Happy Birthday, Charlie


Charlie was here
I was here
Russia
Mongolia
China
South Korea
Japan
Sea of Okhotsk
Bering Sea
Sea of Japan
East China Sea
North Pacific Ocean
United States
Mexico
Gulf of Mexico
Cuba
Puerto Rico
Guatemala
Caribbean Sea
Nicaragua
Venezuela
Colombia
Ecuador
Peru
Bolivia
Chile
Argentina
Myanmar (Burma)
Thailand
Vietnam
Philippines
Gulf of Thailand
Malaysia
Indonesia
Banda Sea
Arafura Sea
Papua New Guinea
Coral Sea
Australia
Great Australian Bight
Tasman Sea
New Zealand
South Pacific Ocean

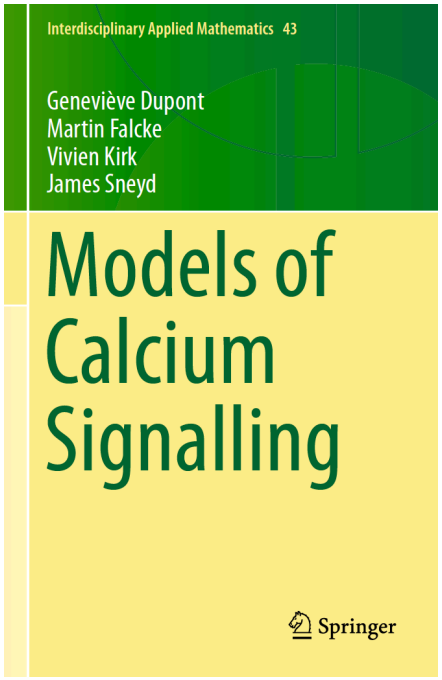
In 1984

The Dynamics of Calcium

James Sneyd

University of Auckland, NZ

as well as numerous postdocs, PhD students and colleagues who did most of the work.



Just published

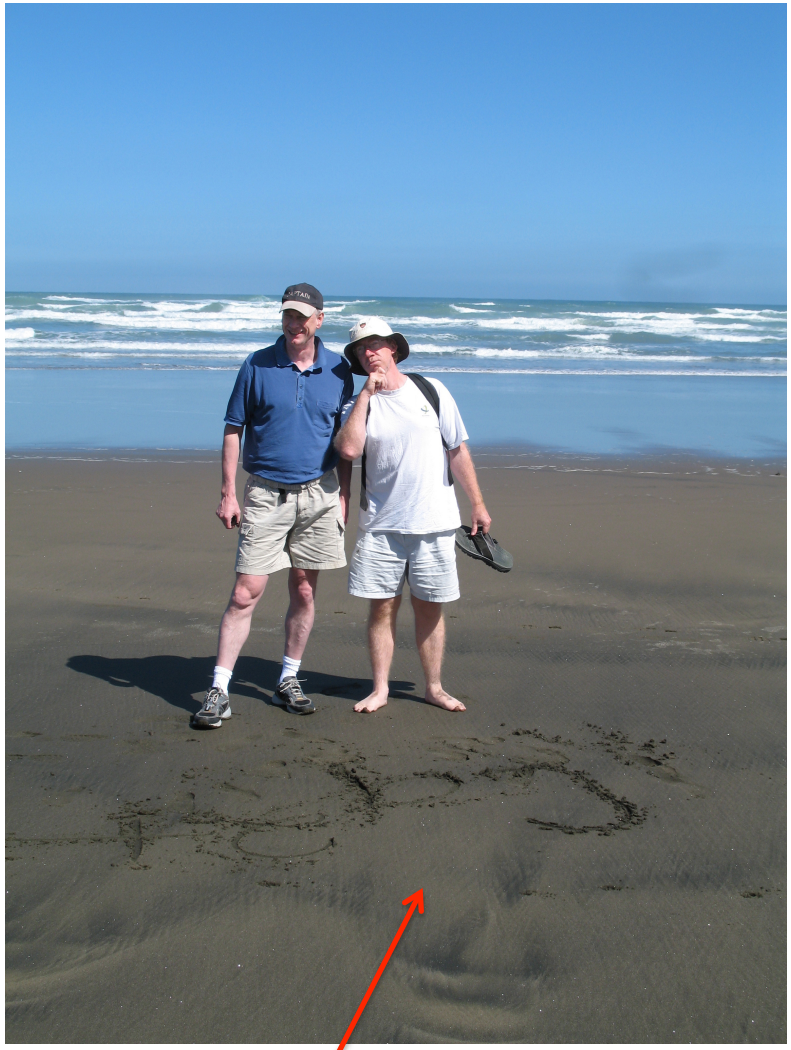
NIDCR National Institute of Dental and Craniofacial Research

