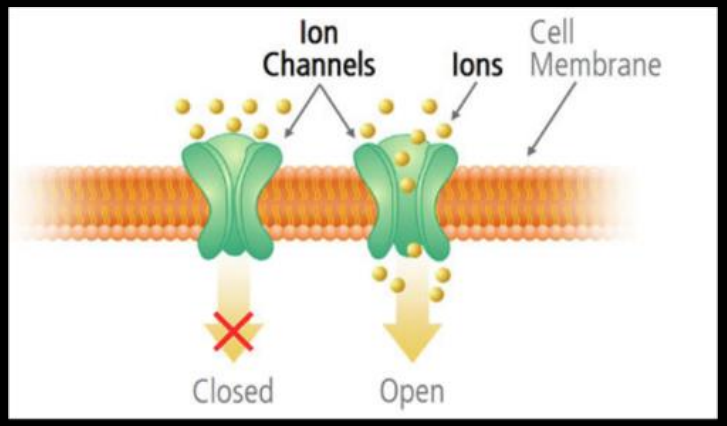
biologyboom.com

The membrane potential arises from differences in the concentrations of ions inside and outside the cell

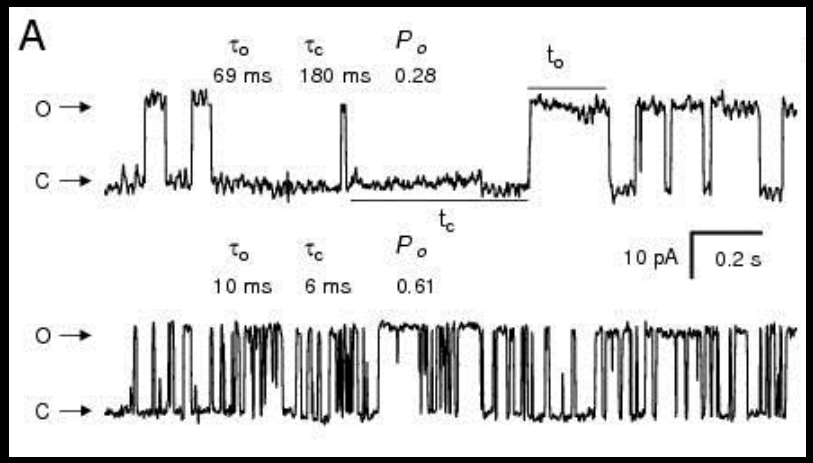


mikeclaffey.com

Some ion channels can open and close depending on the membrane potential, and help to propagate electrical signals with a very fast speed



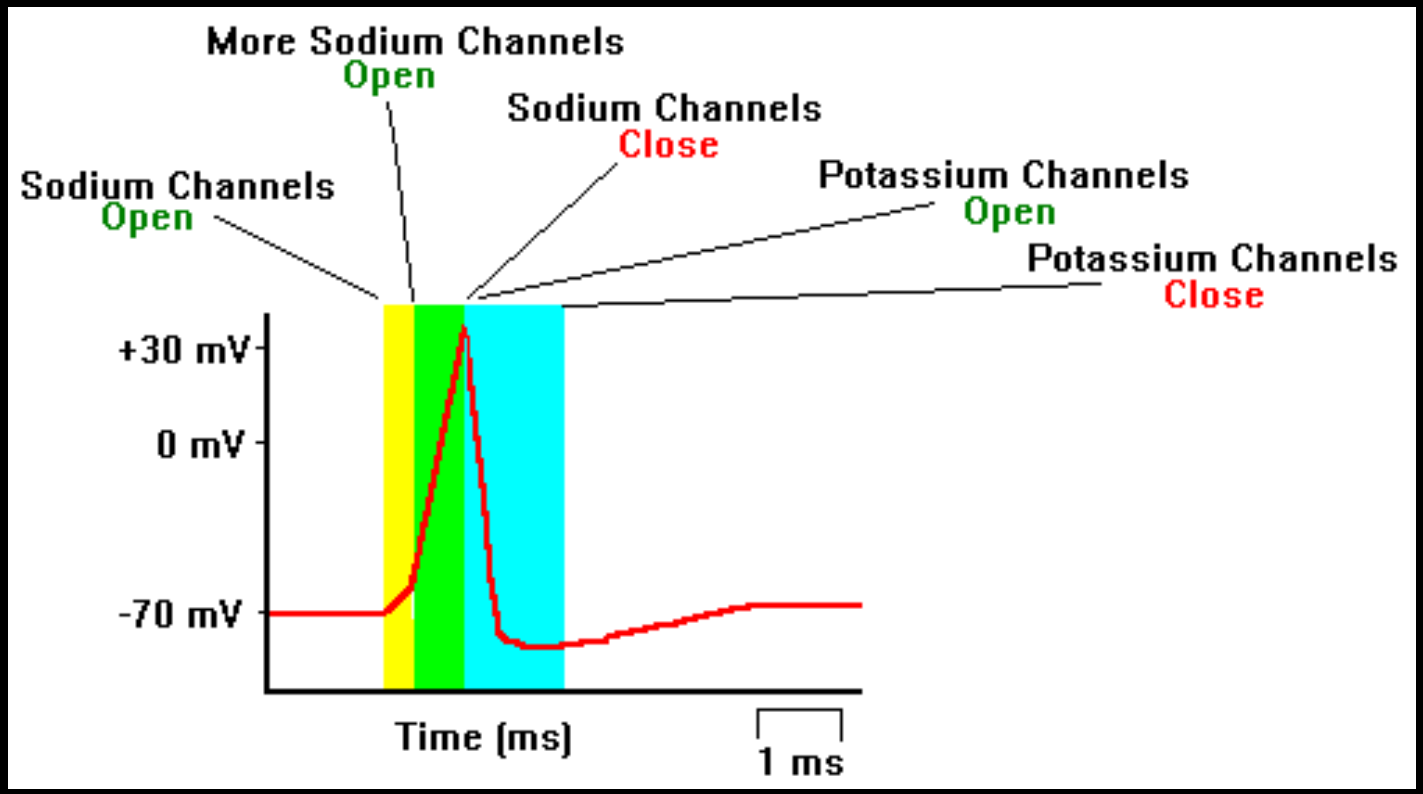
www.emaze.com



a single ion channel opening and closing

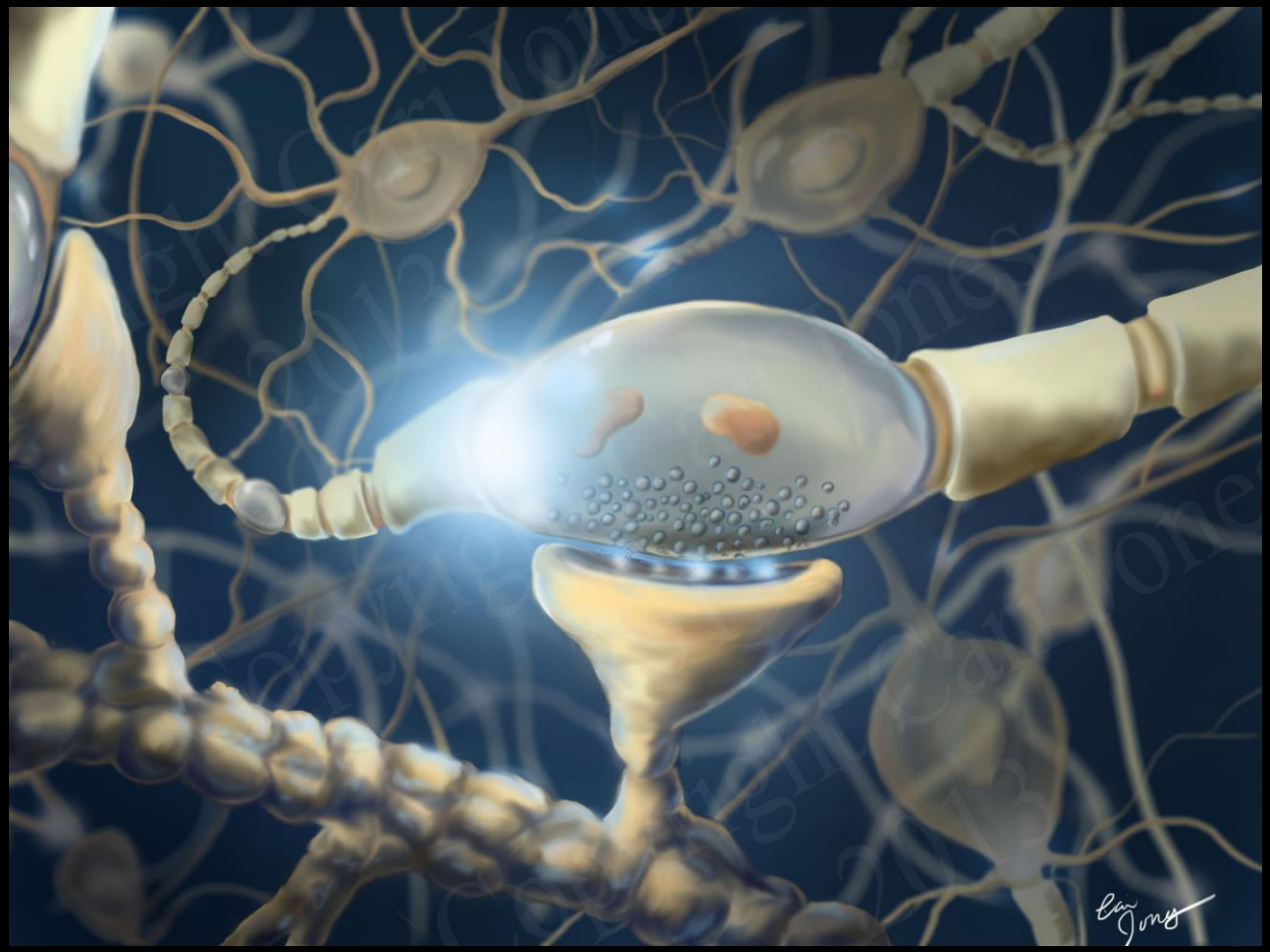
aups.org.au

These electrical signals are known as actions potentials and are propagated by opening and closing of sodium and potassium channels



