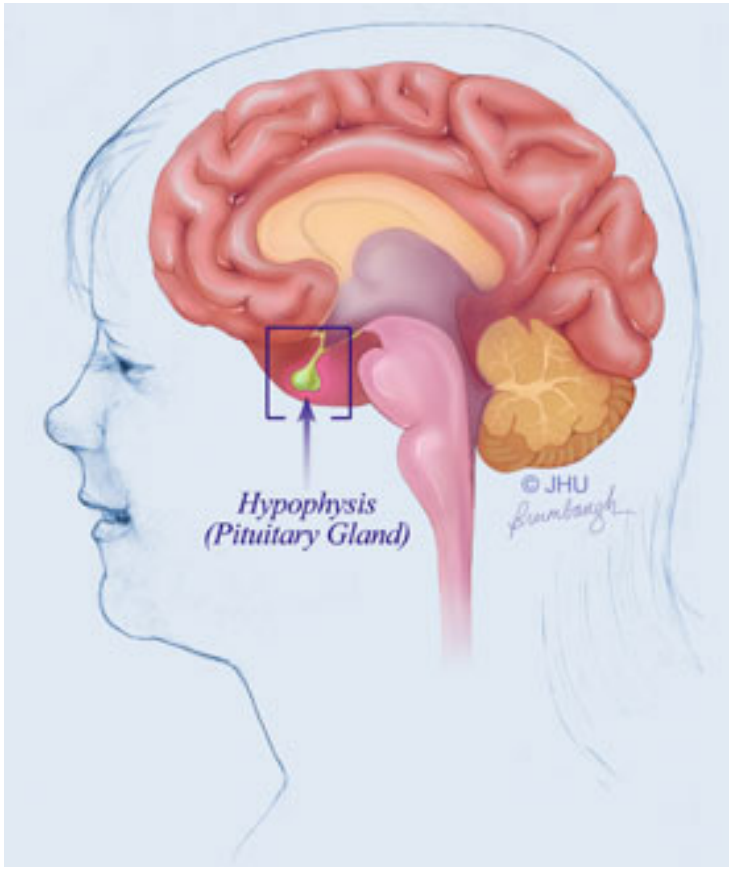
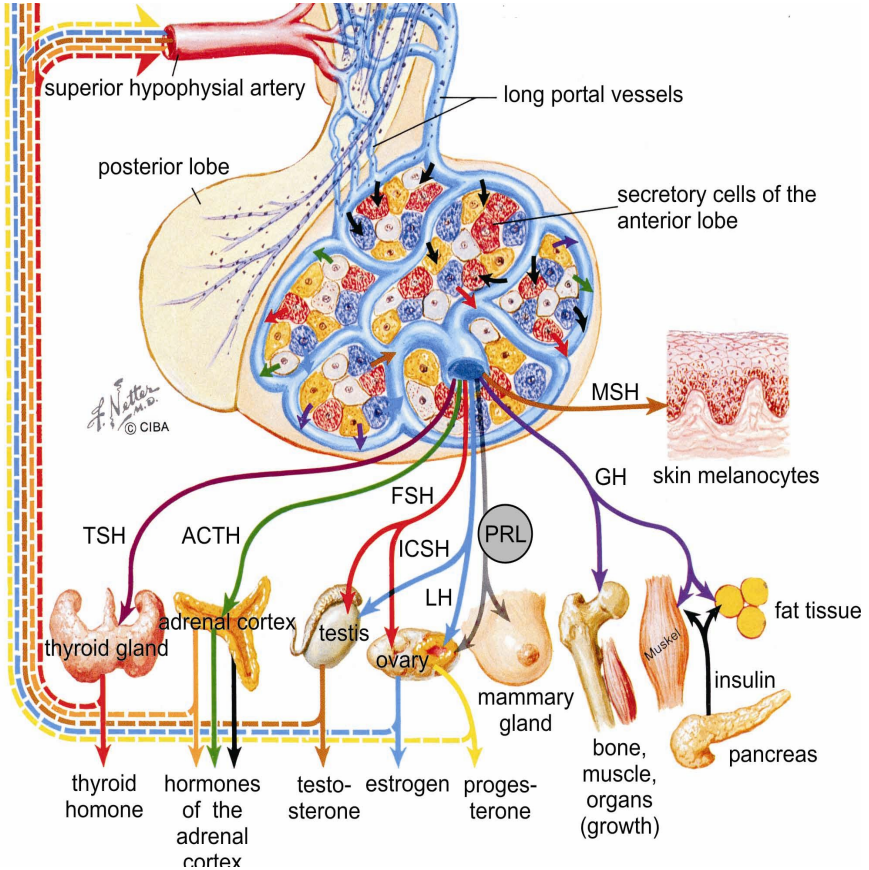
BK channels promote bursting in pituitary cells

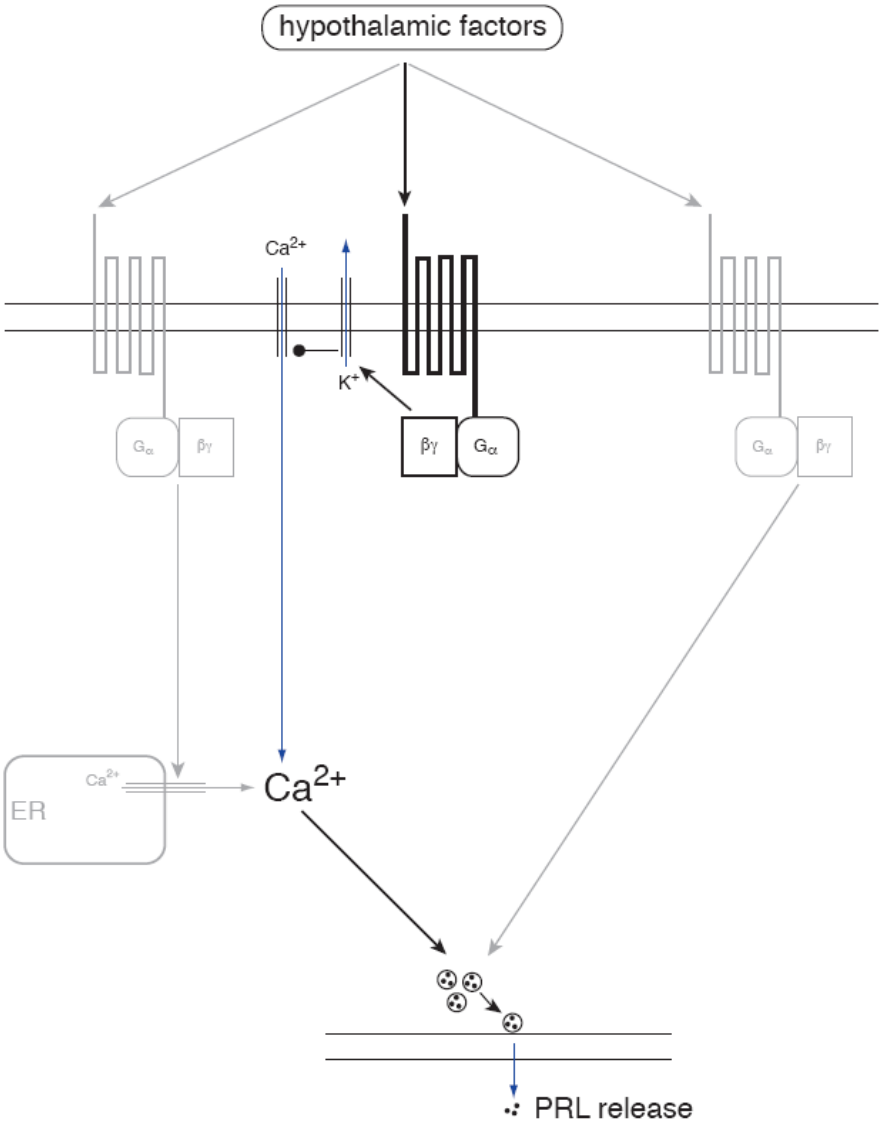
1) Background on pituitary cells and BK channels
2) Experimental evidence and its problems
3) Modeling evidence and its problems
4) Using the dynamic clamp to prove the point