NIH National Heart, Lung, and Blood Institute

MARSDEN FUND
TE PŪTEA RANGAHAU A MARSDEN

the ROYAL SOCIETY of NEW ZEALAND

The University of Auckland

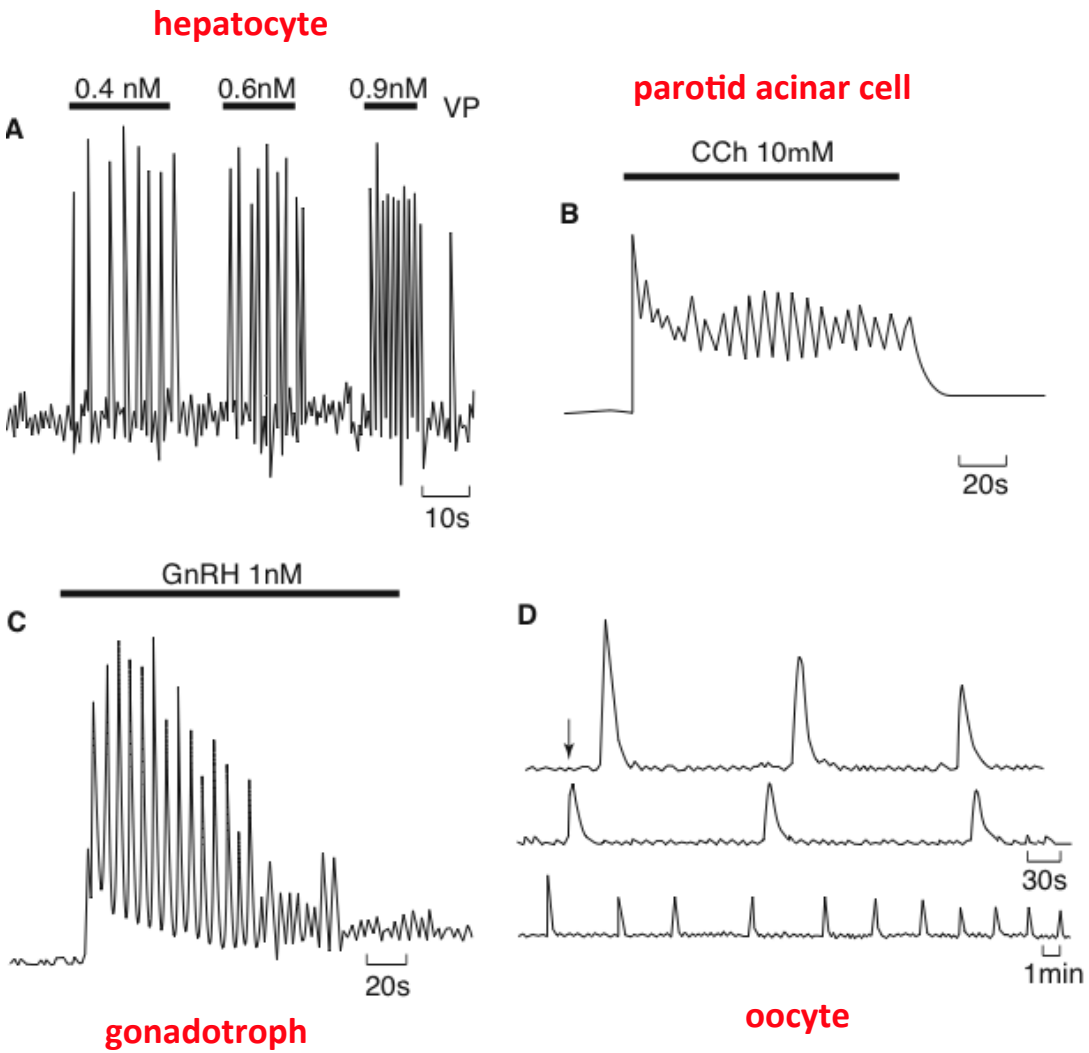


Note the Ca^{2+} on the sand

Michael J. Sanderson, one of my closest friends and colleagues, died suddenly and unexpectedly on the 24th of April, 2016.

A lot of what I'll be talking about today (and for the past 20 years) has been strongly influenced by Mike.