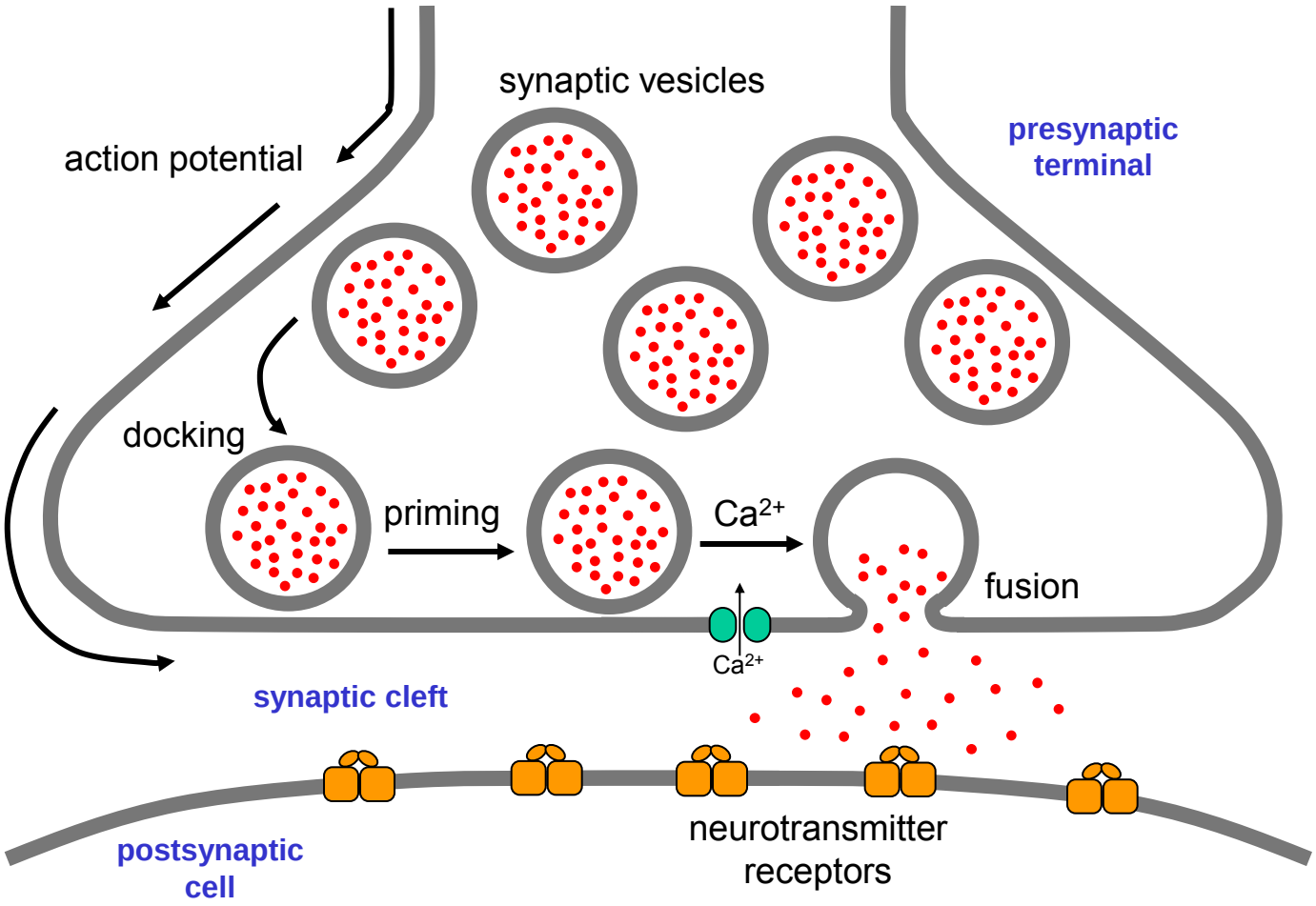
faculty.washington.edu

Synaptic transmission occurs at synapses

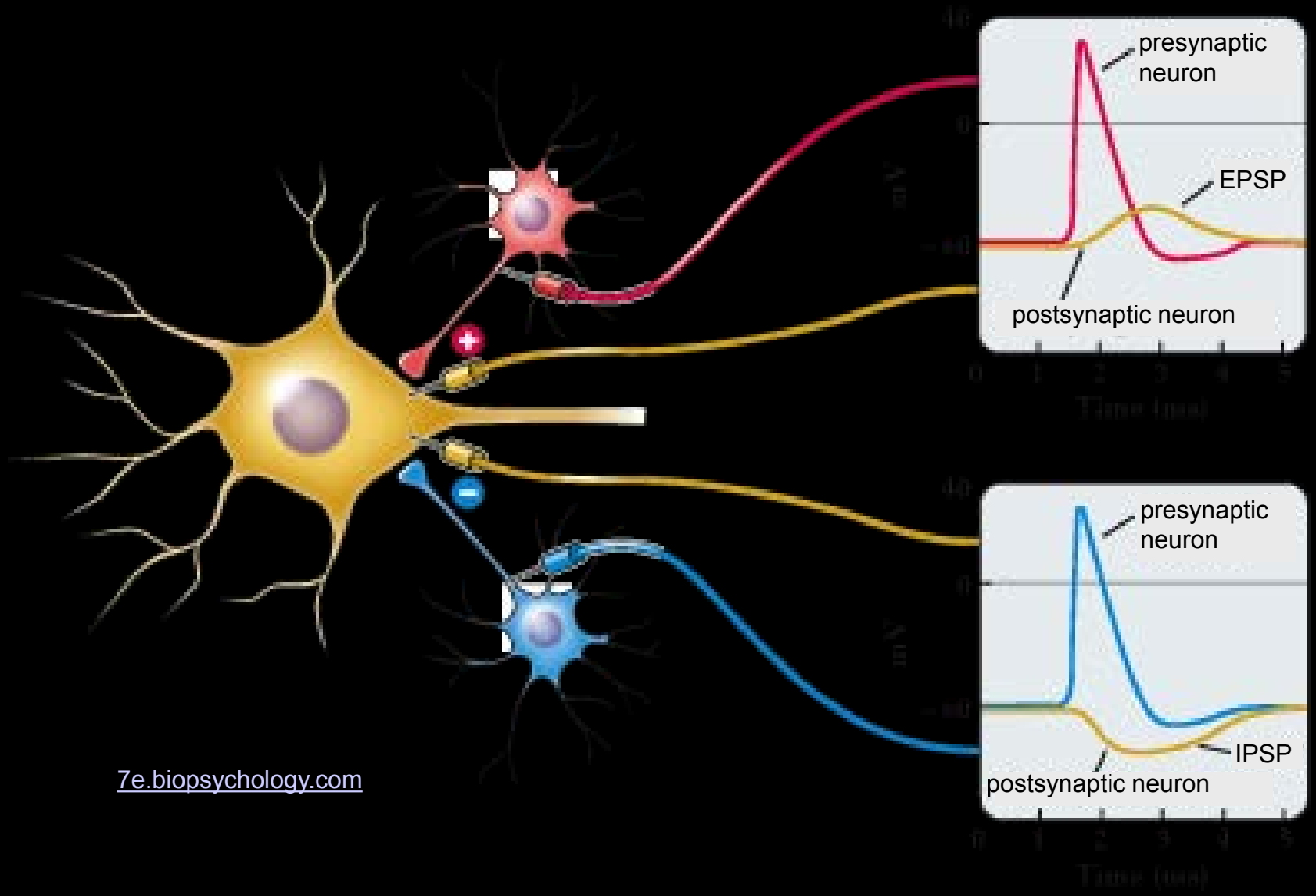


cjonesbvis518.wordpress.com

Chemical synaptic transmission

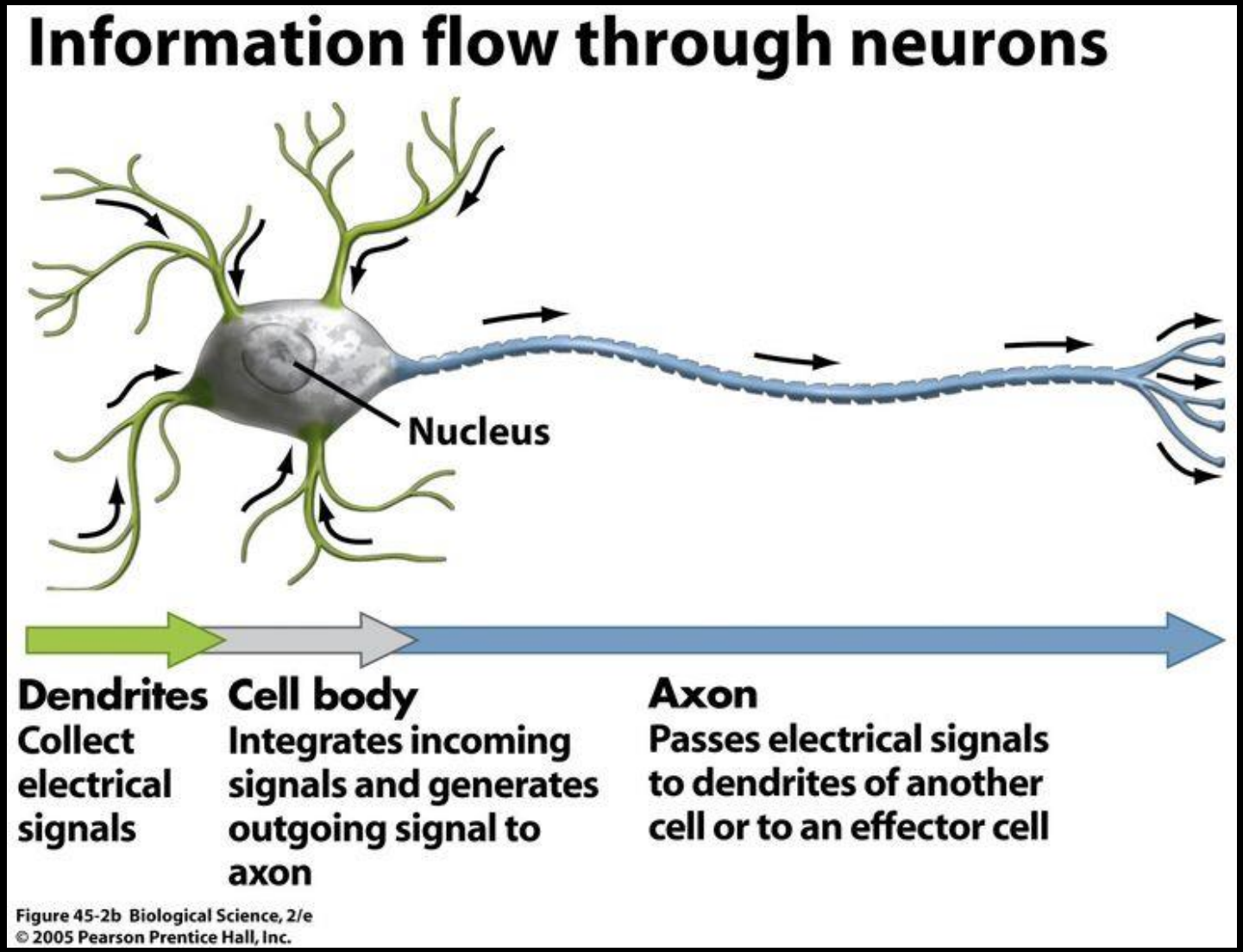


Binding of neurotransmitters to postsynaptic receptors can cause excitatory or inhibitory postsynaptic potentials (EPSPs or IPSPs), depending of the type of synapse and the neurotransmitter released



7e.biopsychology.com

Different inputs are integrated at the cell body, leading to an action potential in the axon depending on the balance of the inputs

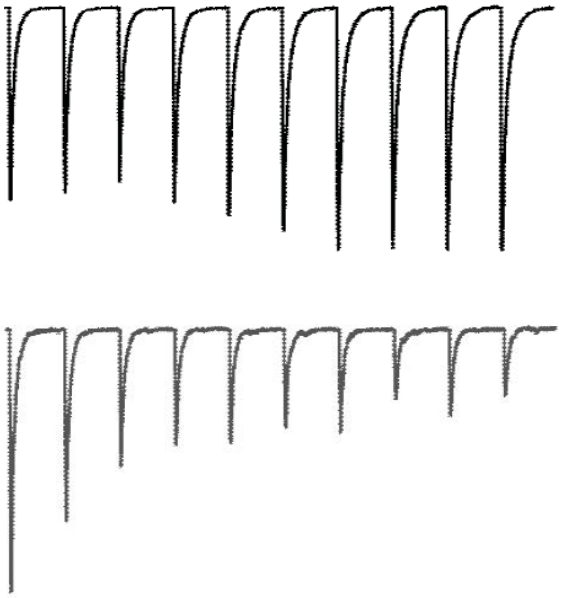


www.pinterest.com

- Repetitive stimulation can lead to stronger or weaker postsynaptic potentials

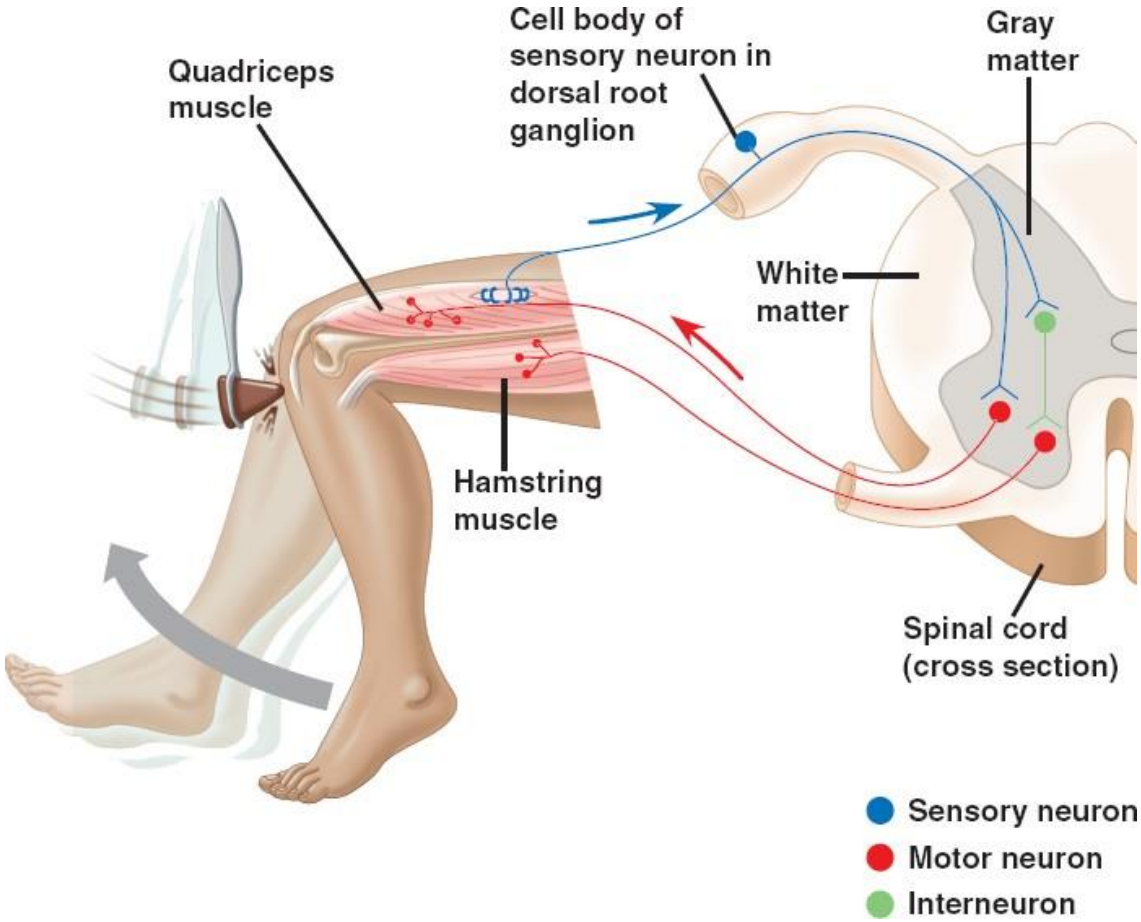
- This plasticity can arise from:
  presynaptic changes in the efficiency of neurotransmitter release
  and/or changes in the postsynaptic responses

