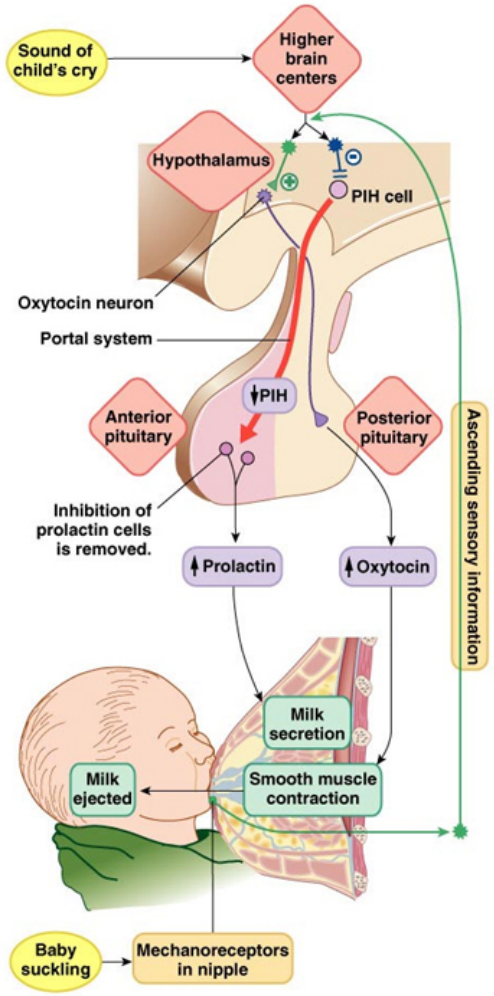
Modeling the Milk-Ejection Reflex

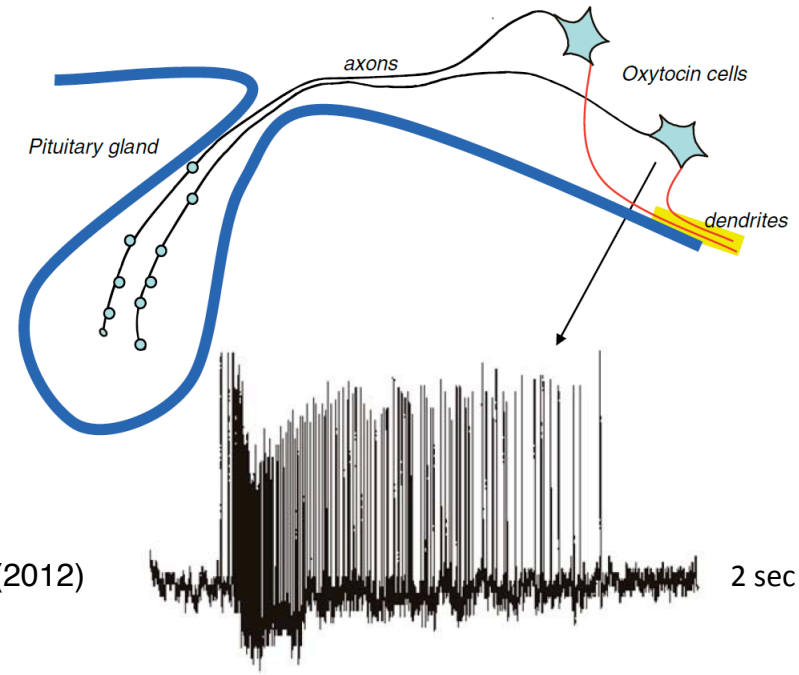
Gareth Leng and collaborators



Why the milk-ejection reflex?

- One of the best studied neuroendocrine reflex
- Good example of peptide-mediated communication between neurons
- The oxytocin (OT) neuronal network model clearly distinguishes the respective roles of cell and network properties
- The model explains paradoxical experimental observations

Milk-Ejection is triggered by synchronized bursts in OT neurons

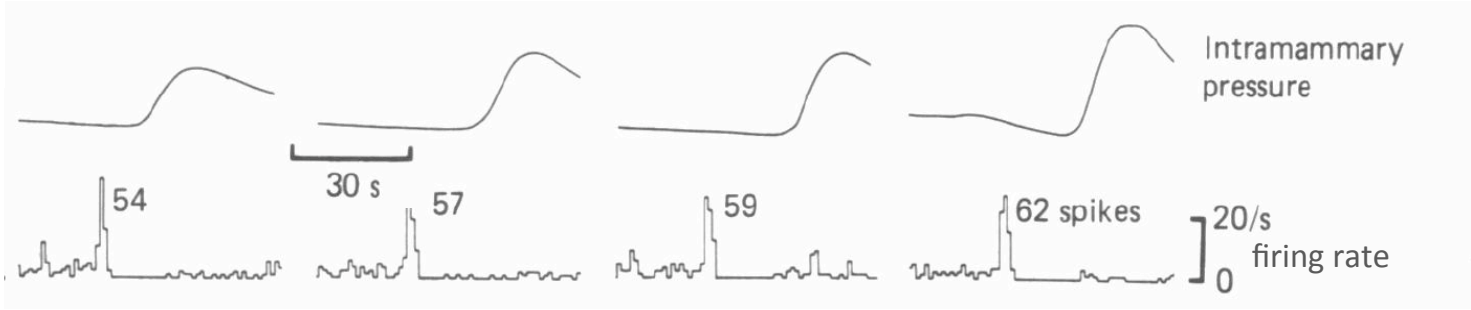


Leng and Feng (2012)

In vivo recordings – it is practically impossible to reproduce these bursts in vitro.