The anterior pituitary gland

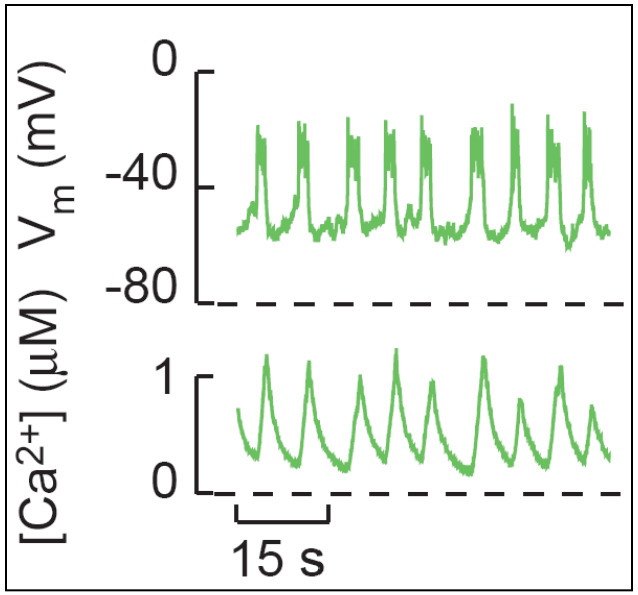




Calcium influx induces hormone secretion

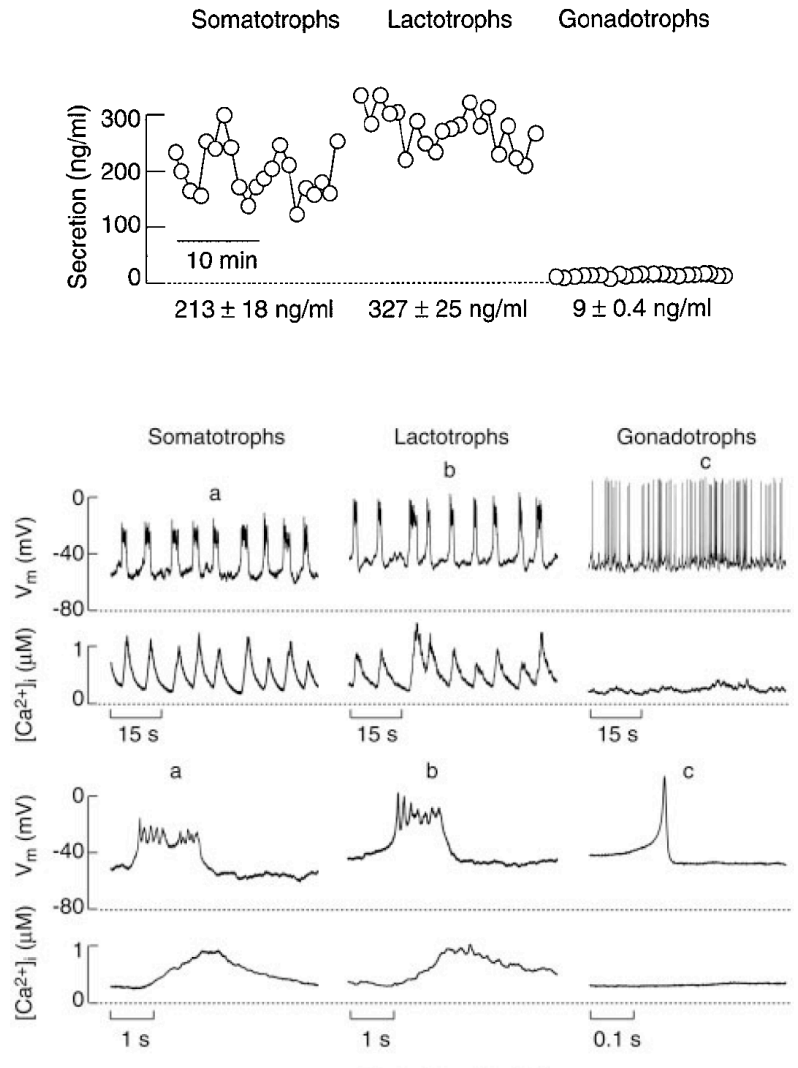


spontaneous bursts
induce calcium influx



(from Stojilkovic et al 2005)

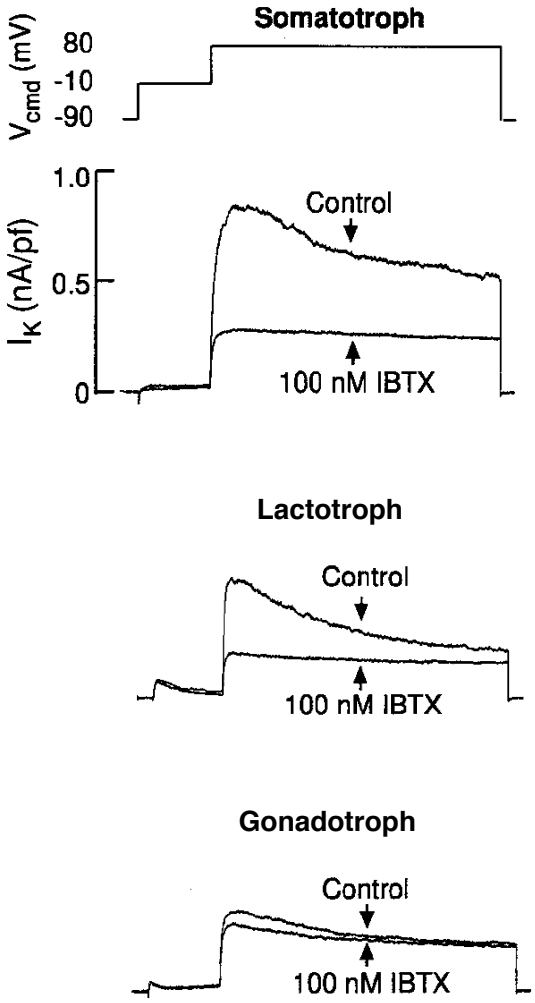
Pituitary cells differ in their basal activity



Why are gonadotrophs different?

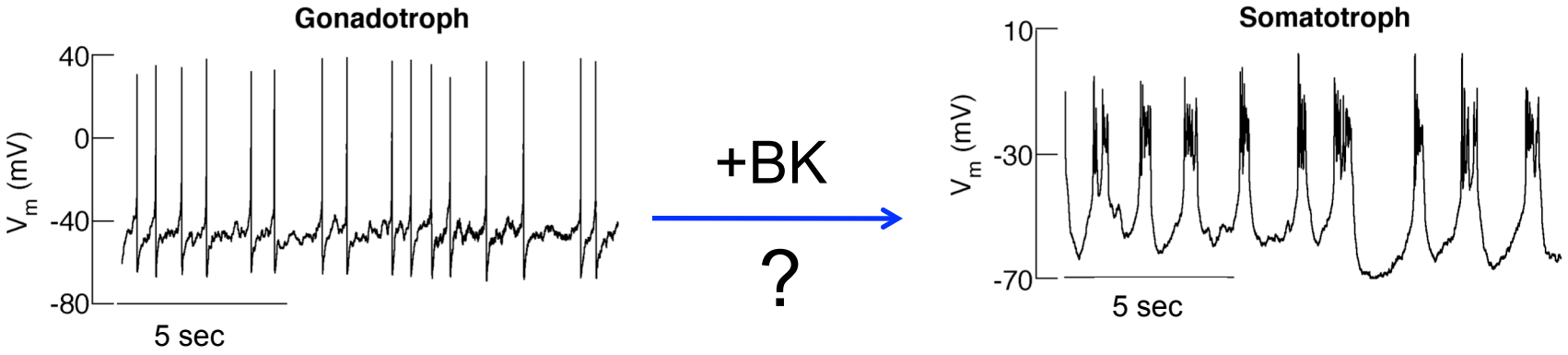
Van Goor et al (2001a)