- Synaptic plasticity underlies many forms of information processing in the brain

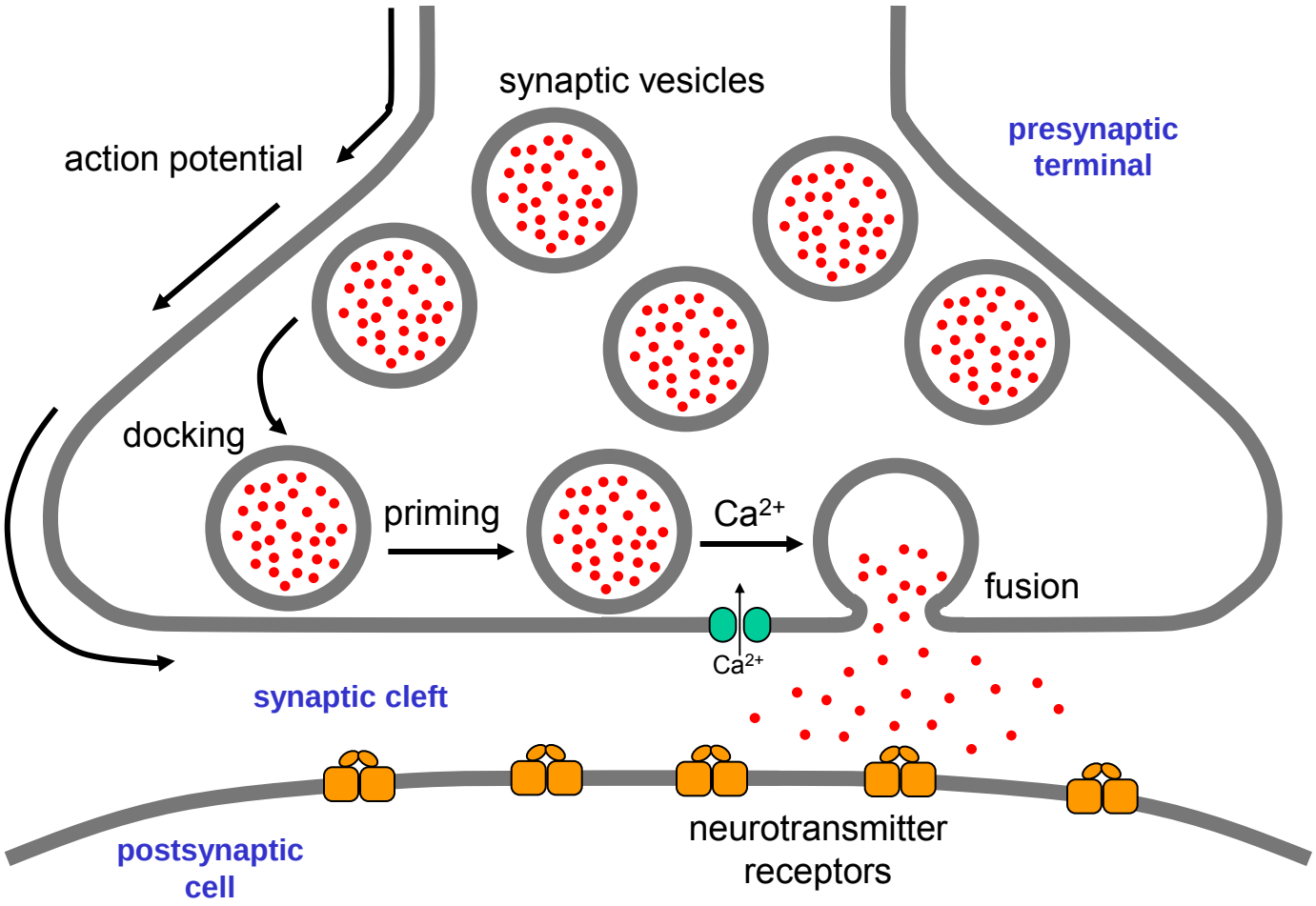


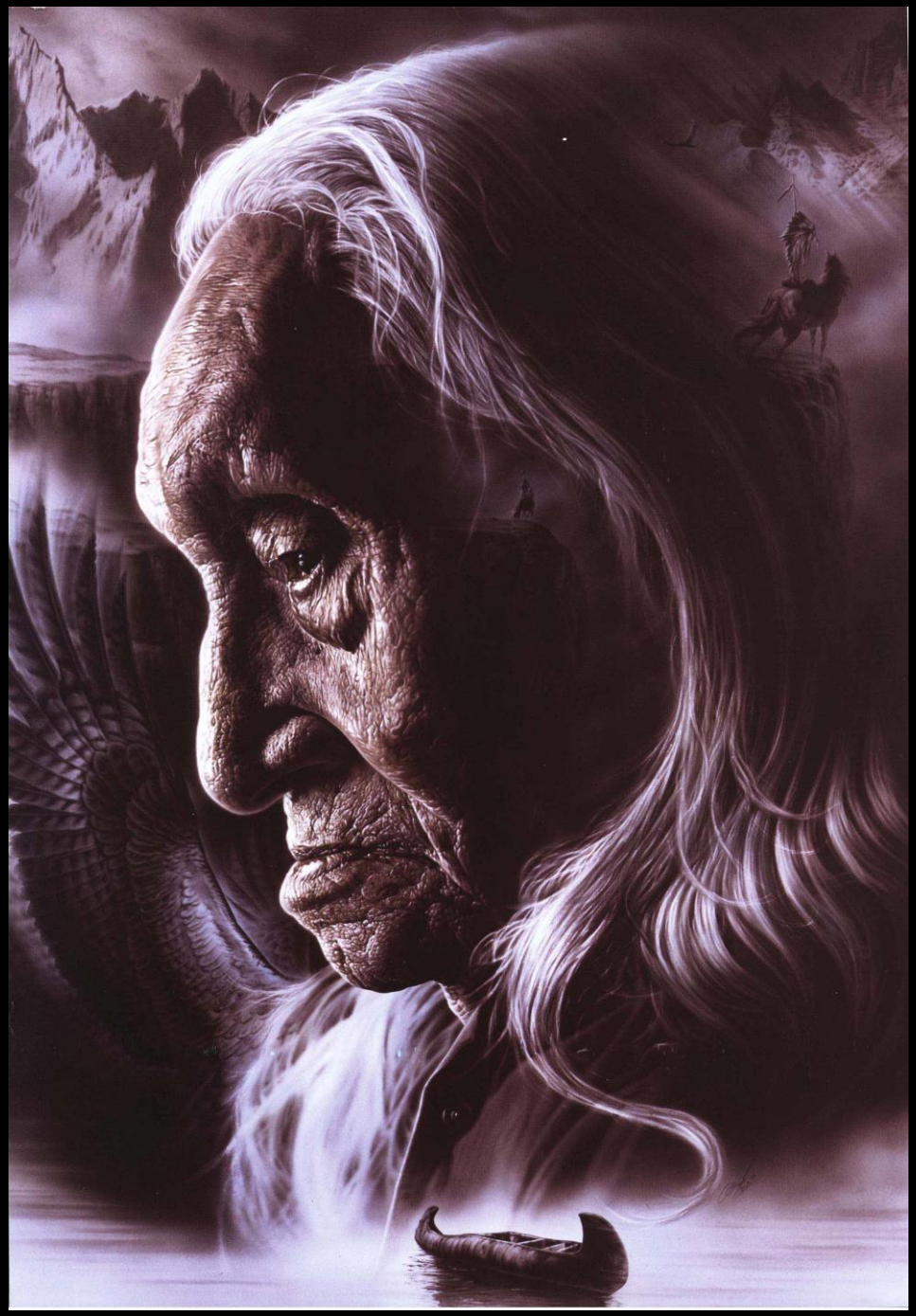
Shin et al. (2010) *Nat. Struct. Mol. Biol.* 2010 *17*, 280

The knee-jerk reflex illustrates a behavior controlled by a system of distinct neurons