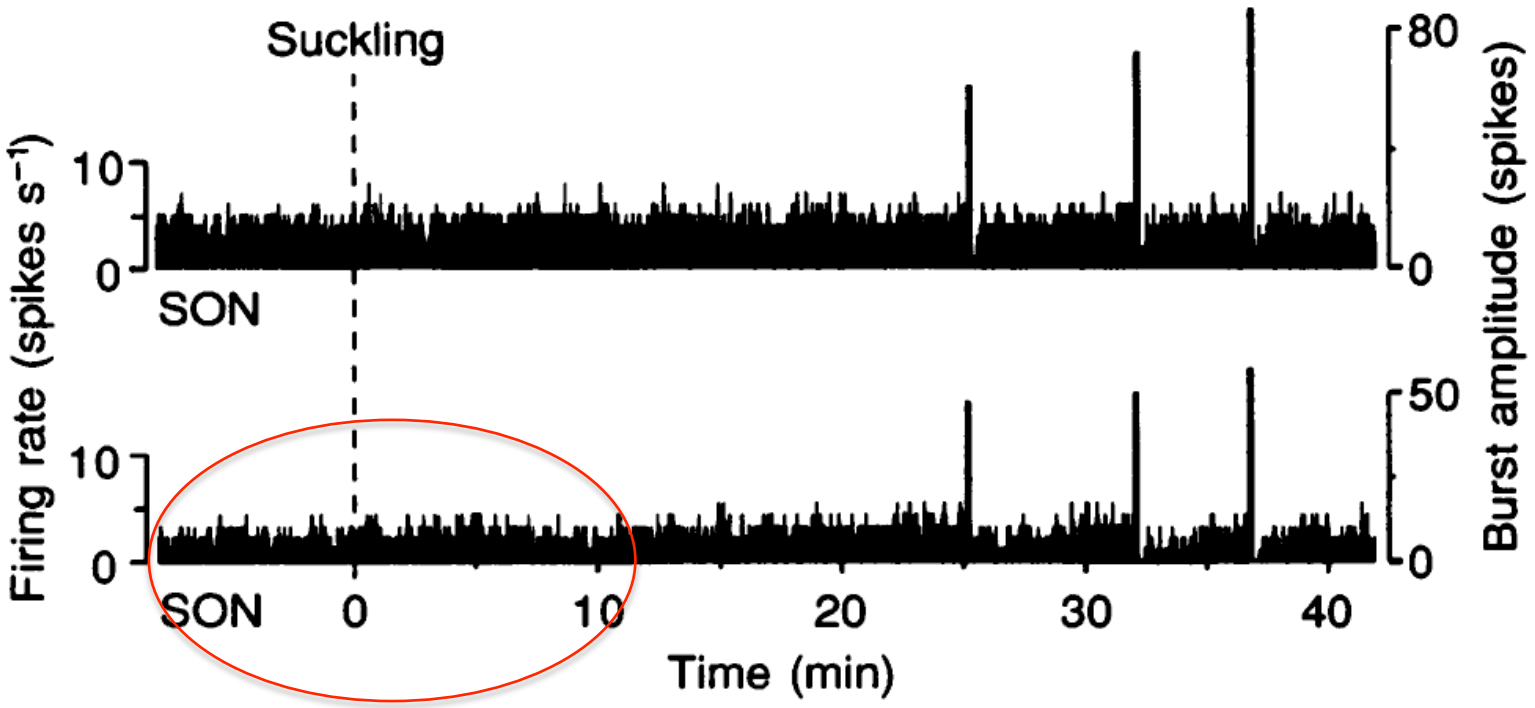
There is a period of silence following each burst

There are a few thousands OT neurons in each nucleus, so synchronized bursts create a large increase in blood OT.



Belin and Moos (1986)