Gonadotrophs lack large potassium (BK) current



Van Goor et al (2001b)

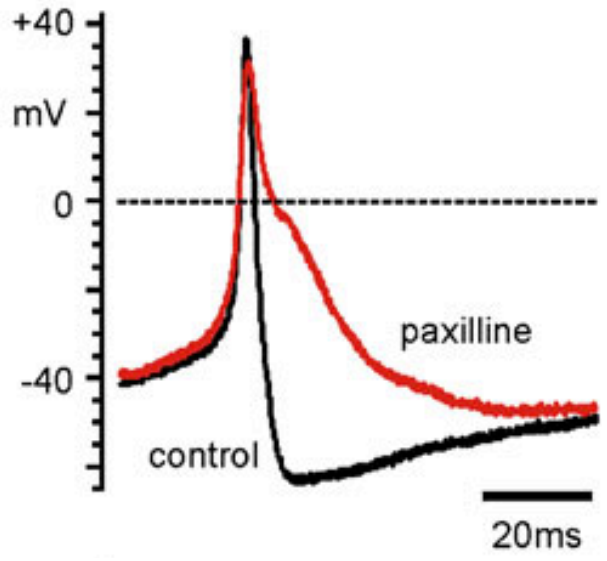
Can the difference in electrical activity be explained by differences in BK channel expression?



BK channels usually have an opposite effect

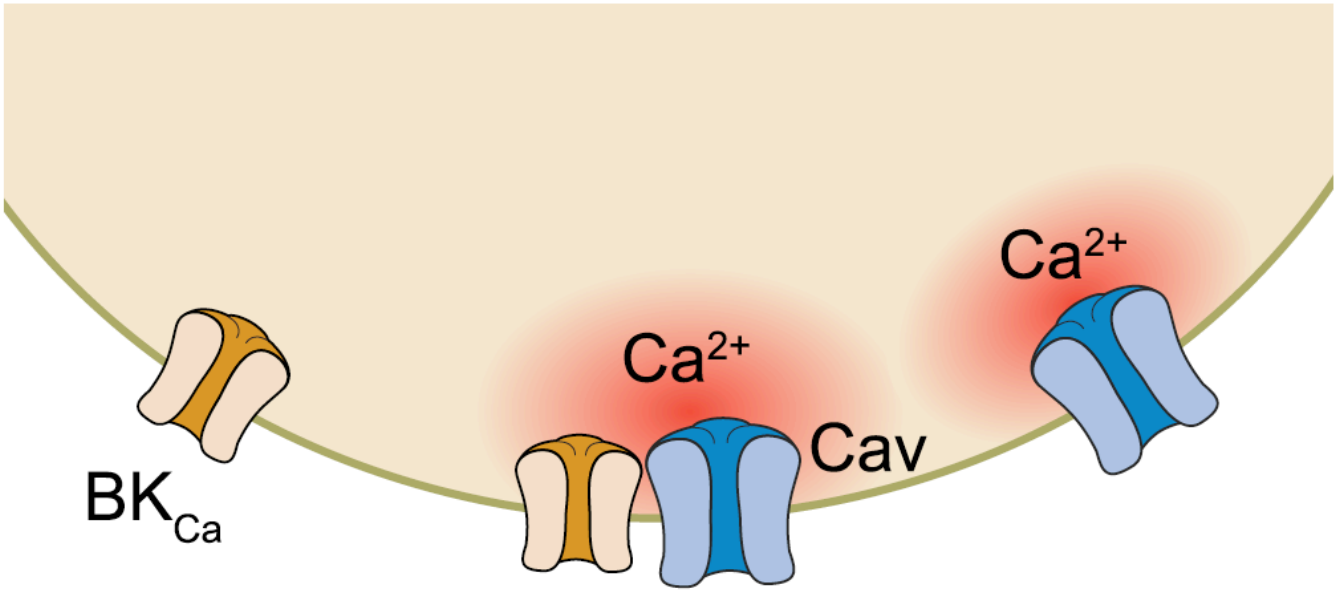
BK channels

- Large conductance (B = Big)
- Calcium- and voltage-dependent
- Activated by inhibitory hormones



Rat chromaffin cells
(Vandael et al 2010)

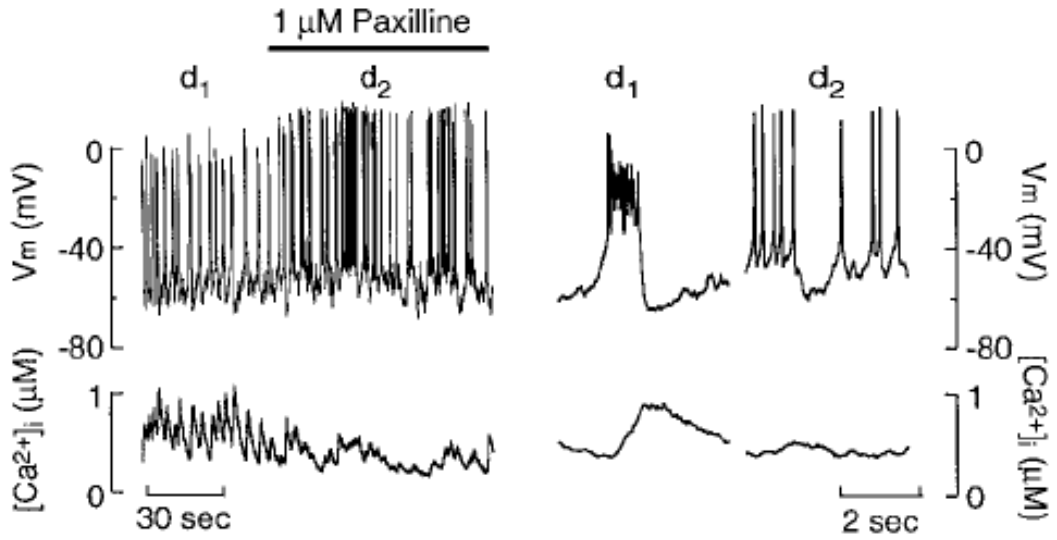
BK channels can associate with Ca^{2+} channels to produce fast activating outward current



Berkefeld et al (2010)

Blocking BK channels switches the activity pattern from bursting to spiking

Somatotroph recordings

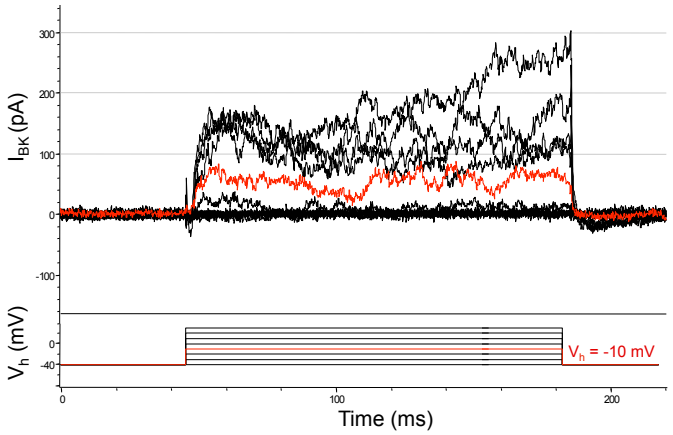


Van Goor et al (2001c)

Problems with blocking experiments

- Blocking a channel can change the system
- BK channels may be necessary for bursting -- but what do they do?
- Which BK channels promote bursting?