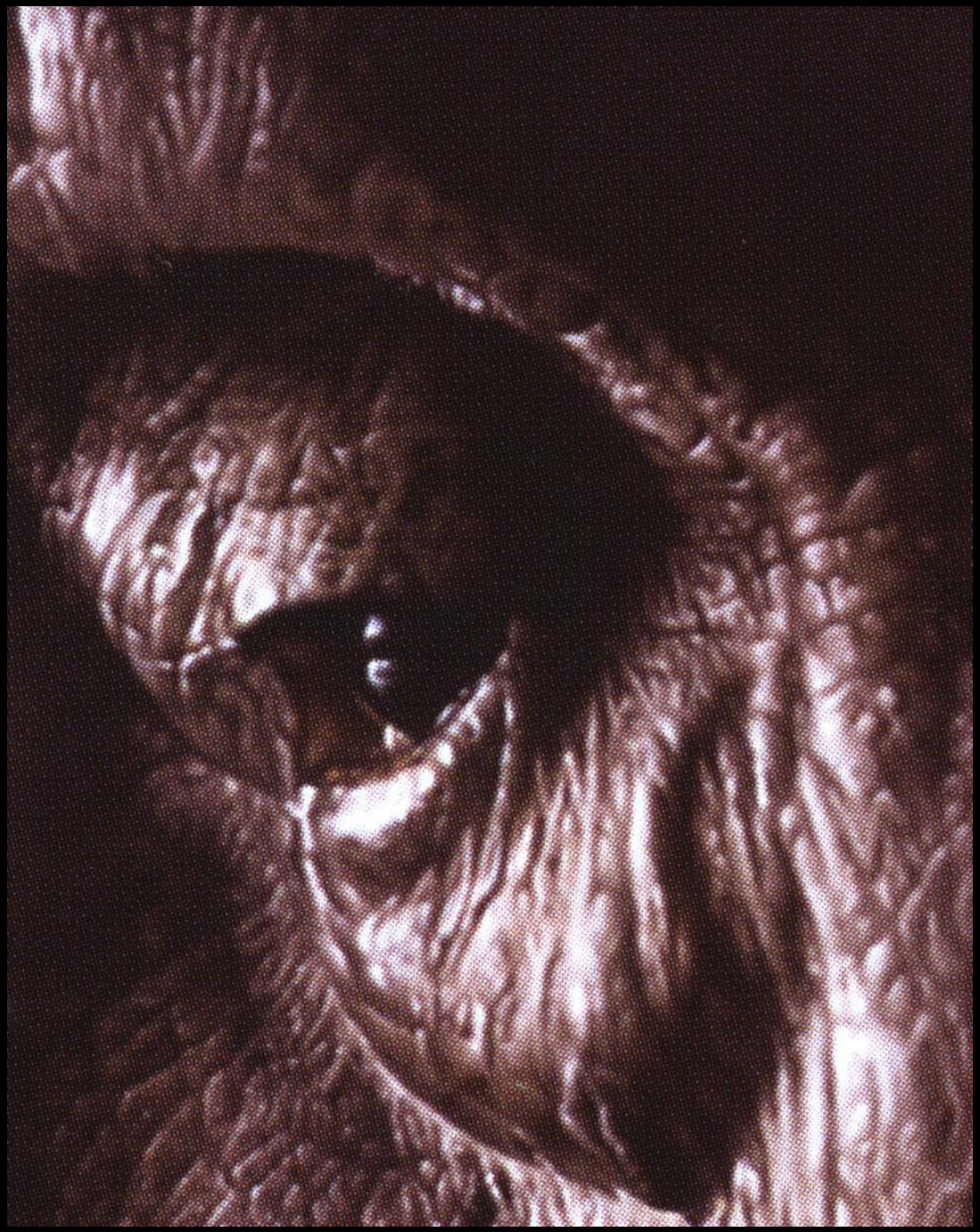


Synaptic vesicle fusion is key for interneuronal communication

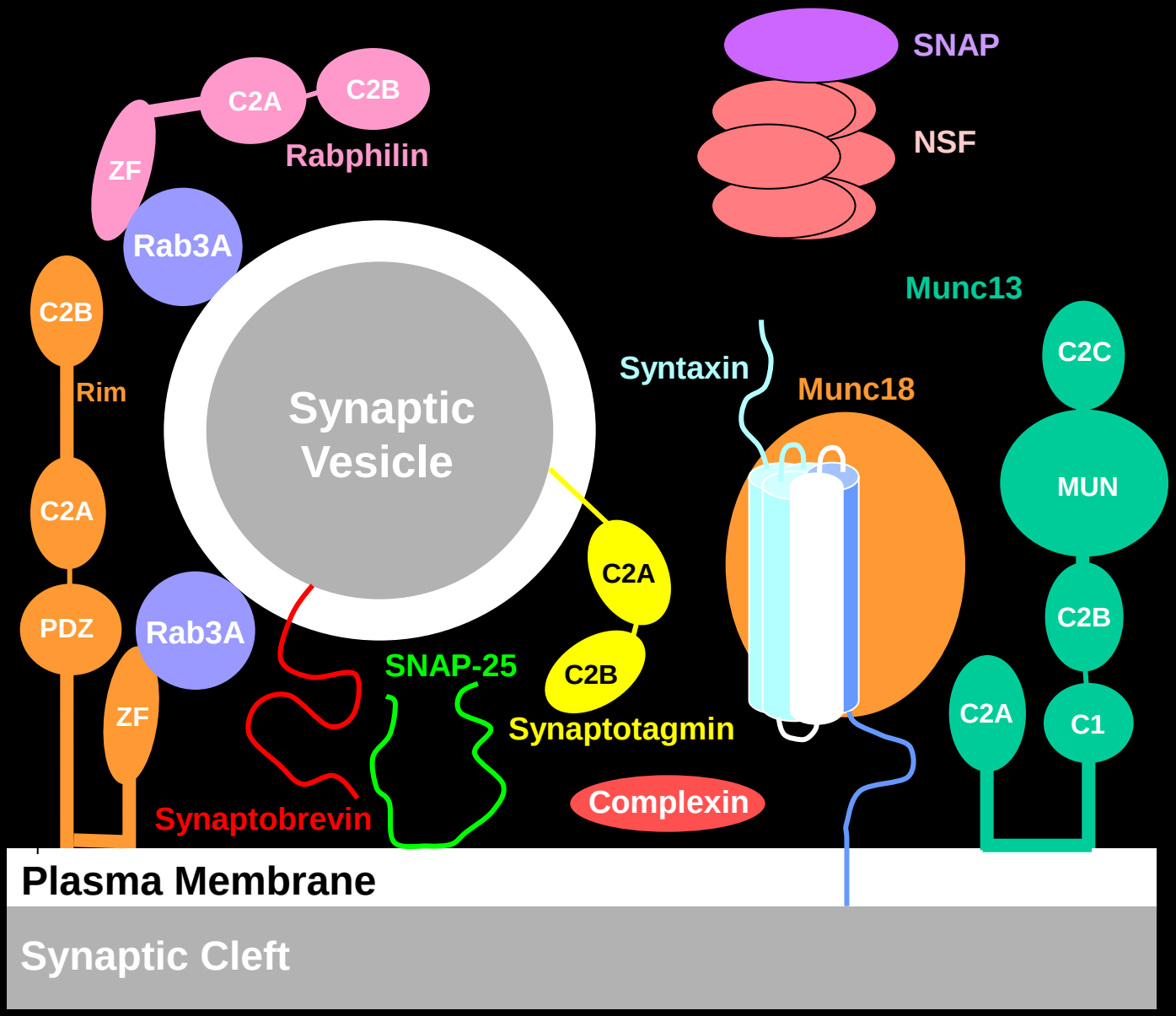




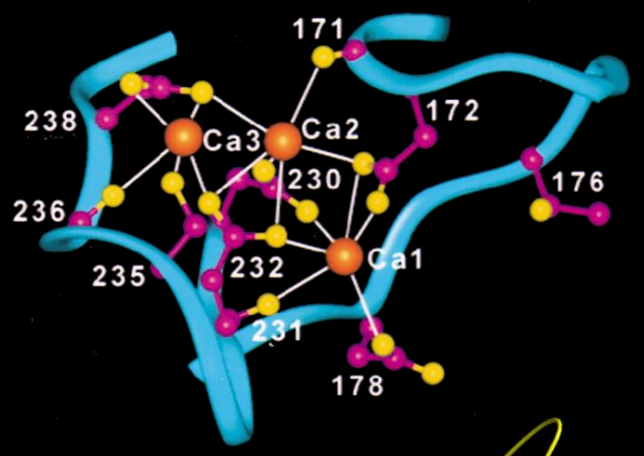
Lluis Rizo

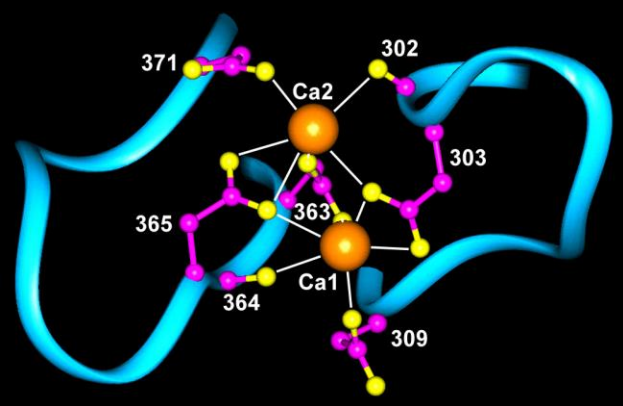


Luis Rizo

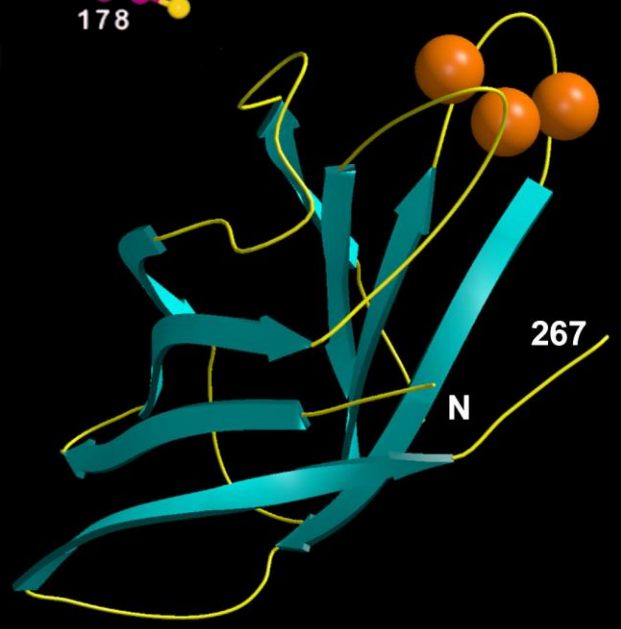

Cytoplasm
SNAP
NSF
C2A
C2B
Rabphilin
ZF
Rab3A
C2B
Rim
C2A
PDZ
Rab3A
ZF
Synaptic Vesicle
Munc13
Syntaxin
Munc18
C2C
MUN
C2B
C2A
C1
C2A
C2B
Synaptotagmin
SNAP-25
Synaptobrevin
Complexin
Plasma Membrane
Synaptic Cleft

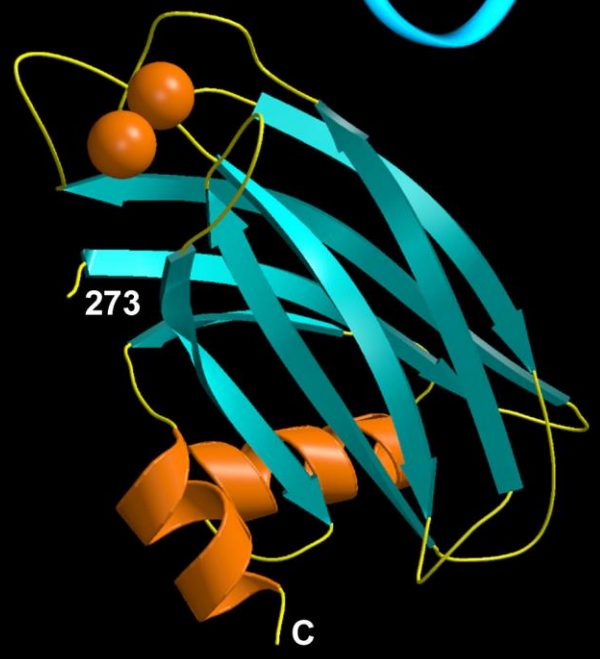
Structures and Ca^{2+} binding modes of the synaptotagmin-1 C_2 domains





C_2A





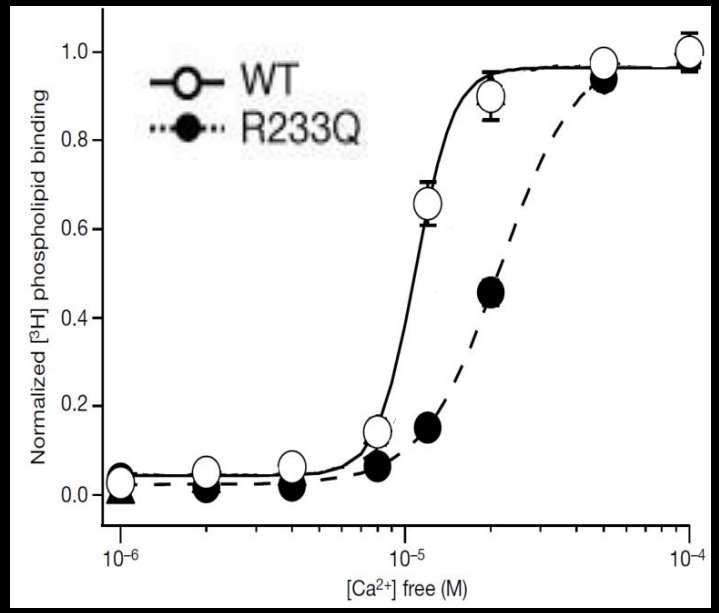
C_2B

Shao et al. Science 273, 248 (1996)
Shao et al. Biochemistry 37, 16106 (1998)

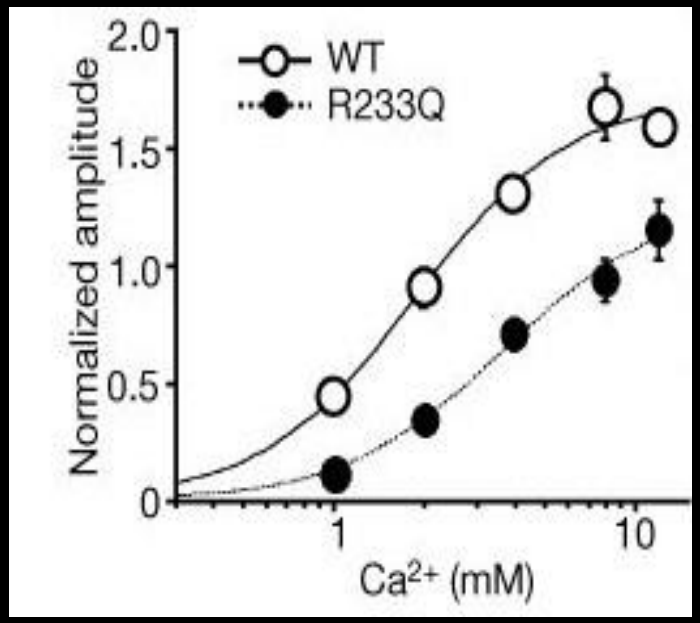
Ubach et al. EMBO J. 17, 3921 (1998)
Fernandez et al. Neuron 32, 1057 (2001)