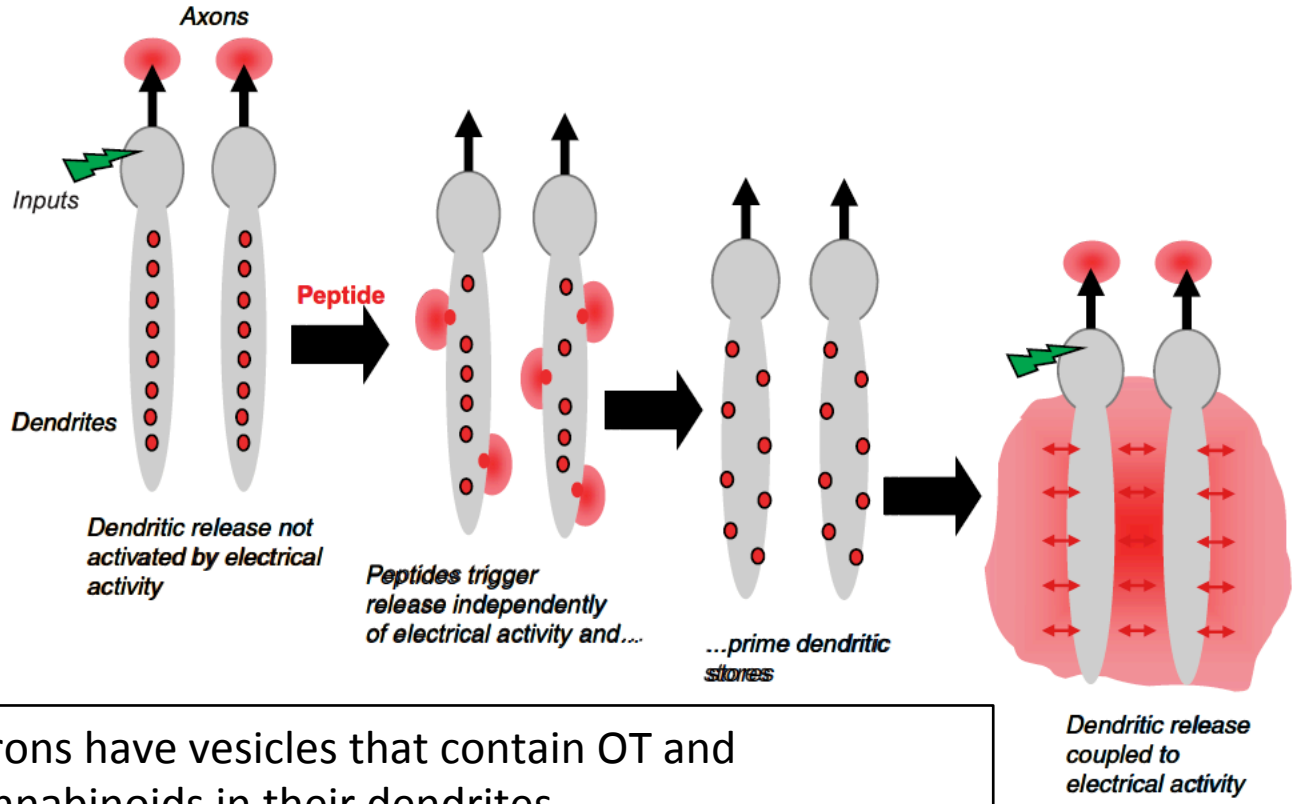
Bursts start several minutes after suckling is initiated



Brown and Moos (1997)

In the absence of suckling:
No spontaneous bursts,
Just low frequency firing, due to random synaptic inputs

What does suckling do?



Leng and Feng (2012)

OT neurons have vesicles that contain OT and endocannabinoids in their dendrites

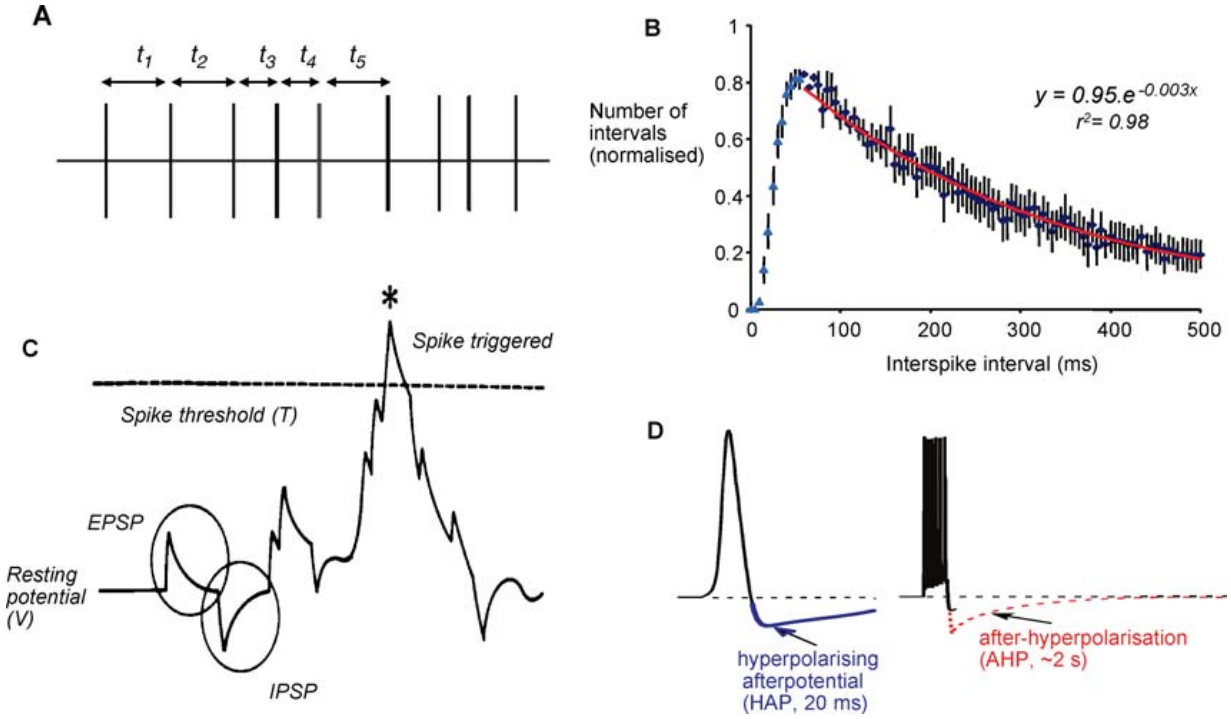
OT triggers Ca^{2+} release, release of vesicles and increases excitability

Endocannabinoids and OT suppress excitatory (glutamatergic) and inhibitory (gabaergic) inputs