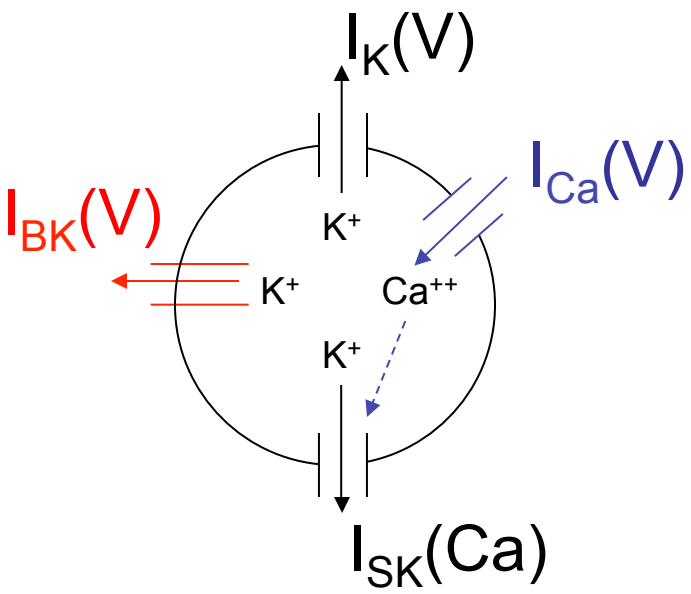
BK current



Transition to spiking after BK block :

Due to block of fast (V-dependent) component
or
block of slow (Ca-dependent) component?

Lactotroph model



$$C\frac{dV}{dt} = g_{Ca}m_\infty(V)(V_{Ca} - V) + g_K n(V_K - V) + g_{SK}\frac{[Ca]^2}{[Ca]^2 + k^2}(V_K - V) - I_{BK}$$

$$\tau_n \frac{dn}{dt} = n_\infty(V) - n$$

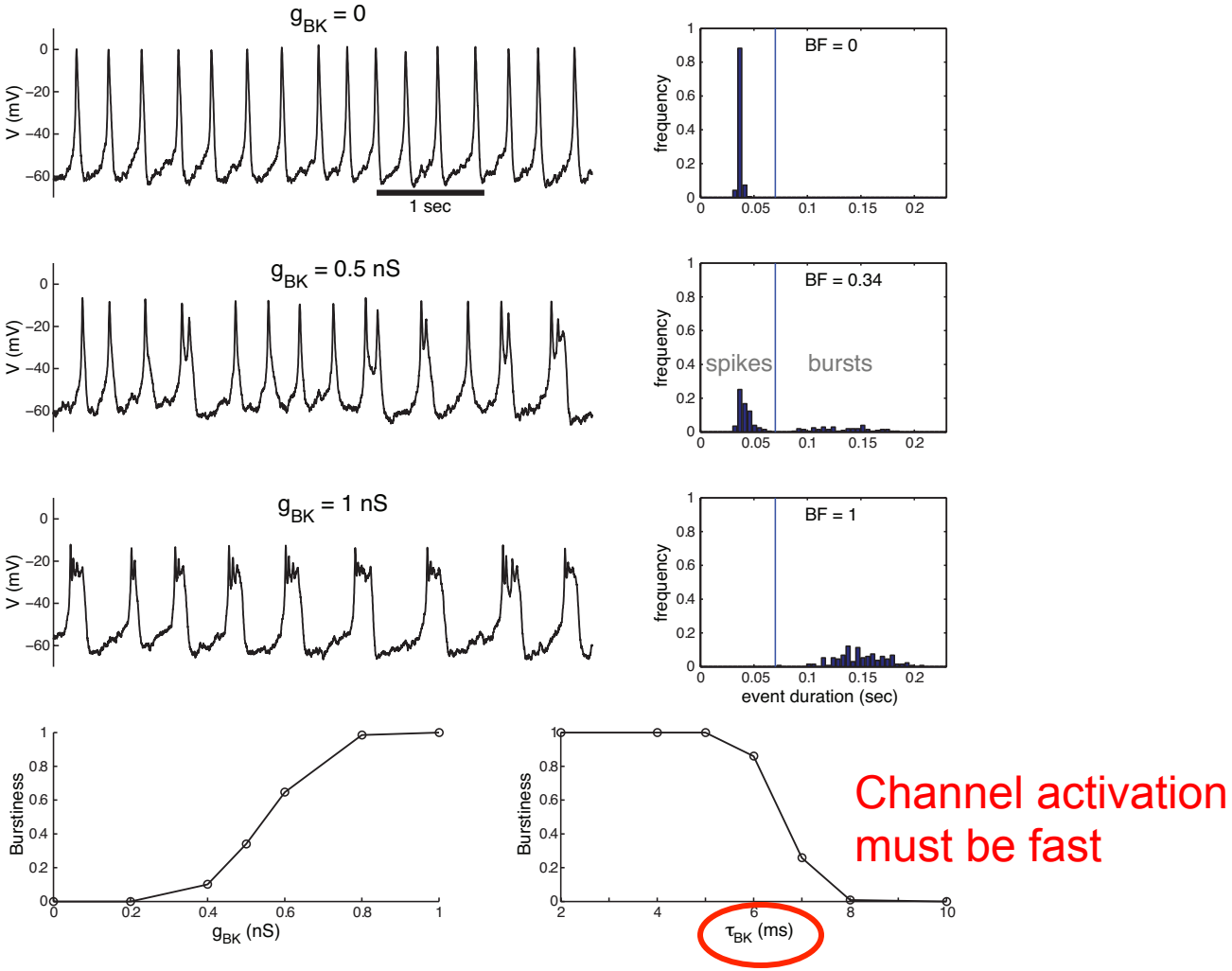
$$\tau_{Ca}\frac{d[Ca]}{dt} = -(\alpha I_{Ca} + k_c[Ca])$$