Typical oscillations



In response to stimulation by hormones or neurotransmitters, many cell types exhibit oscillations in the concentration of free intracellular calcium ions.

How?
And Why?

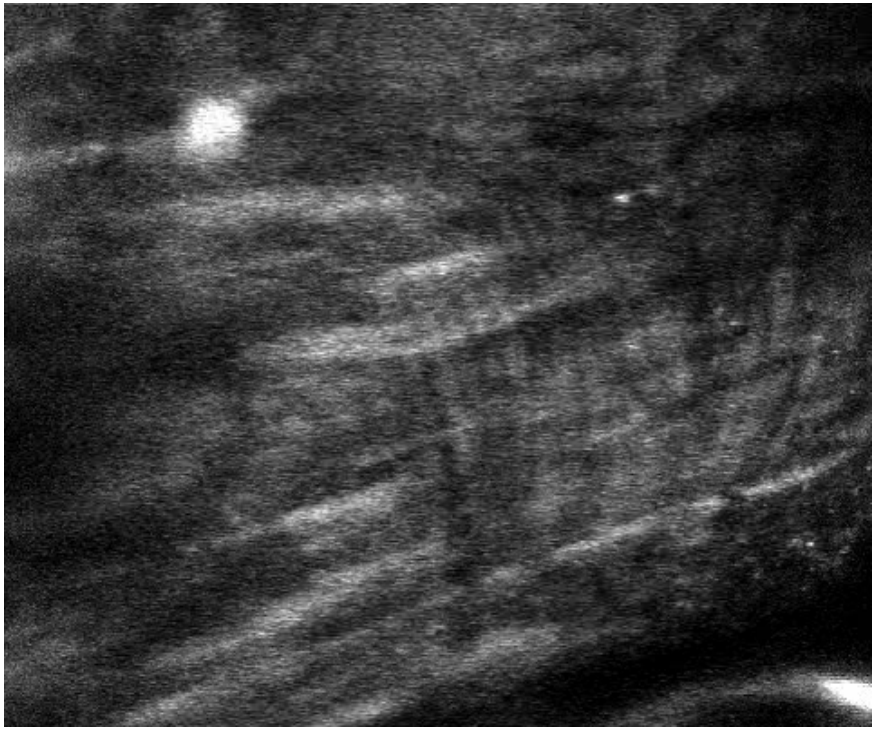
Why?

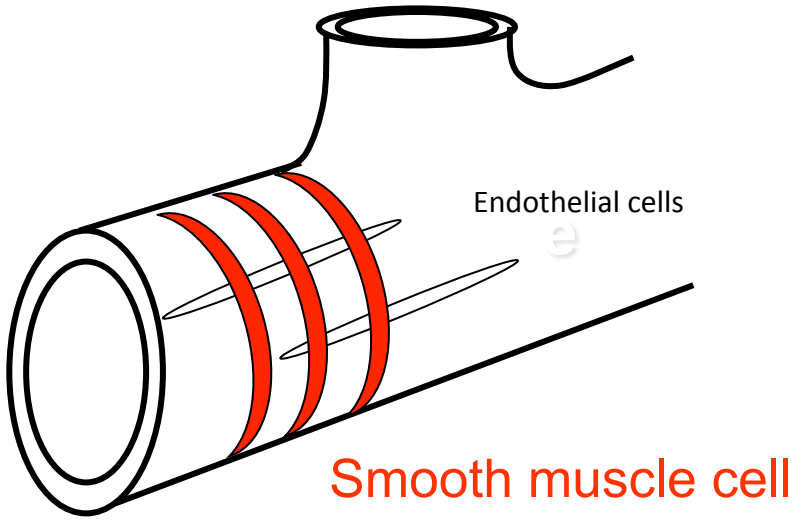
Why do cells expend all this energy to generate calcium oscillations (and waves)?