Building a model of the OT network

- Cell properties:
  - Low firing rate due to synaptic noise
  - Hyperpolarizing after potential (HAP) and after hyperpolarization (AHP)
  - Single cells do not burst
- Network properties: OT neurons are connected to other OT neurons in dendritic bundles
  - OT release at the dendrite primes vesicles and increases excitability
  - endocannabinoids suppress excitatory synaptic inputs

Building a model of the OT network: cell properties

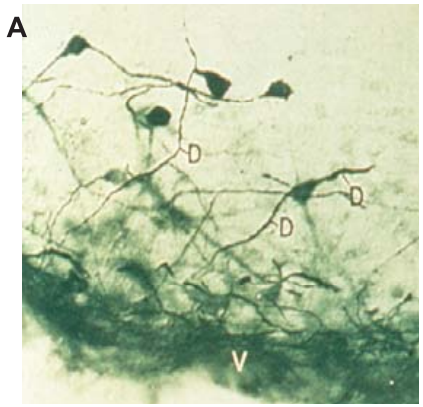


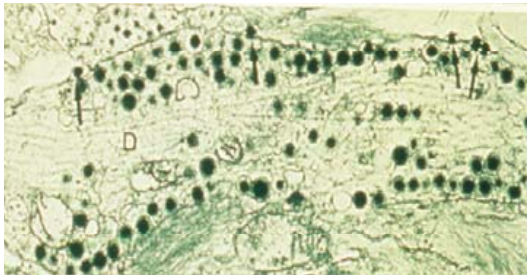
Integrate & Fire model: $$\frac{dv_i}{dt} = \frac{v_{\text{rest}} - v_i}{\tau} + \sum_{j=1}^{2} \left[a_E(v_E - v_i) \frac{dN^j_{E,i}}{dt} - a_I(v_i - v_I) \frac{dN^j_{I,i}}{dt} \right]$$

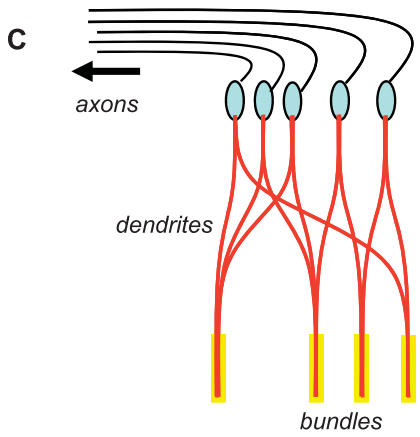
HAP and AHP transiently increase spike threshold T; OT release decreases threshold

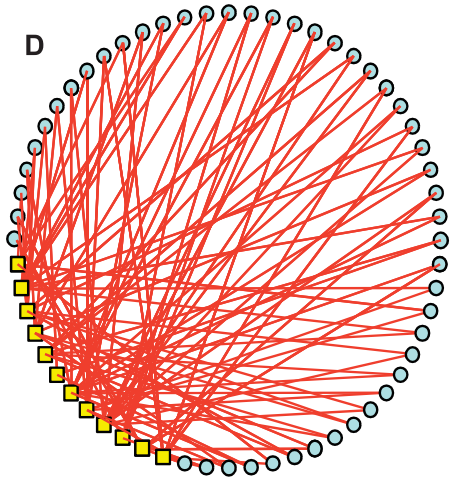
Parameters are adjusted to match the distribution of interspike intervals

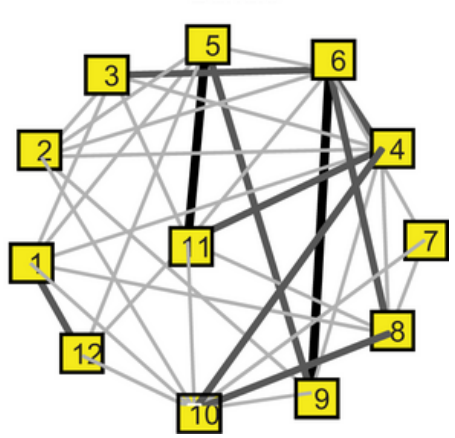
Building a model of the OT network: connectivity











Rossoni et al (2008)
Leng and Feng (2012)

48 cells (up to 3000), 2 dendrites per cell, **8** dendrites per bundle
➔12 dendritic bundles

Building a model of the OT network: dendritic release

$$\frac{dr_i^j}{dt} = -\frac{r_i^j}{\tau_r} + k_p(t) - p_i^j(t)$$

$r^j_i(t)$ releasable pool of vesicles for dendrite j of cell i; increased by priming due to suckling $k_p(t)$; decreased by release $p^j_i(t)$

$$p_i^j(t) = k_r r_i^j(t) \sum \delta(t - t_i^s - \Delta)$$

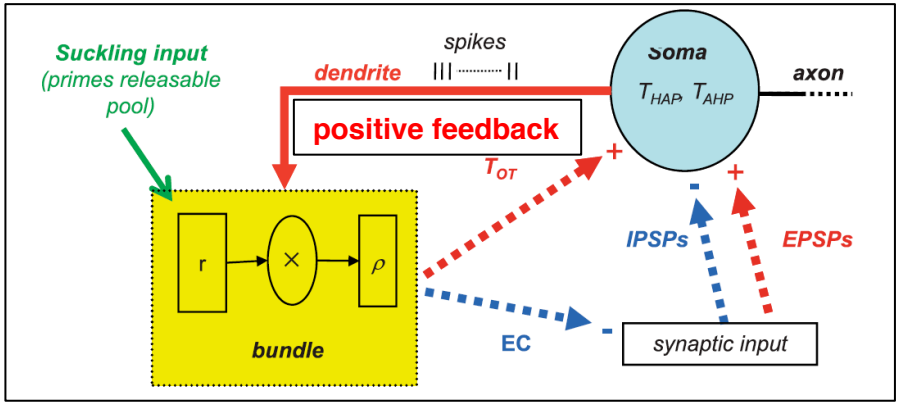
Release $p^j_i(t)$ from dendrite j of cell i due to spiking; Only when spikes are separated by less that t^s=50 ms