$I_K(V)$ kinetics (τ_n) chosen so that the model is spiking

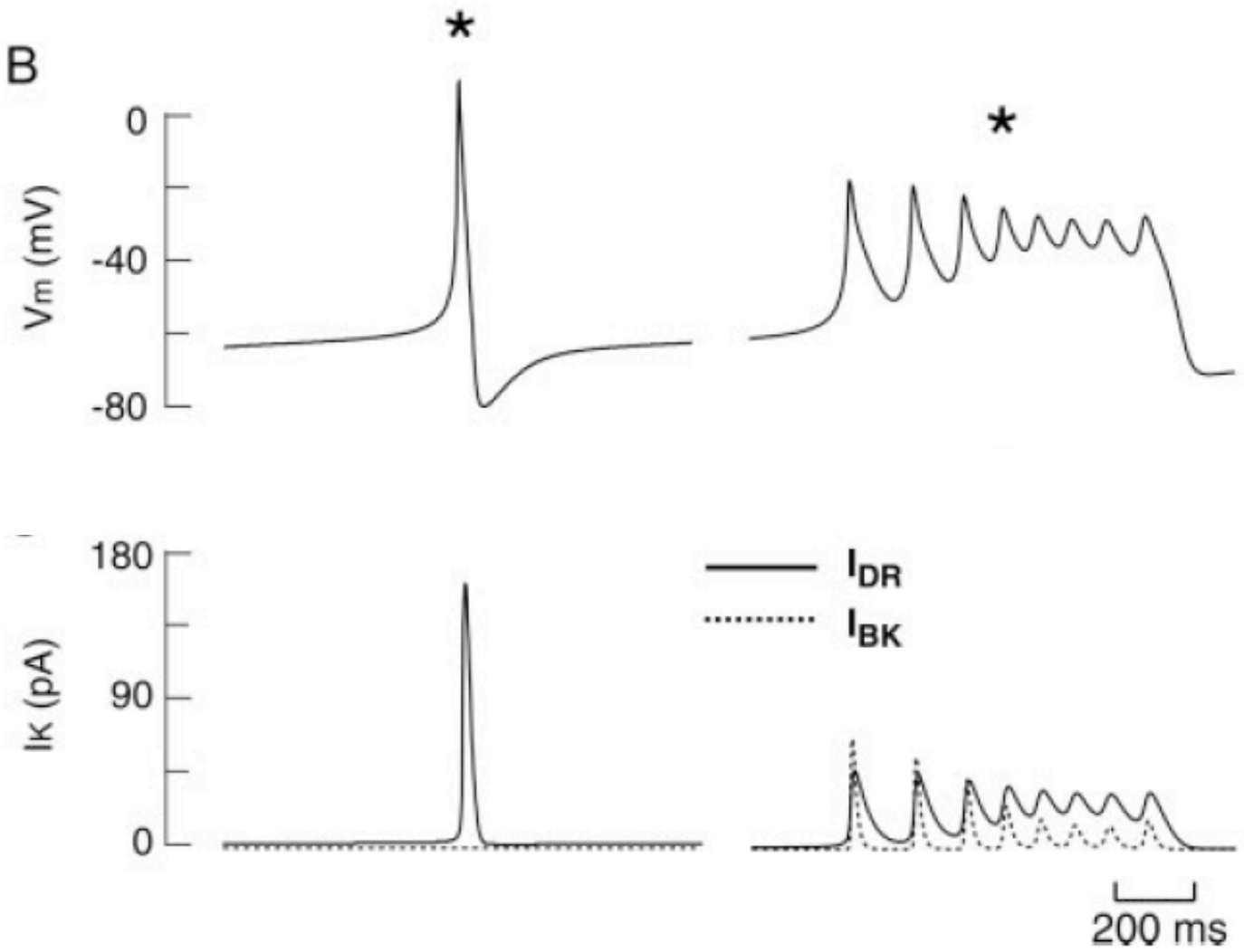
$$I_{BK}(V) = g_{BK} f\ (V - V_K)$$

→ bursting?

BK channels change the activity pattern of a pituitary cell model from spiking to bursting



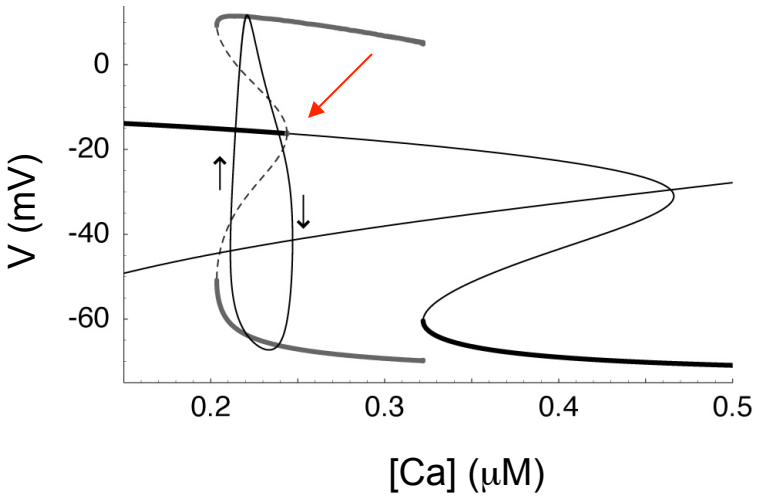
Channel activation must be fast


B
*
*
0
-40
-80
Vm (mV)
180
90
0
IK (pA)
IDR
IBK
200 ms

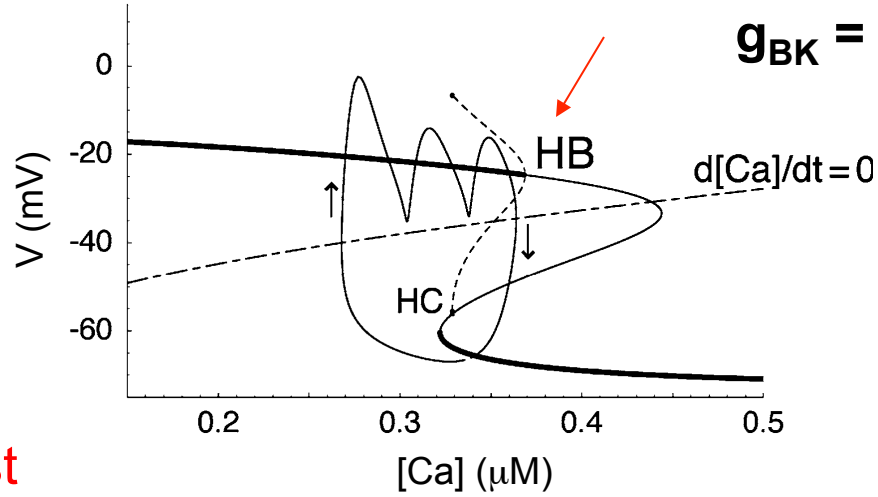
I_{BK} promotes "depolarization block"

fast/slow analysis

V, n fast
[Ca] slow



$g_{BK} = 0$



$g_{BK} = 0.4$ nS

This explains why BK activation must be fast

Problems with the model

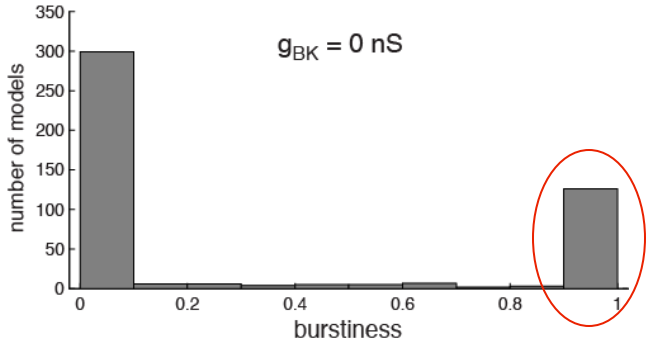
BK channels change activity from spiking to bursting in THIS model.

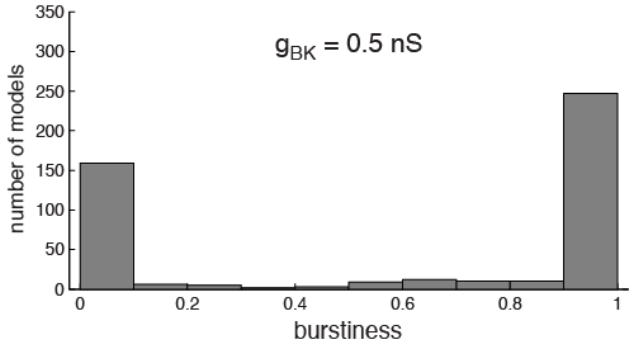
What if we use different parameters or include a more realistic set of channels?

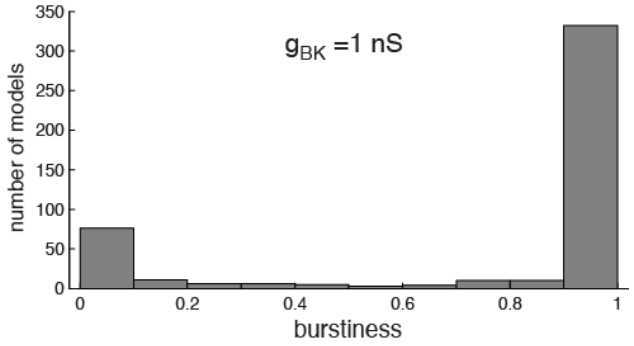
Nevertheless the model makes an important prediction: BK channel activation must be fast