Synaptotagmin I acts as a Ca2+ sensor in neurotransmitter release

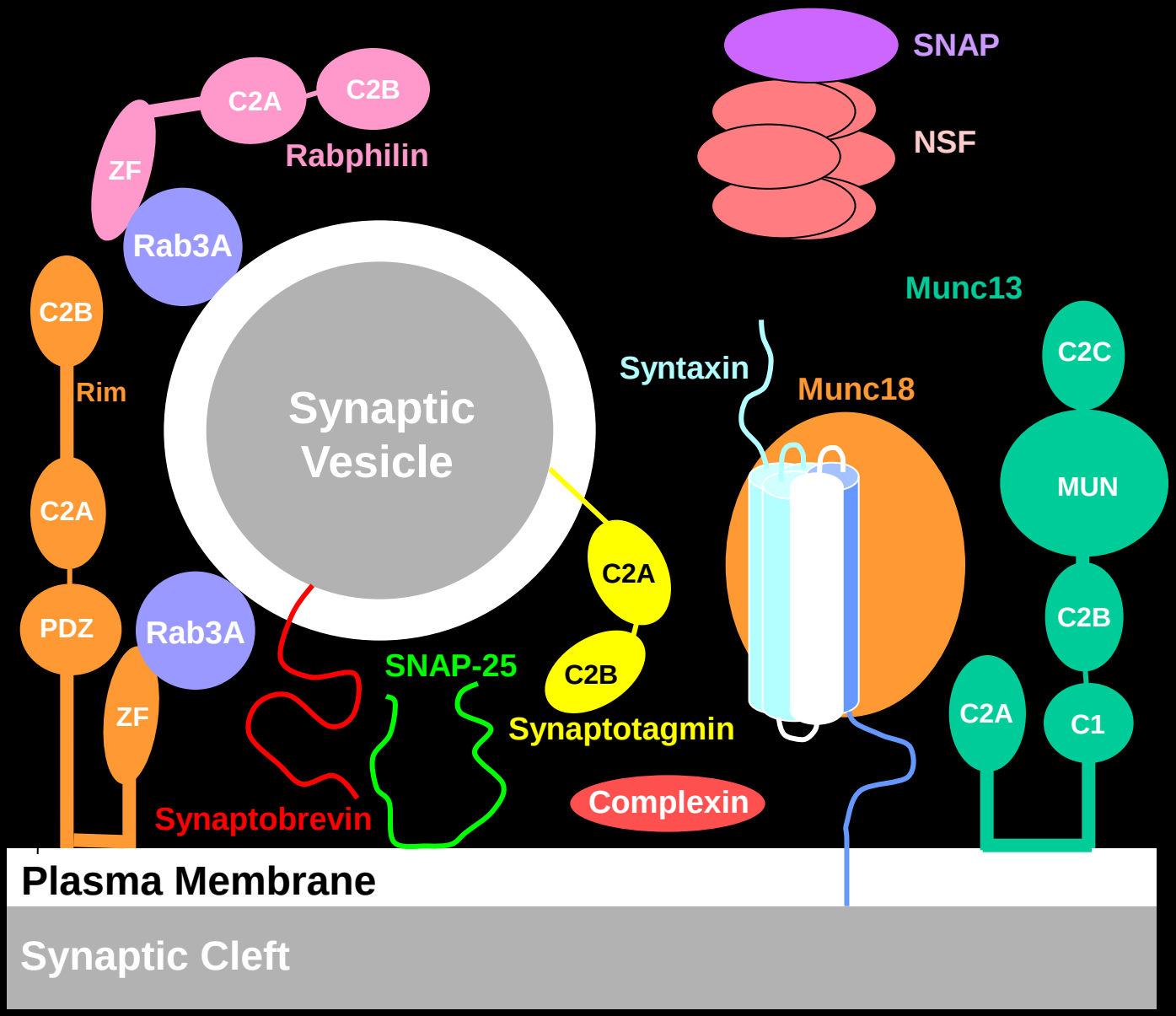
In vitro Ca2+-dependent phospholipid binding



In vivo Ca2+-dependence of neurotransmitter release



Fernandez-Chacon et al. Nature 410, 41 (2001)


Cytoplasm
SNAP
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C2A
C2B
Rabphilin
ZF
Rab3A
C2B
Rim
C2A
PDZ
Rab3A
ZF
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Munc13
Syntaxin
Munc18
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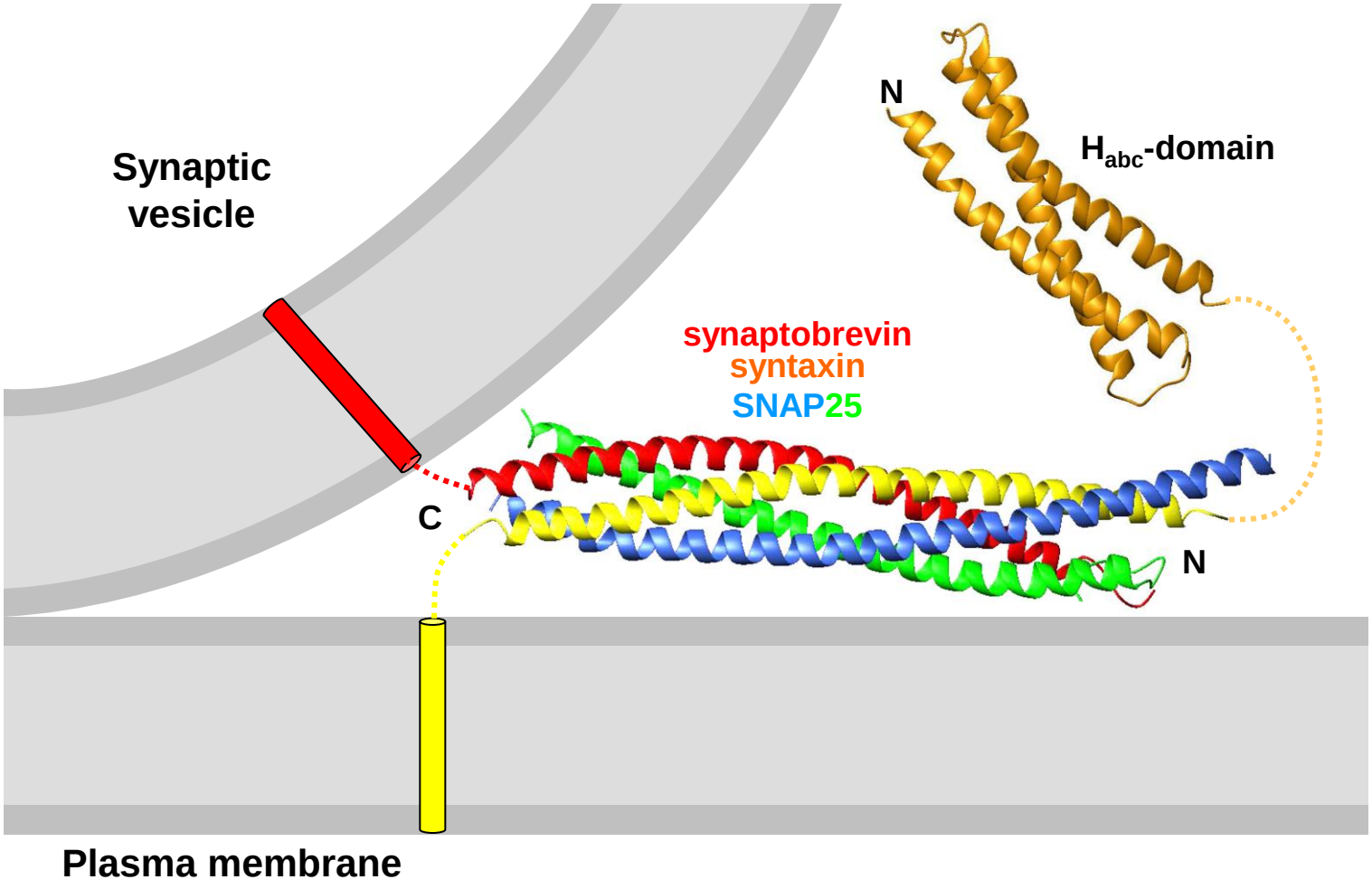
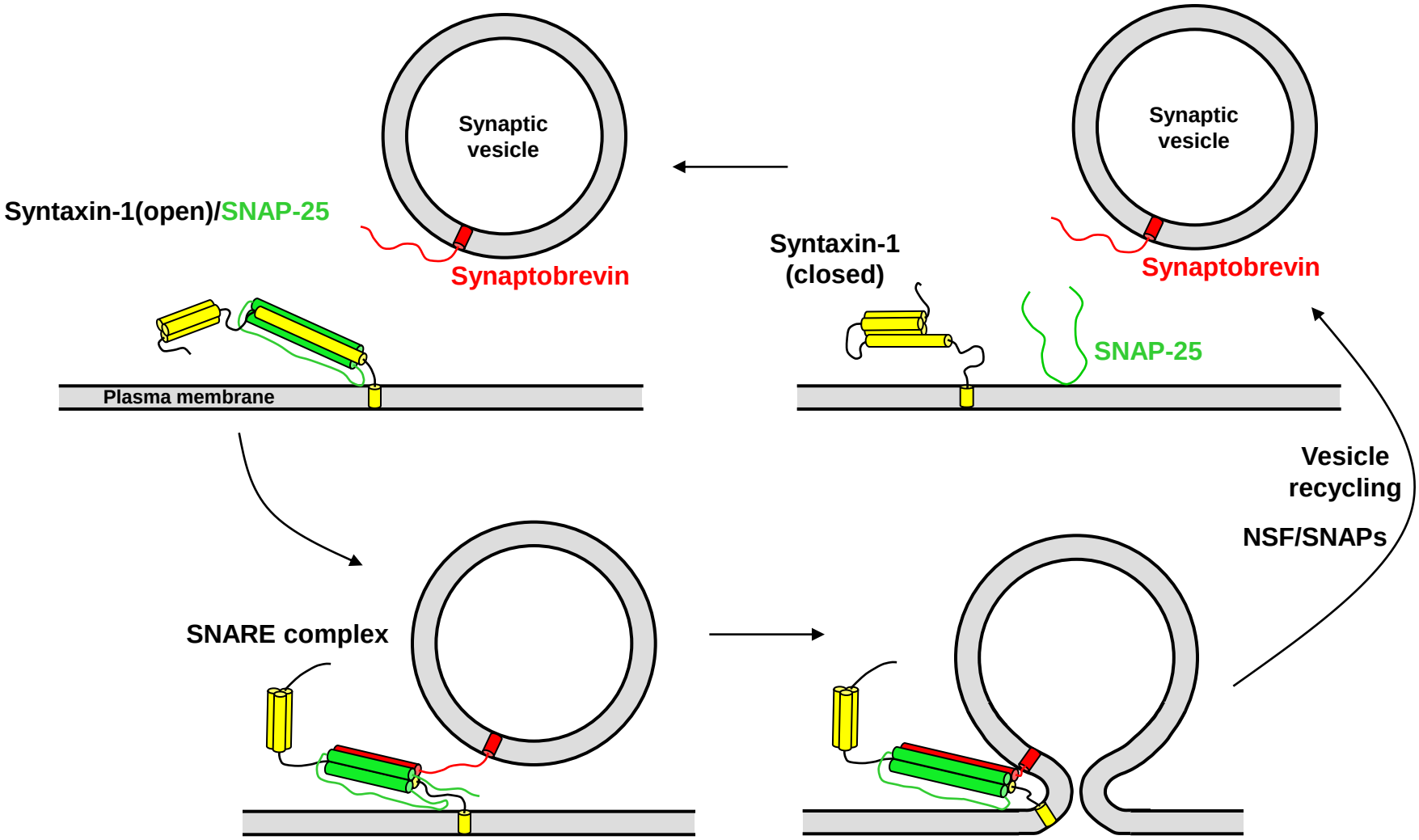
C2B
C2A
C1
C2A
C2B
Synaptotagmin
SNAP-25
Synaptobrevin
Complexin
Plasma Membrane
Synaptic Cleft