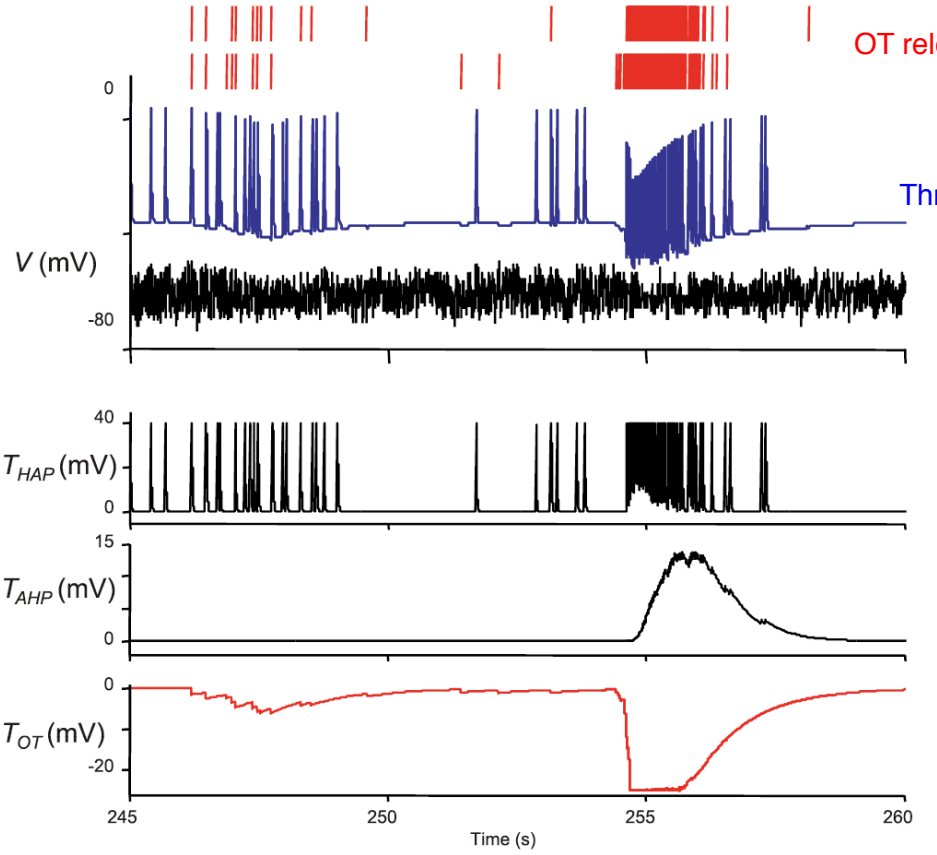
$$\frac{dT_{OT,i}}{dt} = -\frac{T_{OT,i}}{\tau_{OT}} + k_{OT} \sum_{k=1}^{n_b} \sum_{j=1}^{n} \sum_{l,m=1}^{2} c_{il}^k c_{jm}^k p_j^m(t)$$

OT released by all dendrites sharing the same bundles decreases spike threshold T_i of cell i by $T_{OT,i}$

Finally, endocannabinoids decrease the rates of synaptic inputs on the dendrites that feel vesicle release $p^j_i(t)$