BK channels have a robust burst promoting effect on pituitary cell models

512 models
± 50% variations in parameter values

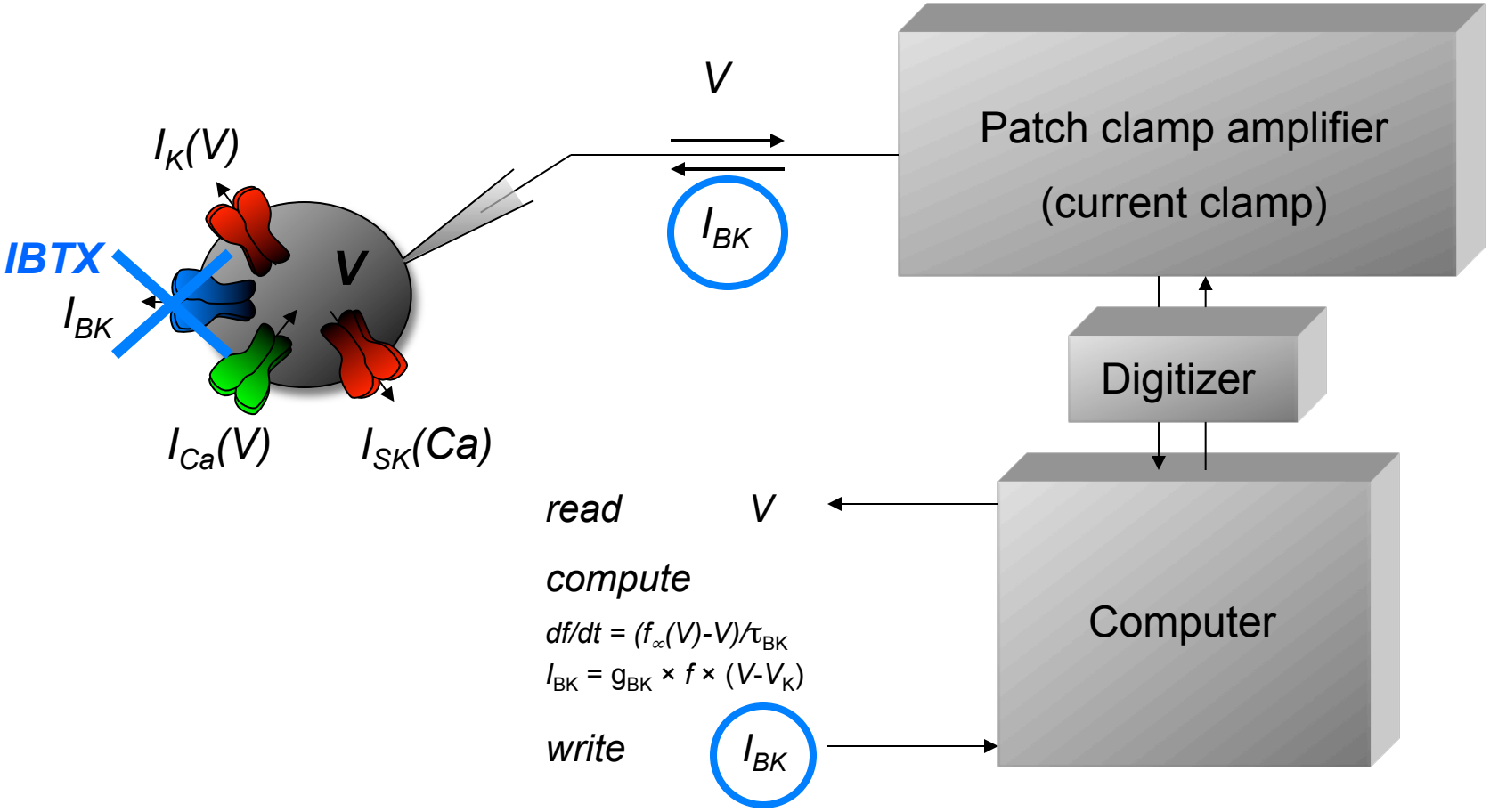






but BK channels are not necessary for bursting

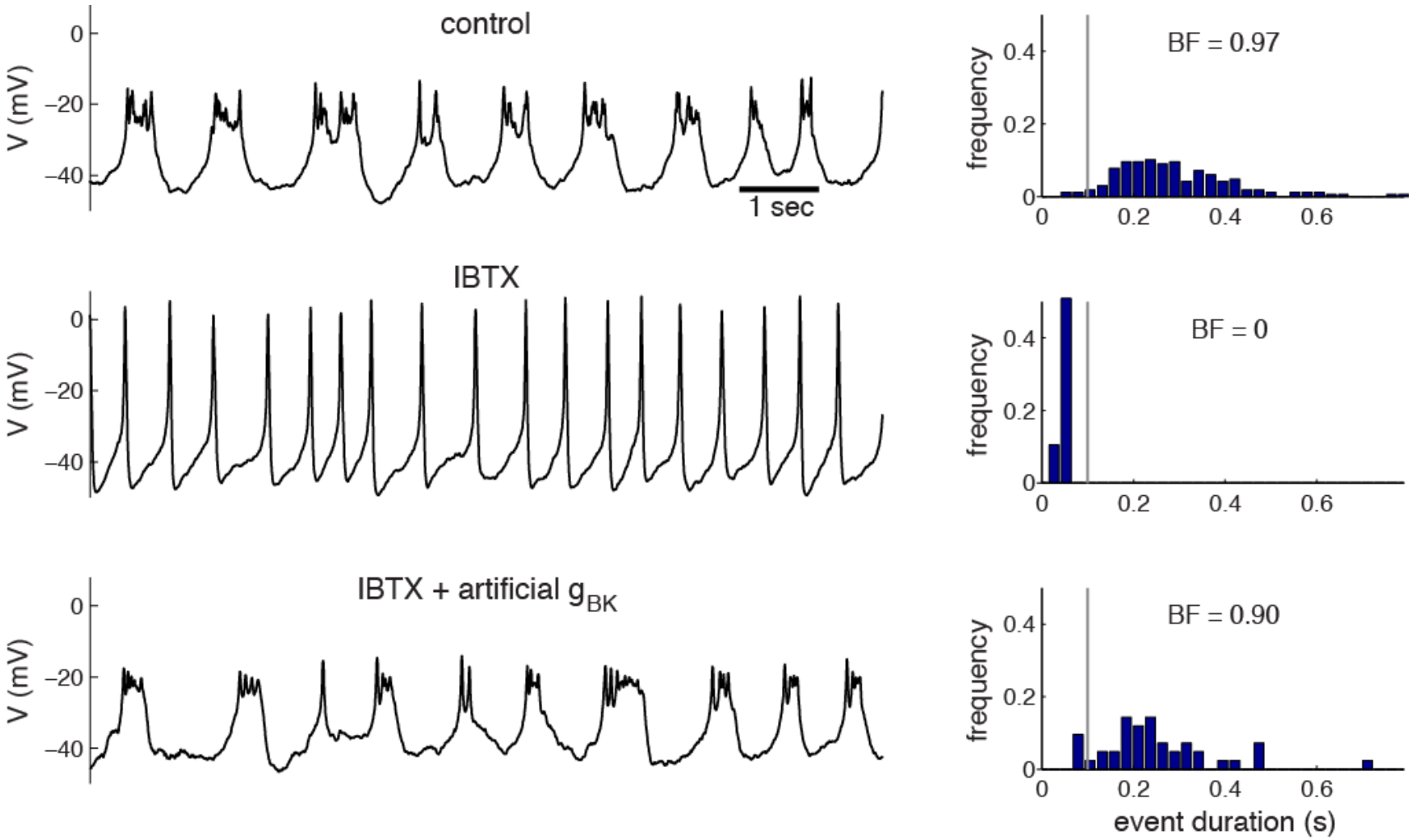
Dynamic clamp: one small step for a setup, one giant leap forward for electrophysiology