The SNARE complex

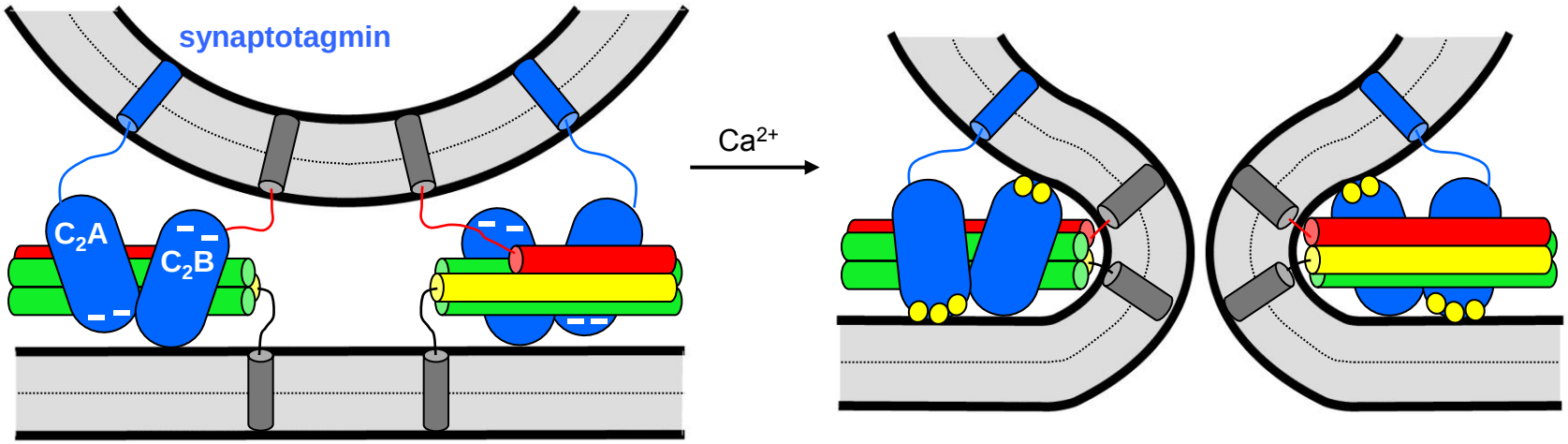


Sutton et al. (1998) Nature 395, 347
Fernandez et al. (1998) Cell 18, 841

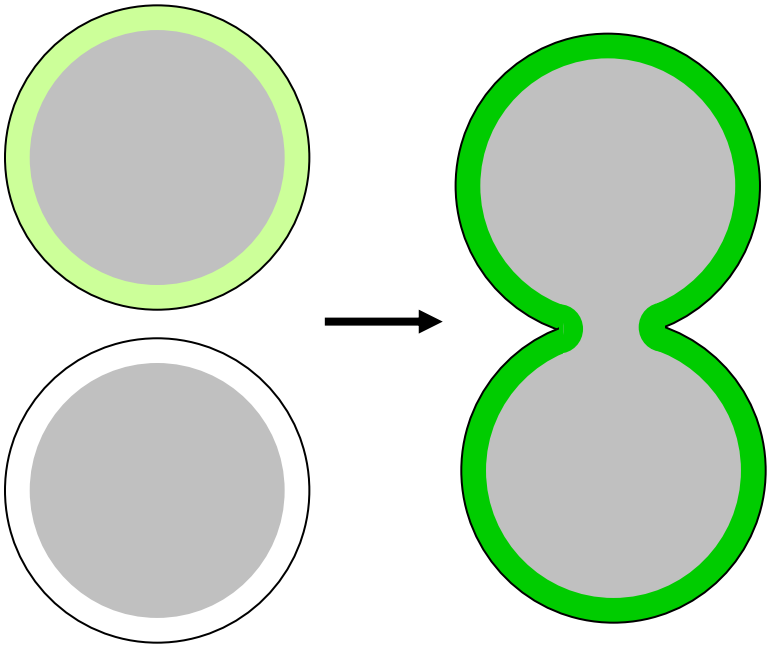
Widespread, SNARE-centric model of synaptic vesicle fusion

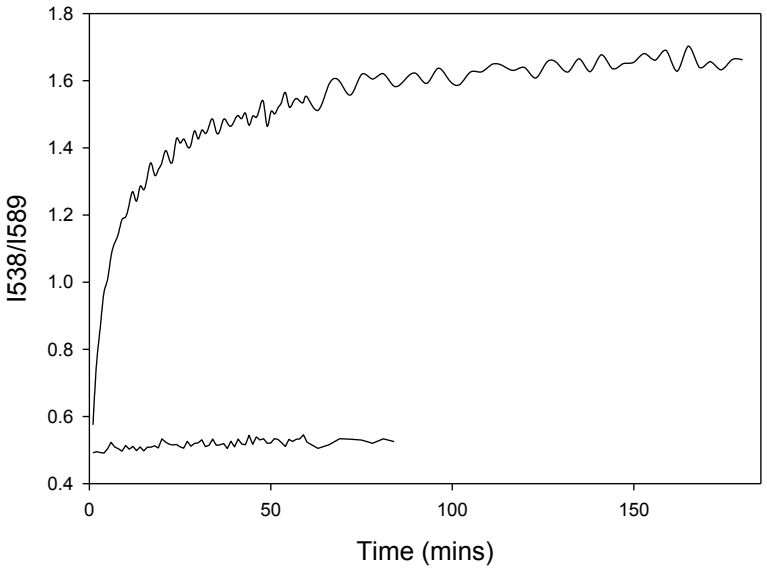


Model for how synaptotagmin cooperates with the SNAREs to induce calcium-dependent membrane fusion



LIPID MIXING ASSAY TO STUDY MEMBRANE FUSION IN VITRO

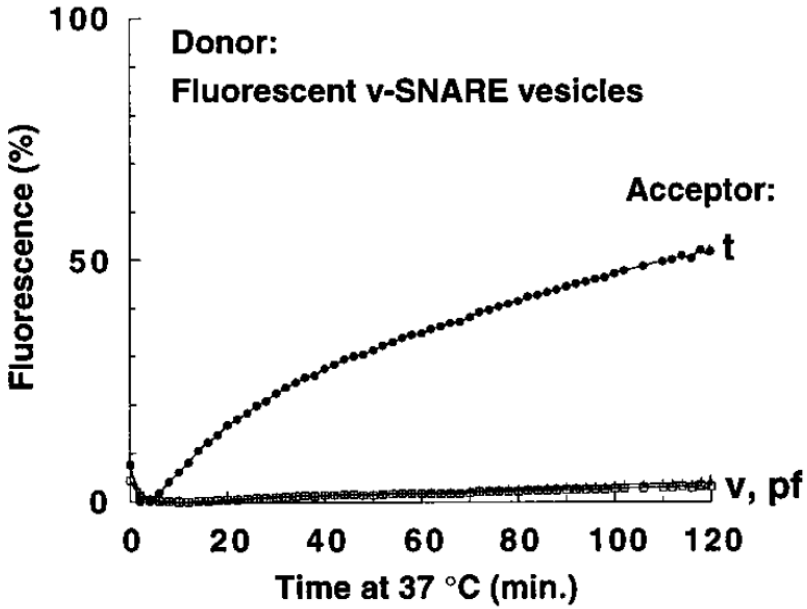


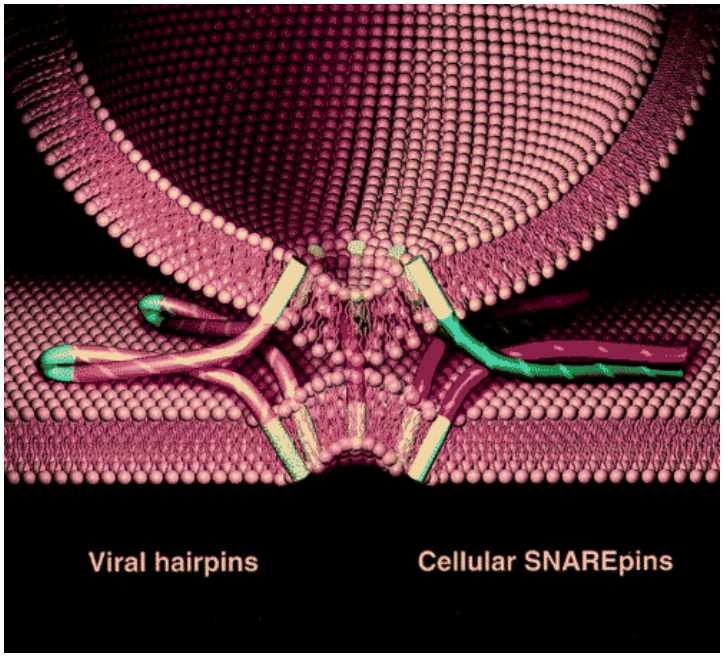


Cell, Vol. 92, 759–772, March 20, 1998, Copyright ©1998 by Cell Press

SNAREpins: Minimal Machinery for Membrane Fusion

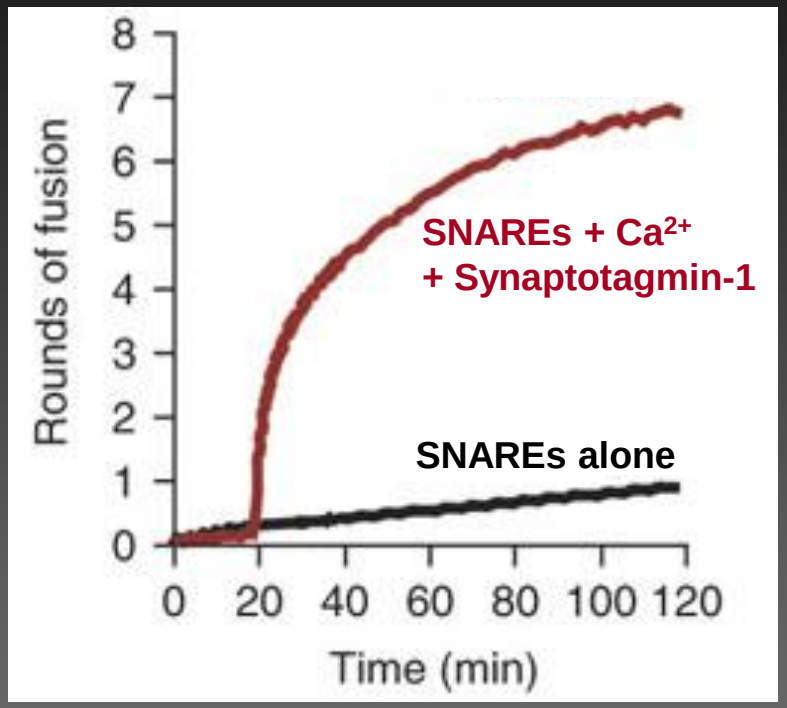
Thomas Weber, Boris V. Zemelman,‡
James A. McNew,‡ Benedikt Westermann,†‡
Michael Gmachl, Francesco Parlati,
Thomas H. Söllner, and James E. Rothman*
Cellular Biochemistry and Biophysics Program
Memorial Sloan-Kettering Cancer Center





Weber et al. (1998) Cell 92, 759

Efficient membrane fusion in vitro with SNAREs and Synaptotagmin-1

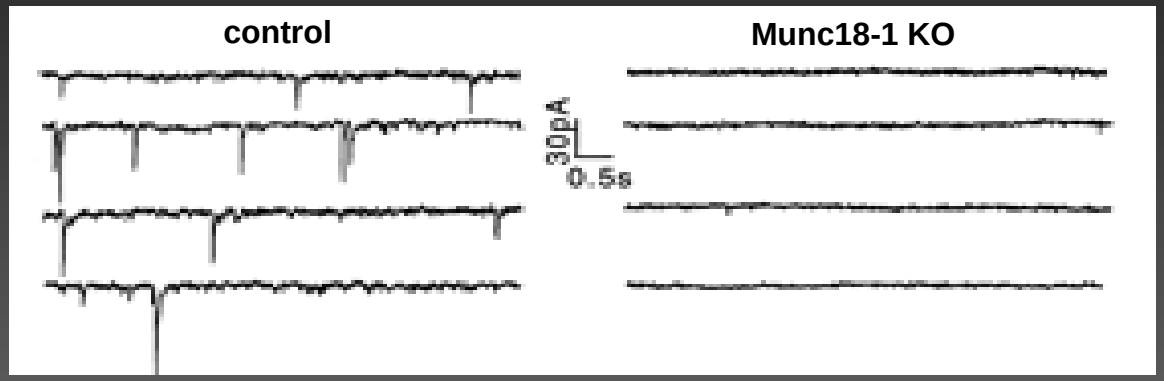


Tucker et al. Science *304*, 435 (2004)
Chicka et al. Nat. Struct. Mol. Biol. *15*, 827 (2008)
Xue et al. Nat. Struct. Mol. Biol. *15*, 1160 (2008)

But without Munc18-1 or Munc13!