The structure and activity of a single model neuron



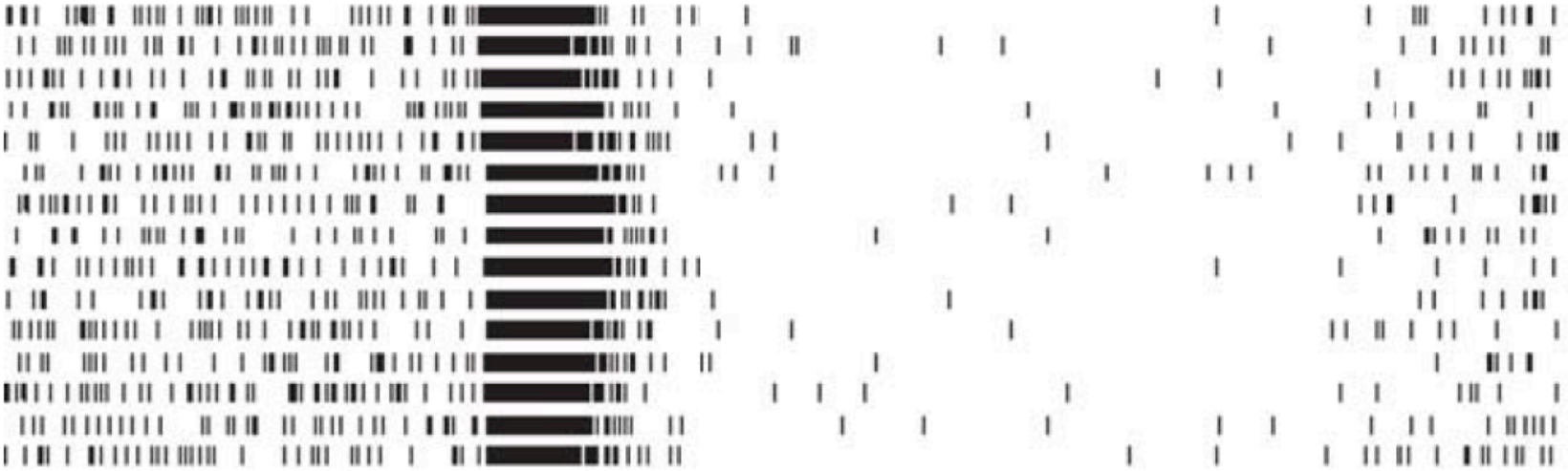


Name	Description	Value	Units
N	Number of cells	48	
n_b	Number of bundles	12	
τ	Membrane time constant	10.8	ms
v_{rest}	Resting potential	−62	mV
$a_E(v_E - v_{rest})$	EPSP amplitude	4	mV
$a_I(v_{rest} - v_I)$	IPSP amplitude	4	mV
v_E	EPSP reversal potential	0	mV
v_I	IPSP reversal potential	−80	mV
$\bar{\lambda}_E$	Excitatory input rate	80	Hz
$\bar{\lambda}_I$	Inhibitory input rate	80	Hz
k_{HAP}	HAP, maximum amplitude	40	mV
τ_{HAP}	HAP, decay time constant	12.5	Ms
k_{AHP}	AHP, maximum amplitude	40	mV
τ_{AHP}	AHP, time constant	2	s
f_{th}	AHP, half-activation constant	45	a.u.
τ_{OT}	Time decay of oxytocin-induced depolarization	1	s
k_{OT}	Depolarization for unitary oxytocin release	0.5	mV
Δ	Time delay for oxytocin release	5	ms
$T_{OT,\ max}$	Maximum oxytocin-induced depolarization	25	mV
k_p	Priming rate	0.5	s^{-1}
τ_r	Time constant for priming	400	s
k_r	Fraction of dendritic stores released per spike (max)	0.045	
τ_{EC}	Time constant for [EC] decay	6	s
k_{EC}	Endocannabinoid increase per unit oxytocin release	0.0025	a.u.
ε_{th}	[EC] threshold for synaptic attenuation	0.03	a.u.
τ_{rel}	Maximum interspike interval for release	50	ms
α	Fractional attenuation of synaptic input rate (max)	0.6	

doi:10.1371/journal.pcbi.1000123.t001

Rossoni E, Feng J, Tirozzi B, Brown D, et al. (2008) Emergent Synchronous Bursting of Oxytocin Neuronal Network. PLoS Comput Biol 4(7): e1000123. doi:10.1371/journal.pcbi.1000123
http://www.ploscompbiol.org/article/info:doi/10.1371/journal.pcbi.1000123

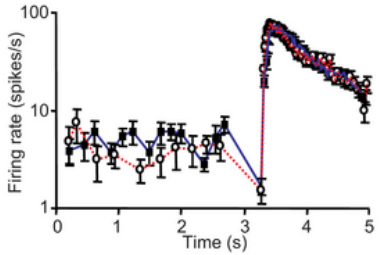
The network model generates synchronized bursts



Asynchronous activity

Pause in asynchronous activity just after a burst

Bursts are triggered randomly



Slight decrease in spike frequency before a burst in both model cell and real cell

Role of the different cell properties (negative feedback)

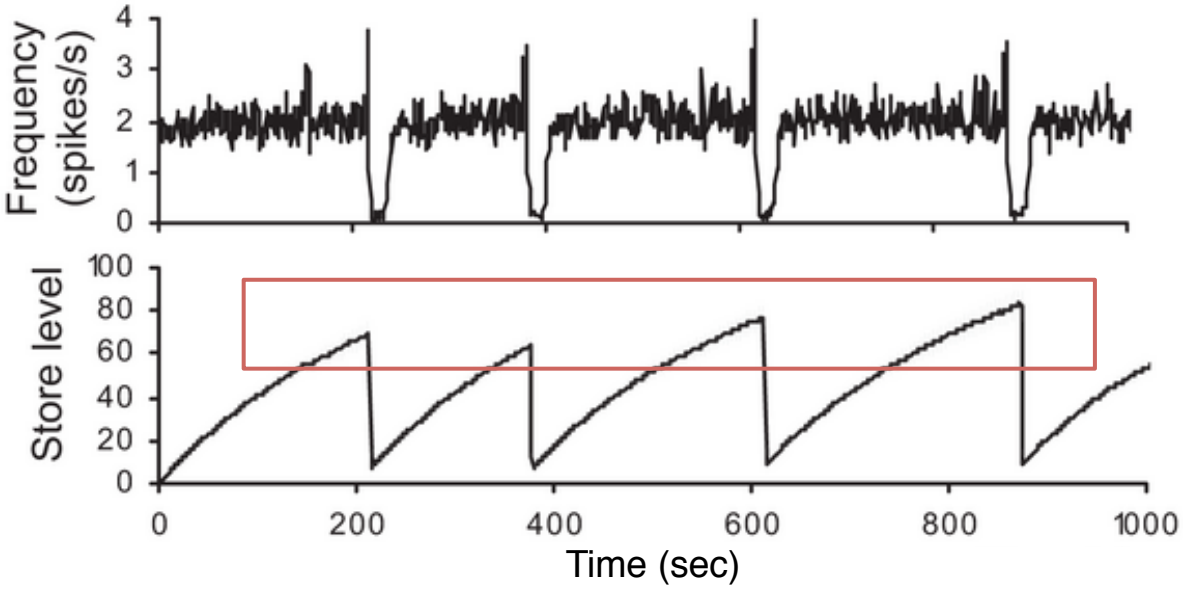
- Endocannabinoids: Responsible for the pause in firing after bursts and the slight decrease in firing before bursts. **Prevent over-excitation.**

- HAP: Very transient effect after each spike, set to match interspike intervals between bursts – it affects burst timing by limiting the occurrence of short interspike intervals.