Dogma: calcium is a second messenger which carries a signal in the frequency of the oscillations.

This allows cells to use calcium (which is toxic) as a second messenger.

Contraction of smooth muscle around an arteriole

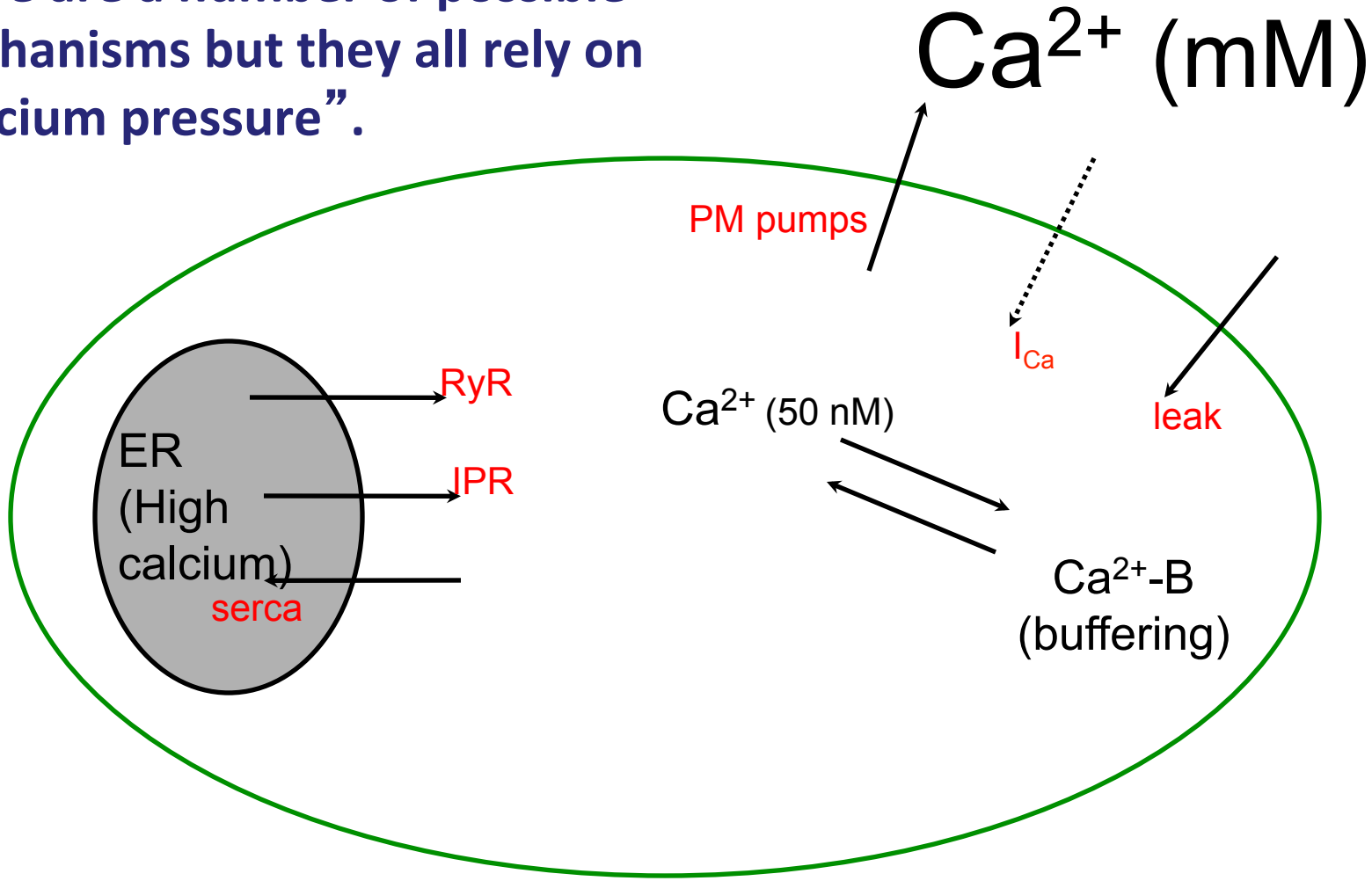




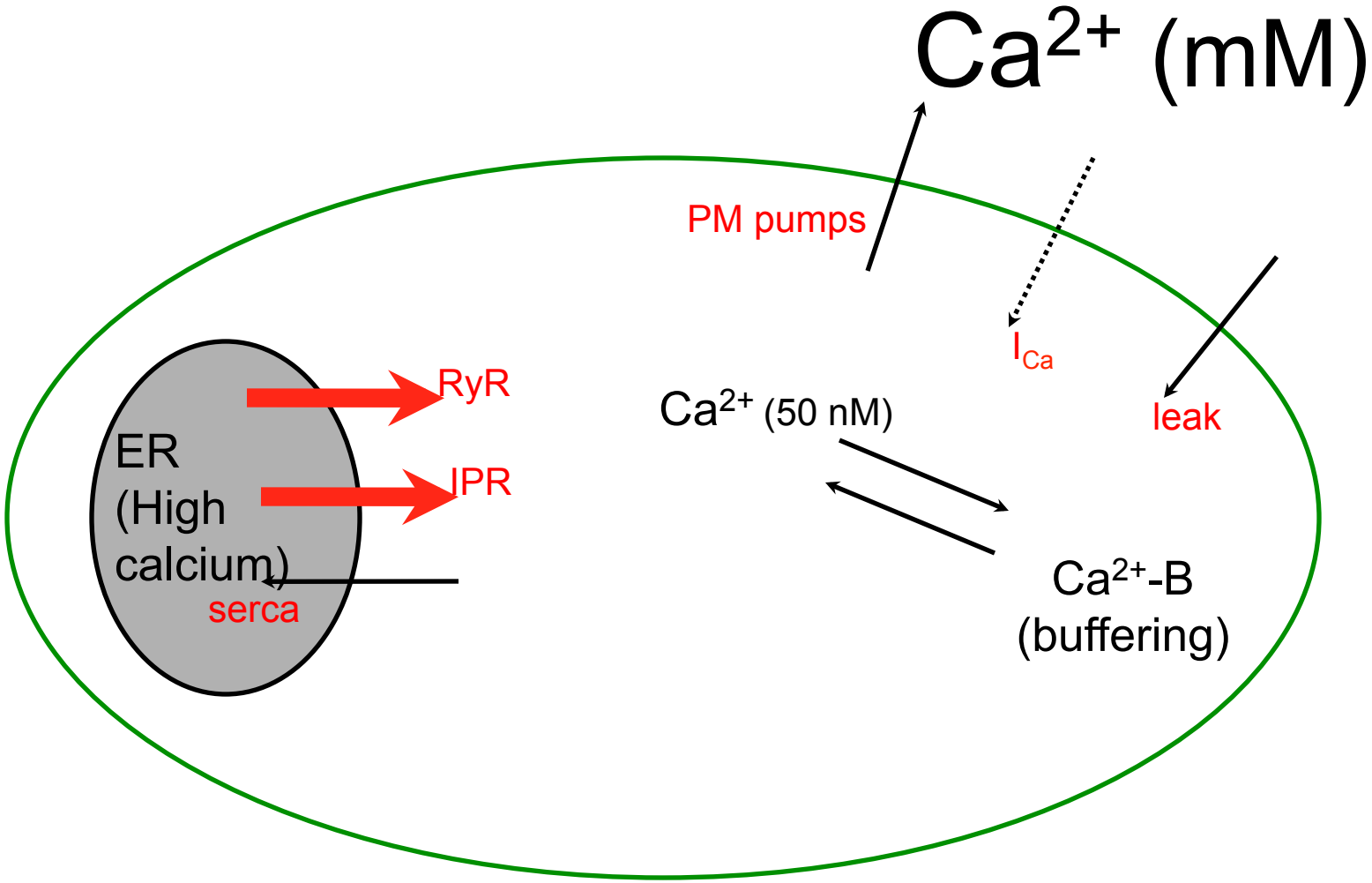
From Mike Sanderson's lab.