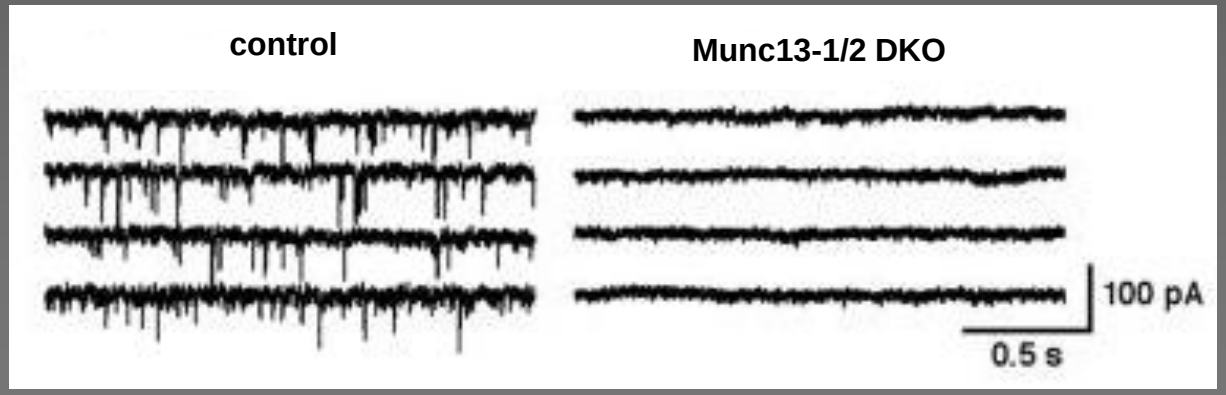
Total abrogation of neurotransmitter release
In the absence of Munc18-1 or Munc13s

Munc18-1 KO
Total silence



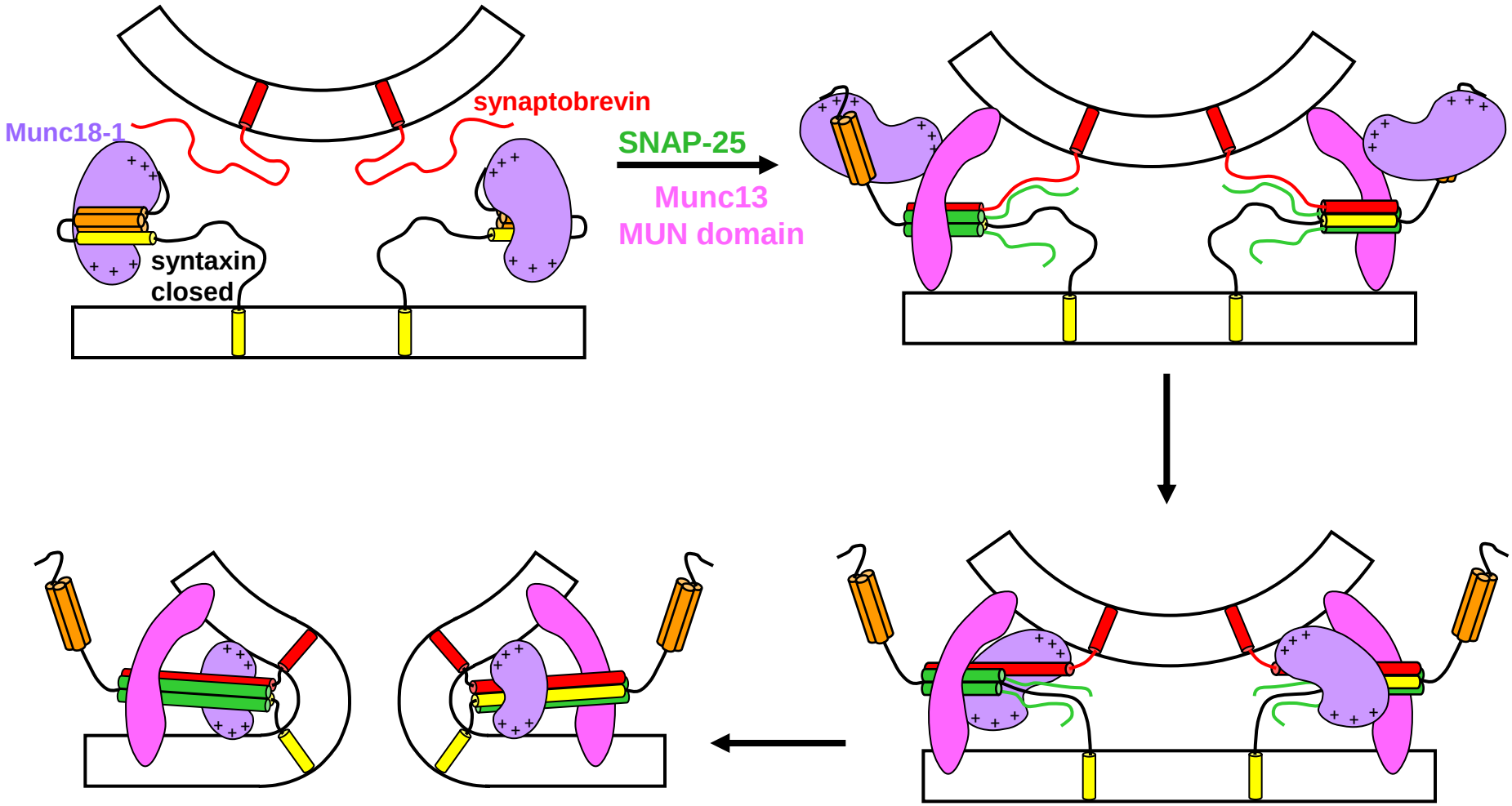
Verhage et al. Science *287*, 864 (2000)

Munc13-1/2 KO
Total silence



Varoqueaux et al. Proc. Natl. Acad. Sci. U. S. A *99*, 9037 (2002)

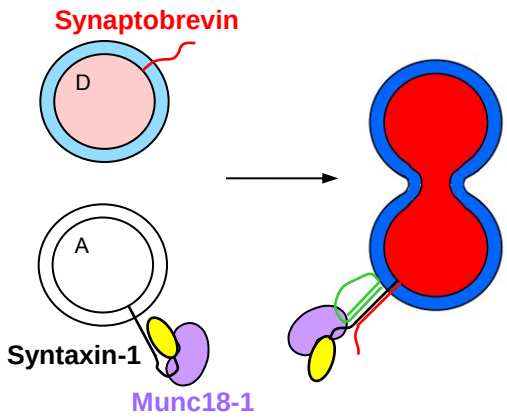
Model of Munc18-1 and Munc13 function

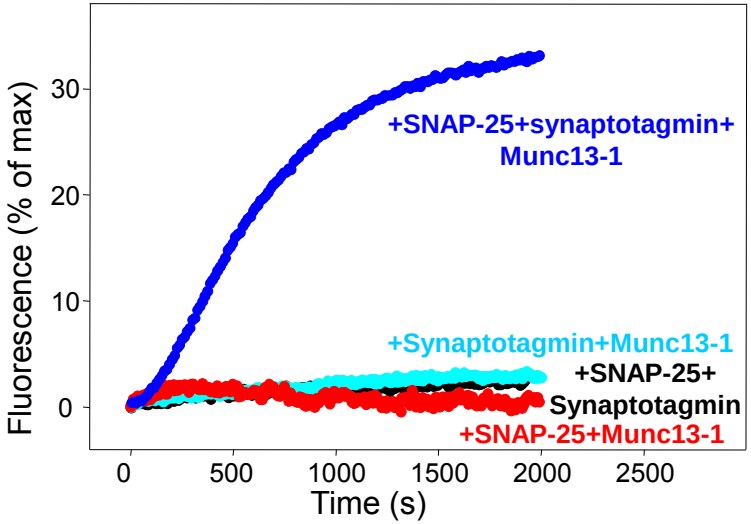


Fernandez et al. Cell 18, 841 (1998)
Carr et al. J. Cell Biol. 146, 333 (1999)
Dulubova et al. *EMBO J. 21*, 3620 (2002)
Dulubova et al. *PNAS 104*, 2697 (2007)
Xu et al., Biochemistry 49, 1568 (2010)

Dulubova et al. *EMBO J. 18*, 4372 (1999)
Yamaguchi et al. *Developmental Cell 2*, 295 (2002)
Dulubova et al. *PNAS 100*, 32 (2003)
Deak, Xu et al., J. Cell. Biol. 184, 751 (2009)
Ma et al., Nat. Struct. Molec. Biol. 18, 542 (2011)

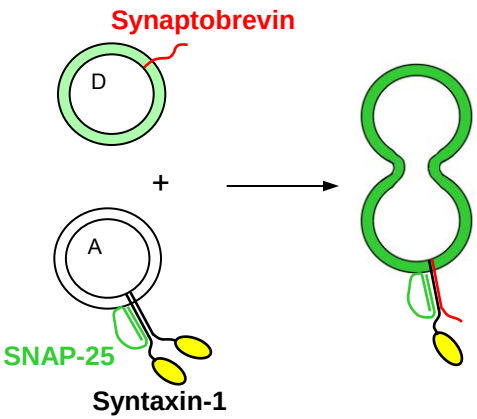
Reconstitution of membrane fusion with Syntaxin-1/Munc18-1 liposomes + Synaptobrevin liposomes + Munc13-1, SNAP-25 and Synaptotagmin-1

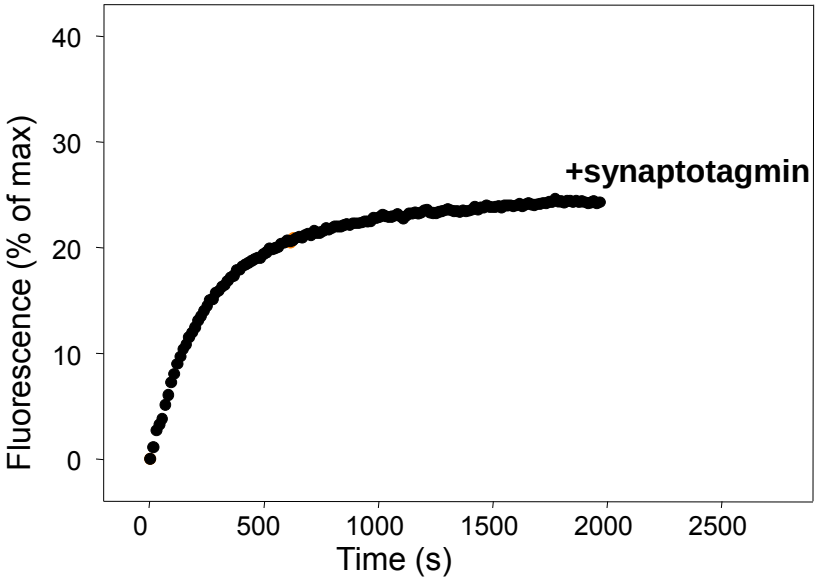




Ma et al. Science 339, 421 (2013)

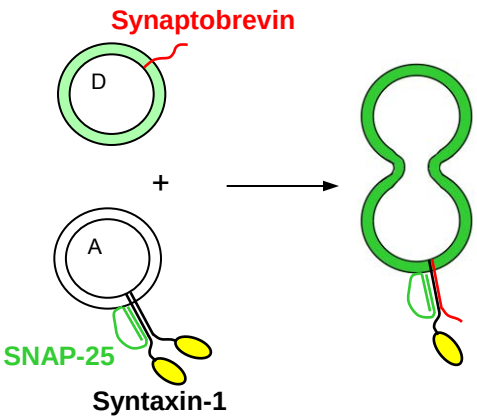
Efficient fusion with Syntaxin-1/SNAP-25 liposomes + Synaptobrevin liposomes + Synaptotagmin-1