- AHP: Shapes bursts by decreasing peak firing rate and shortening burst duration – but **removing AHP has little effect on burst timing.**

What terminates the bursts?

Bursts are terminated by store depletion



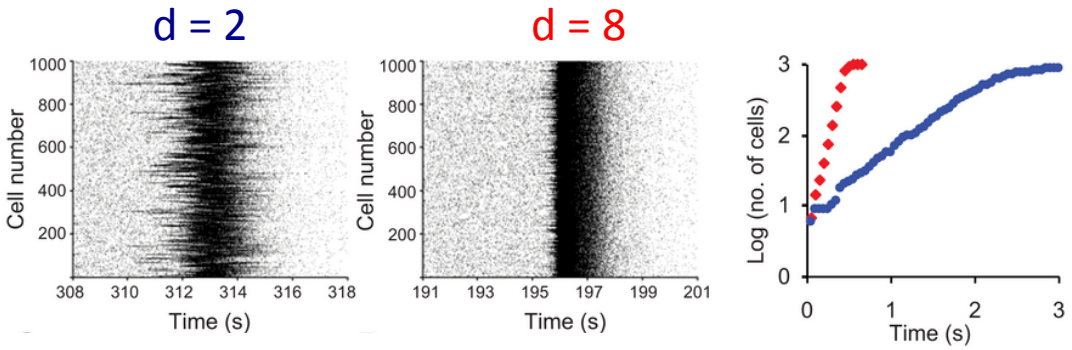
$$\frac{dr_i^j}{dt} = -\frac{r_i^j}{\tau_r} + k_p(t) - p_i^j(t)$$

Burst onset time is stochastic

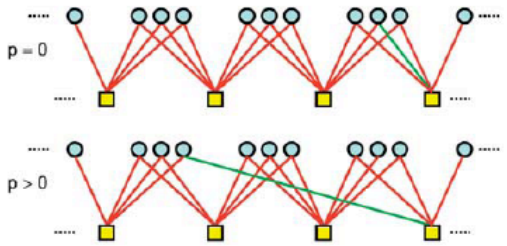
Burst onset location is also random and varies from burst to burst

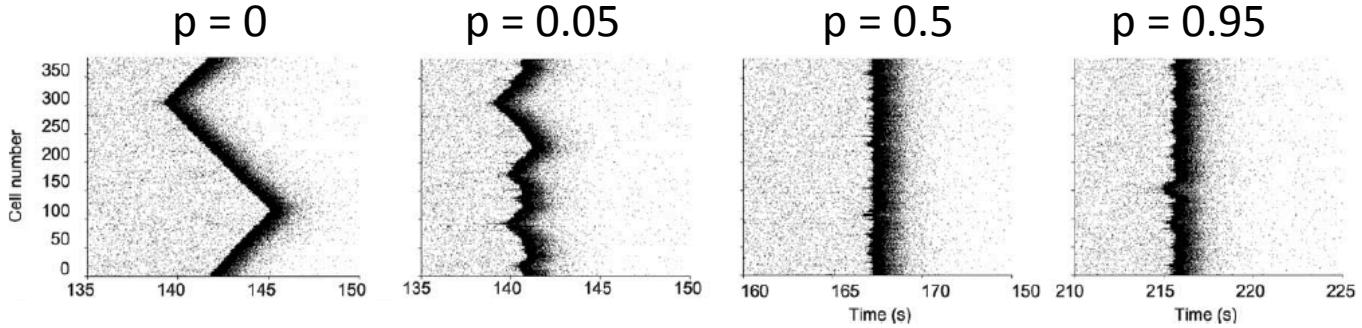
Connectivity affect burst synchronization

More dendrites per bundle improves neuron synchronization during bursts



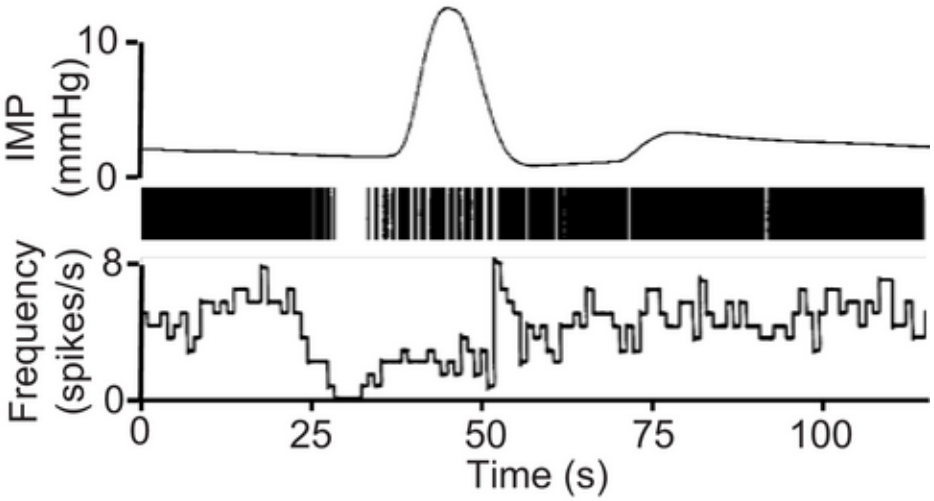
Long range connections are crucial for synchronization