Original concept : Sharp et al 1993

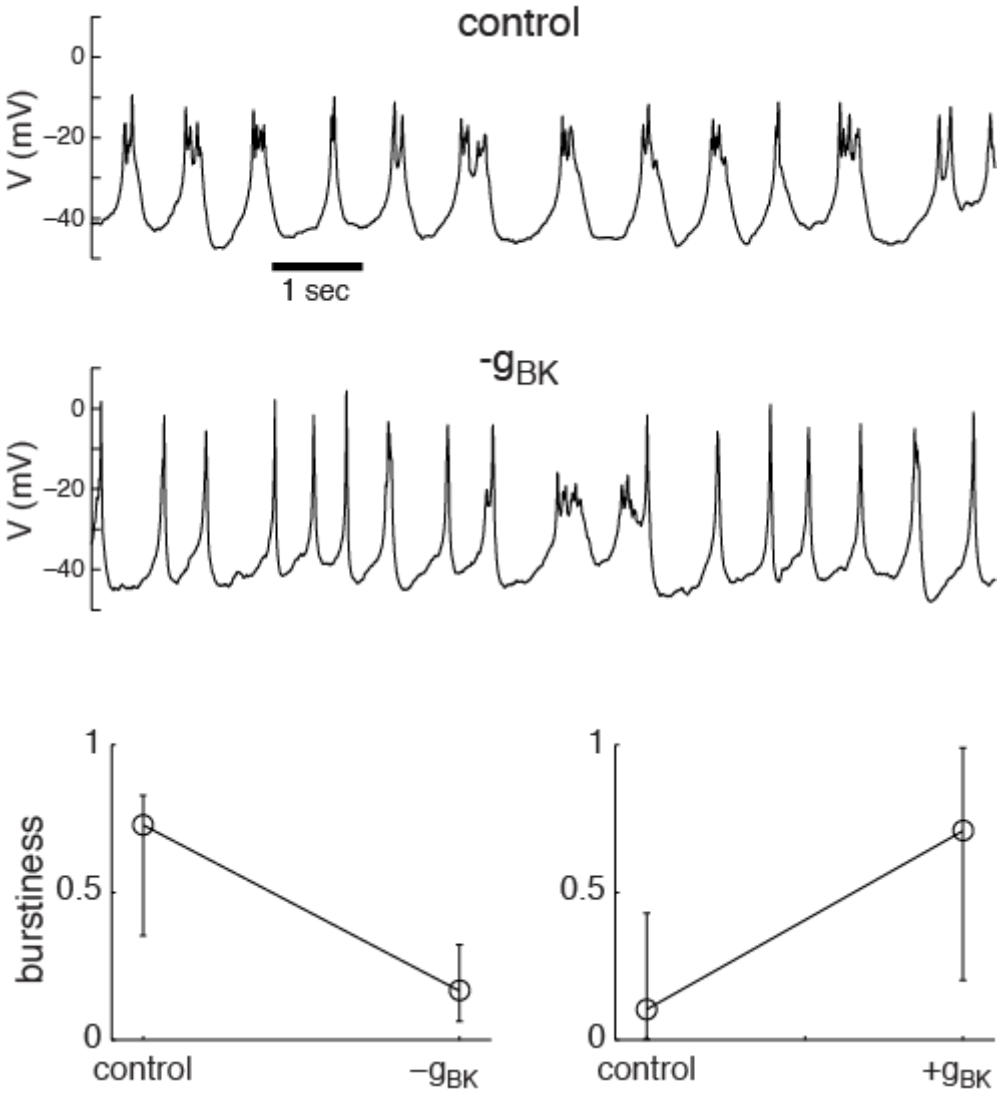
Implementation : **QuB** (Milescu et al 2008)

Adding back $I_{BK}(V)$ with dynamic clamp restores bursting

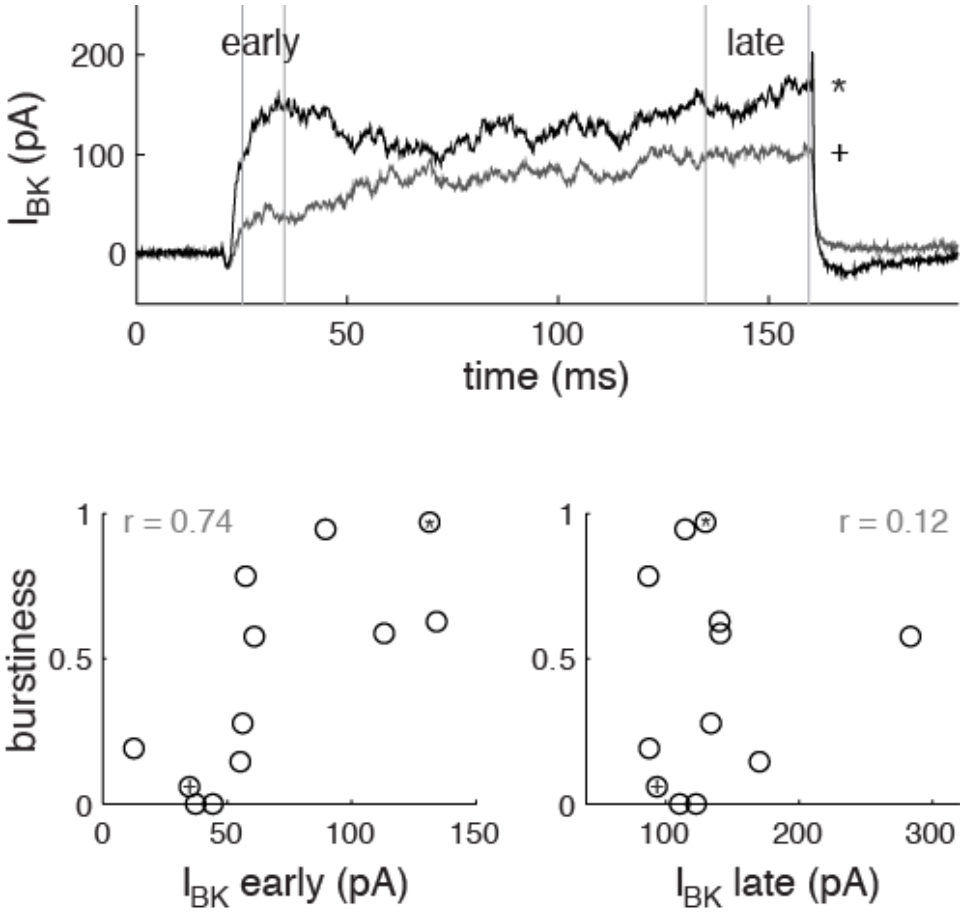


GH4 cells (lacto-somatotroph cell line)
Perforated patch
BK block decreases burstiness in 11/13 cells

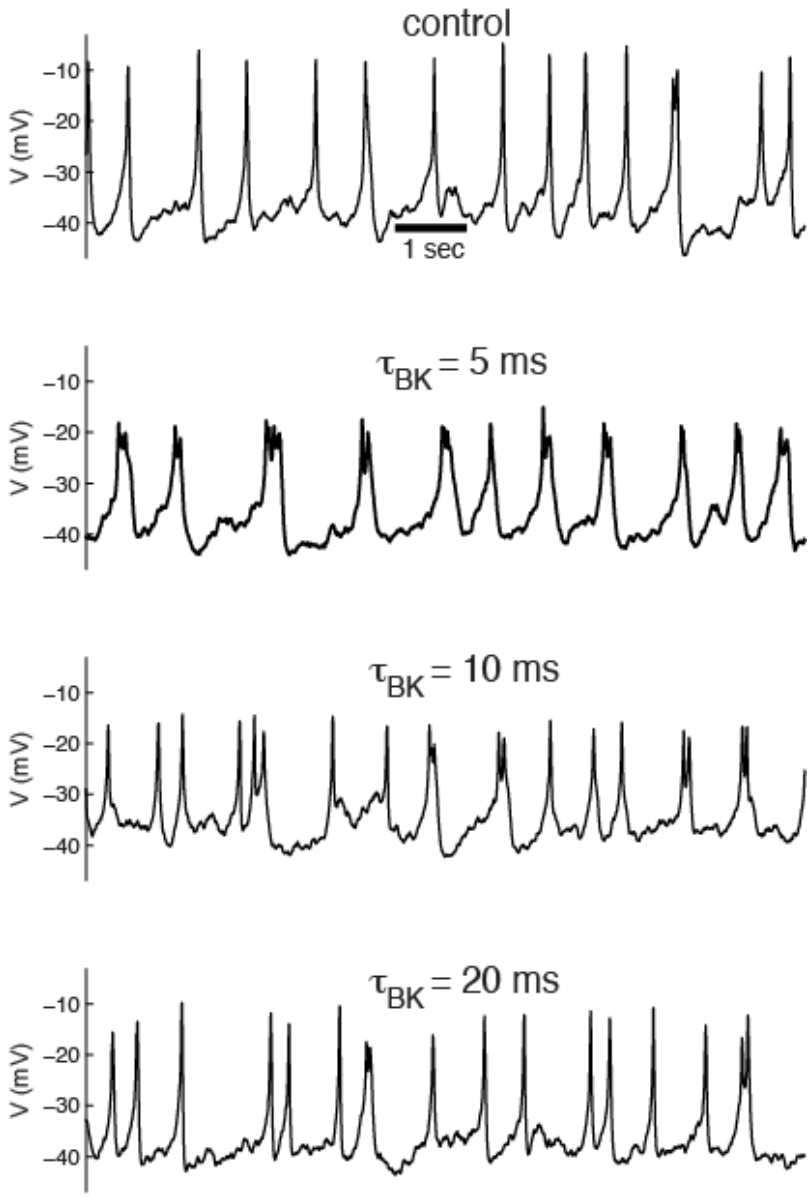
Subtracting I_{BK} converts bursting into spiking