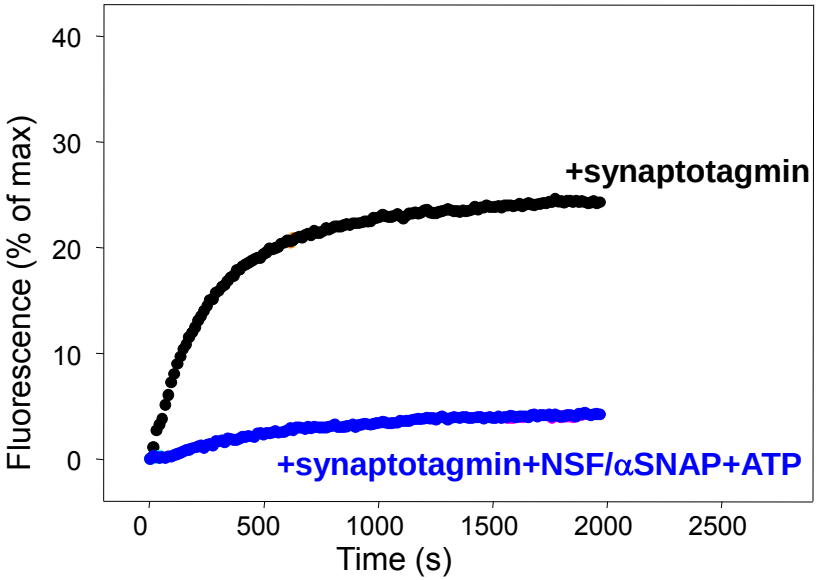




Ma et al. Science 339, 421 (2013)

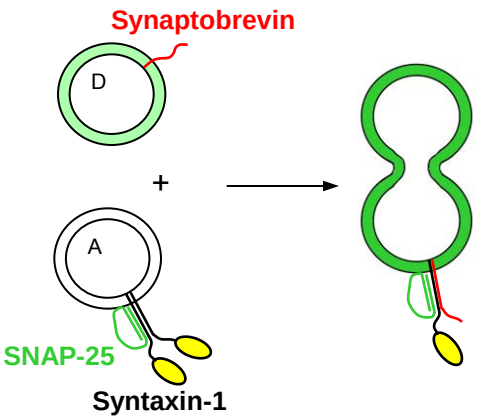
Fusion with Syntaxin-1/SNAP-25 liposomes + Synaptobrevin liposomes + Synaptotagmin-1 is inhibited by NSF, α-SNAP

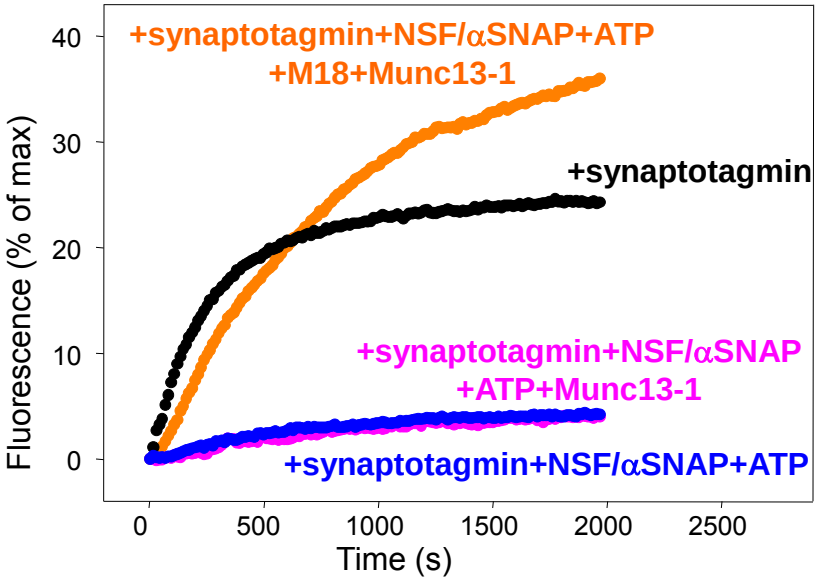




Ma et al. Science 339, 421 (2013)

Reconstitution of synaptic vesicle fusion with Syntaxin-1/SNAP-25 liposomes + Synaptobrevin liposomes + Munc18-1, Munc13-1, NSF, α-SNAP and Synaptotagmin-1!!!!!

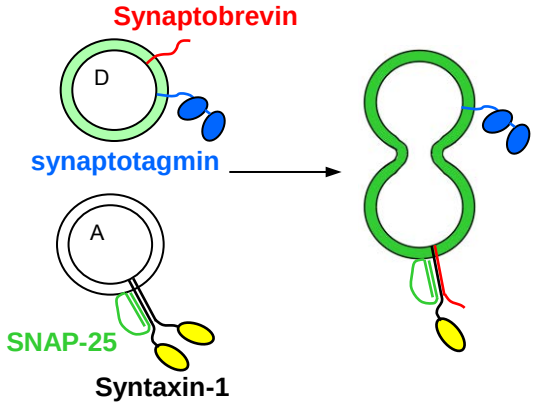


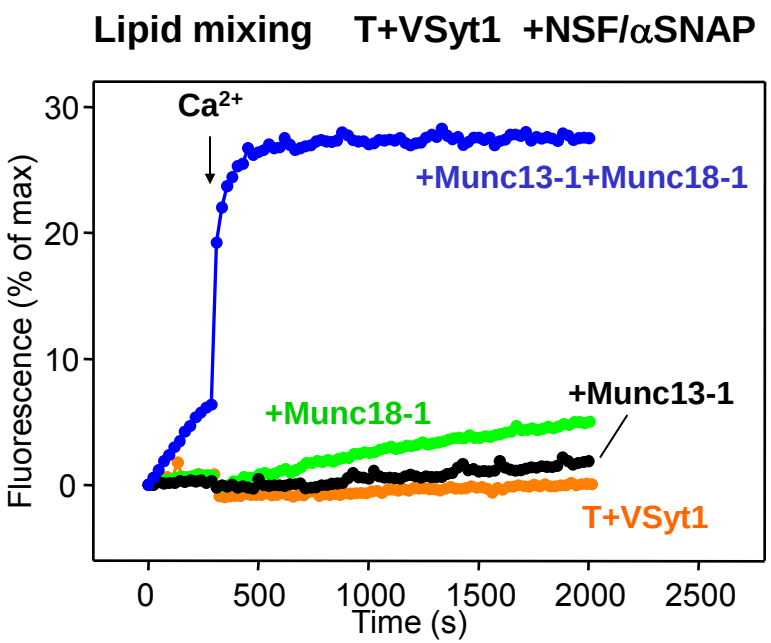


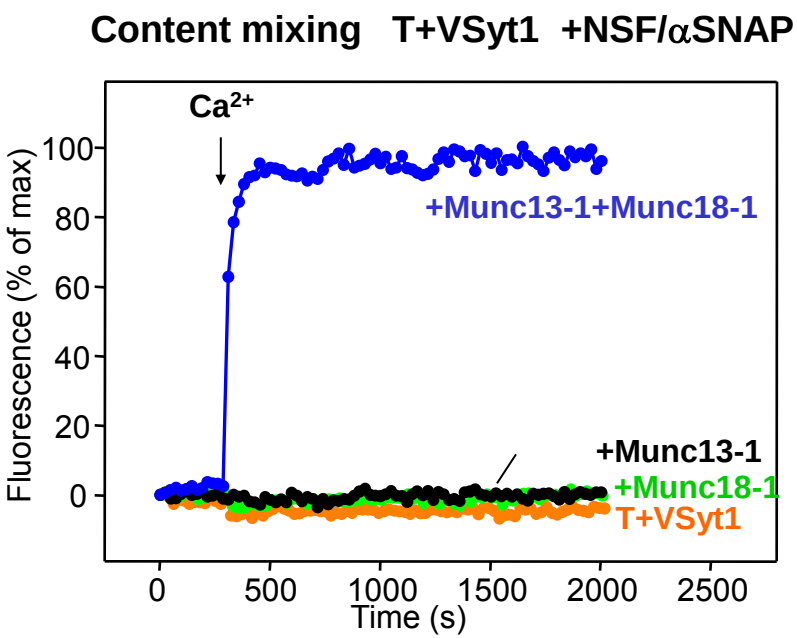
WE GOT IT!

Ma et al. Science 339, 421 (2013)

Highly efficient calcium-dependent membrane fusion supported by the SNARES, Synaptotagmin-1, Mun18-1, Munc13-1, Synaptotagmin-1 and NSF-α-SNAP

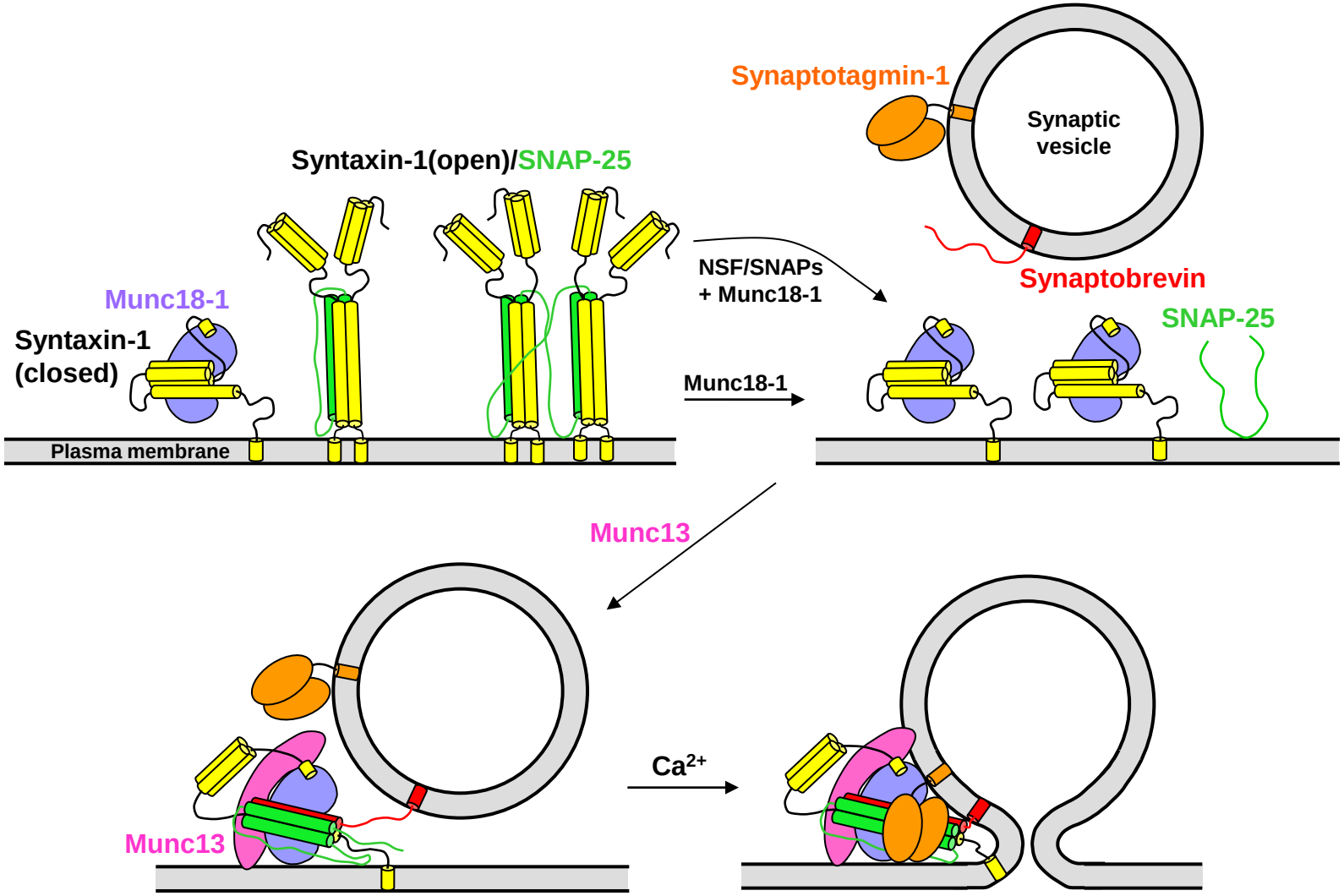






Xiaoxia Liu, Alpay Seven

Model of synaptic vesicle fusion integrating the functions of SNAREs, Munc18-1, Munc13s, NSF/SNAPs and synaptotagmin-1



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