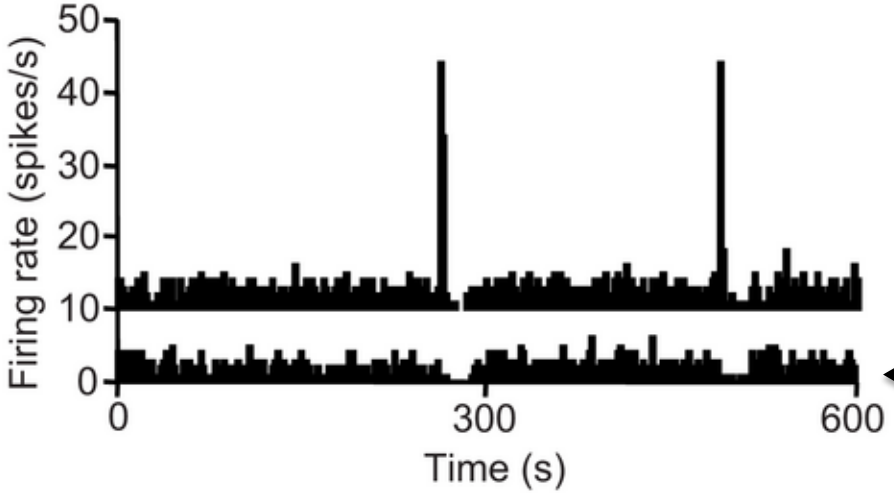




The model explains experimental observations

Non-bursting cells also exhibit pause after a network burst

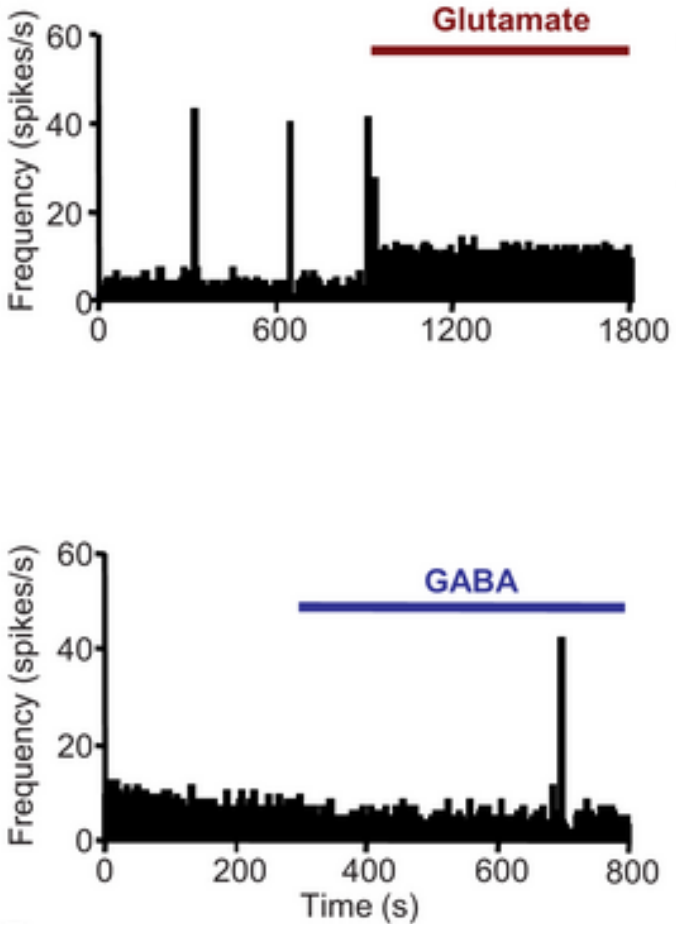




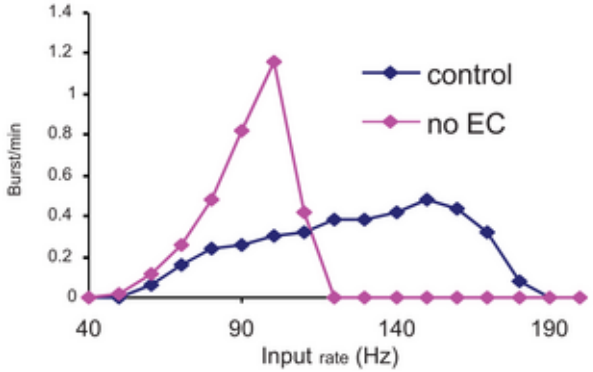
no OT receptors

The model explains paradoxical observations

Increased excitatory drive suppresses bursts
Decreased inhibitory drive triggers bursts



Endocannabinoids increase the max input rate for bursting



Take home points

- Bursting of OT neurons induced by suckling is an emergent network property
- Clear explanation of the respective roles of cell properties (HAP, AHP, …) and network properties
- Dendritic release and peptidergic transmission have the leading role, synaptic connections have a supporting role
- The model explains paradoxical observations