How?

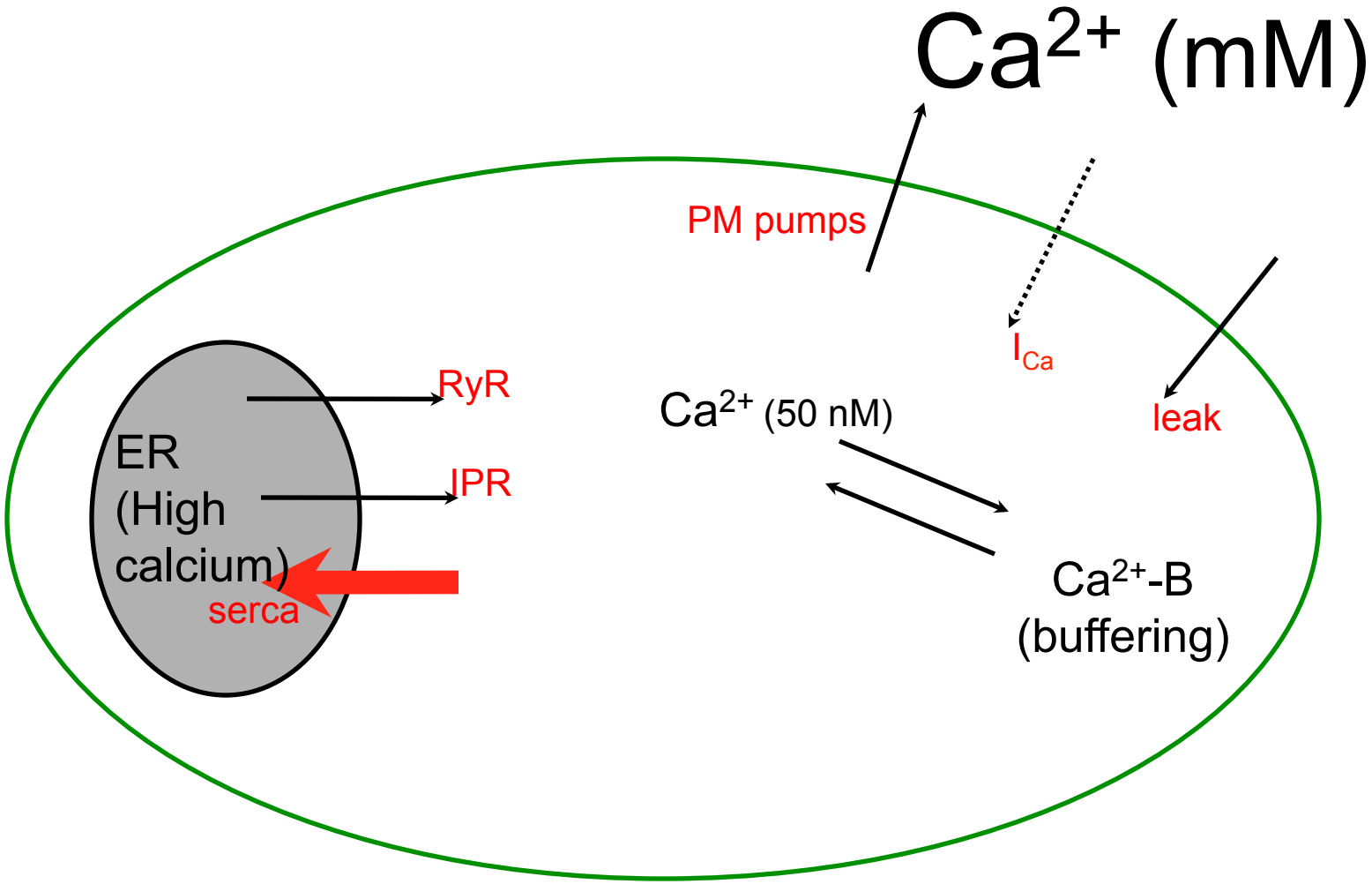
There are a number of possible mechanisms but they all rely on "calcium pressure".