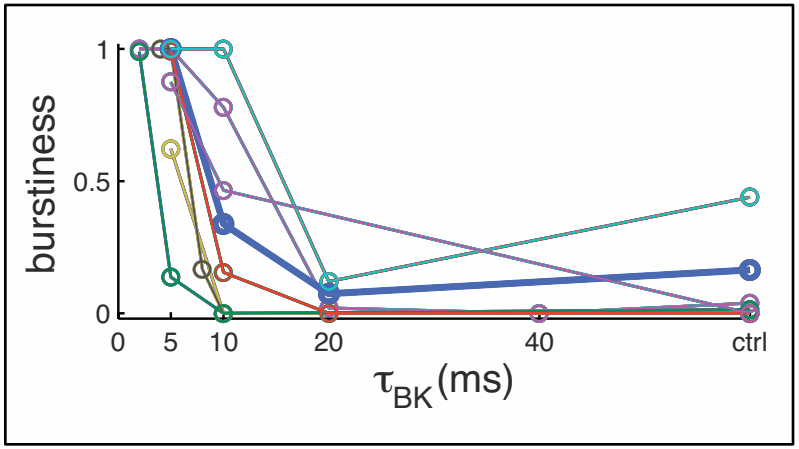


BK current correlates with cell burstiness

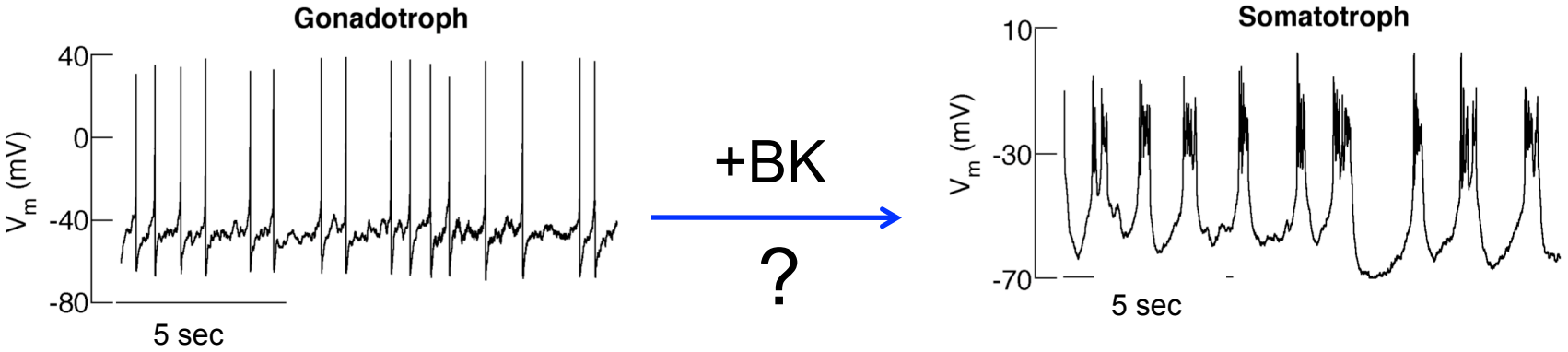


I_{BK} must activate rapidly to restore bursting

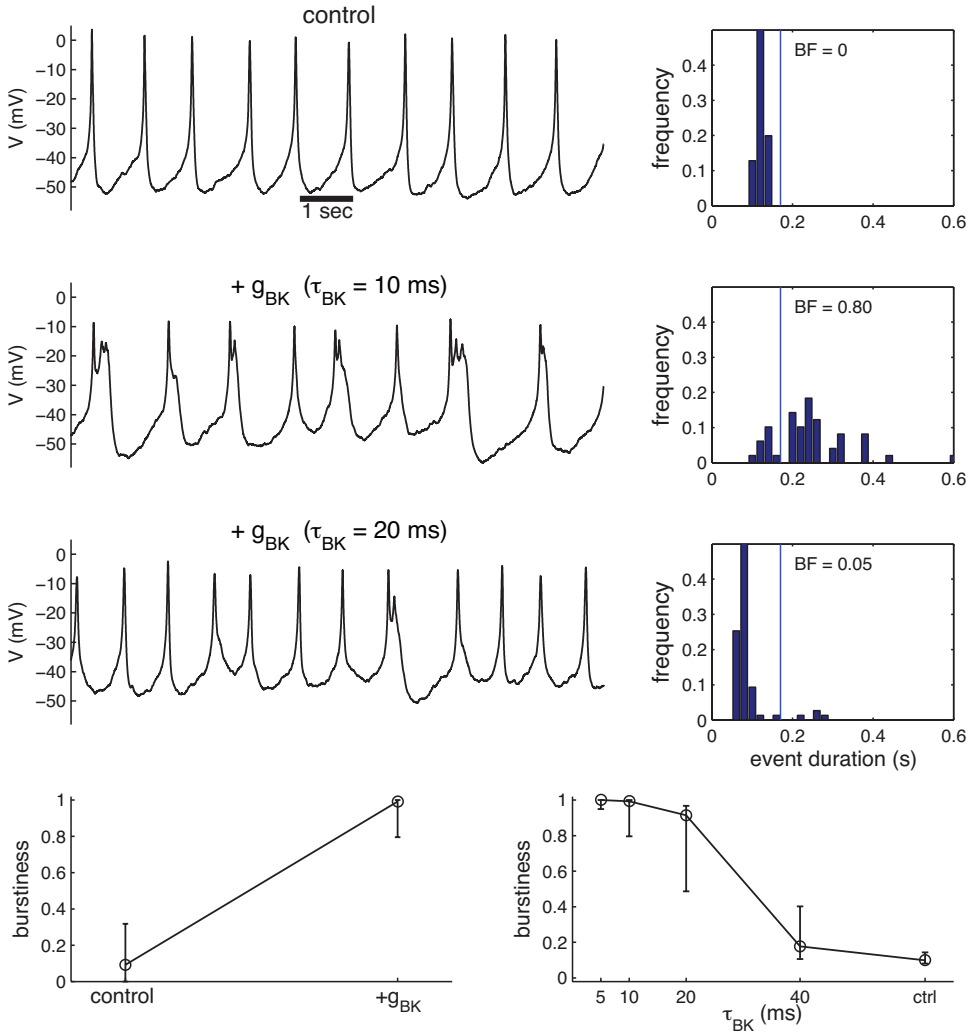




Can BK channels transform spiking gonadotrophs into bursters?



I_{BK} switches the activity of gonadotrophs from spiking to bursting



Summary of results

- BK channels do promote bursting in pituitary cells
- Their activation/deactivation must be fast -- they must be closely associated with calcium channels
- Hormonal signals may modulate BK channels and other channels, so BK effect (stimulatory or inhibitory) may depend on physiological status

Take home message

The dynamic clamp technique can overcome limitations of experimental techniques and modeling by bridging them together.

It is easy to implement. If you can do current- and voltage-clamp, you can do dynamic clamp.

It is cheap (if you already have a patch setup)

Collaborators

M. Tomaiulo Department of Biological Science, Florida State University (now at U Penn)

A. Gonzalez-Iglesias Department of Biological Science, Florida State University

L. Milescu Division of Biological Sciences, University of Missouri

R. Bertram Department of Mathematics, Florida State University