Release from internal stores…



Followed by reuptake.



Calcium excitability

- **IPR release calcium in an excitable manner. They respond to a calcium challenge by the release of even more calcium.**

- **Ca^{2+} oscillations (mostly) result from the cycling of Ca^{2+} into and out of the internal store, the ER.**

- **An IPR behaves very like a Na^{+} channel (in some ways). In response to an increase in $[Ca^{2+}]$ it first activates quickly, and then inactivates slowly, resulting in the short-term release of a large amount of calcium.**

- **Thus, the math of calcium dynamics is very similar to generic excitable system theory.**

But...how similar is similar?

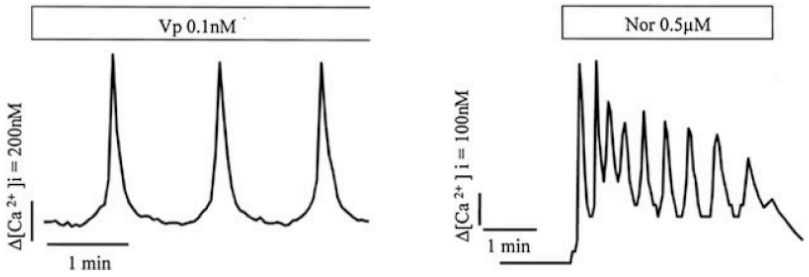
In honour of Charlie, the rest of this talk is unpublished and speculative.

He does this all the time, quite brilliantly. I don't.

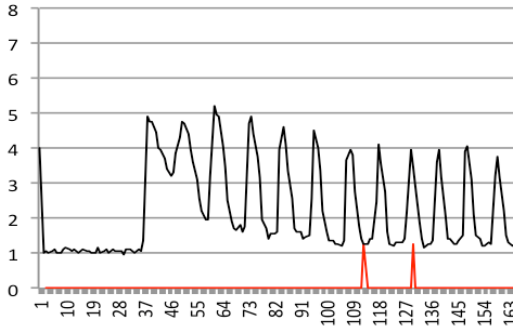
But this time, for Charlie, I'll try.

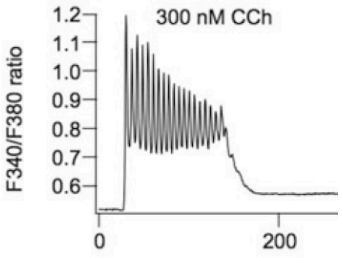
Is there a unifying structure underlying all calcium oscillations?

- **No. Of course not. What a silly question.**
- **There is too much variability between cell types, and a variety of quite different mechanisms.**
- **But for one class of calcium oscillations (Class I, closed cell), it might be possible...**

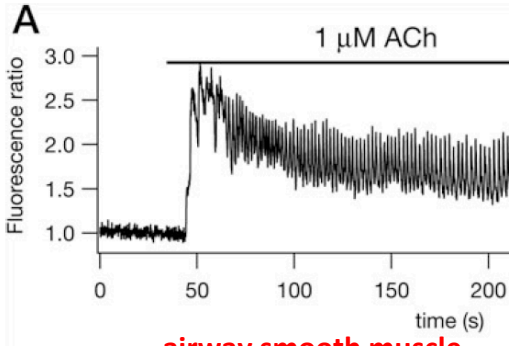


hepatocytes

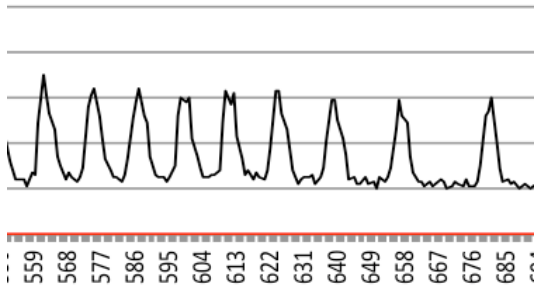




parotid acinar cells

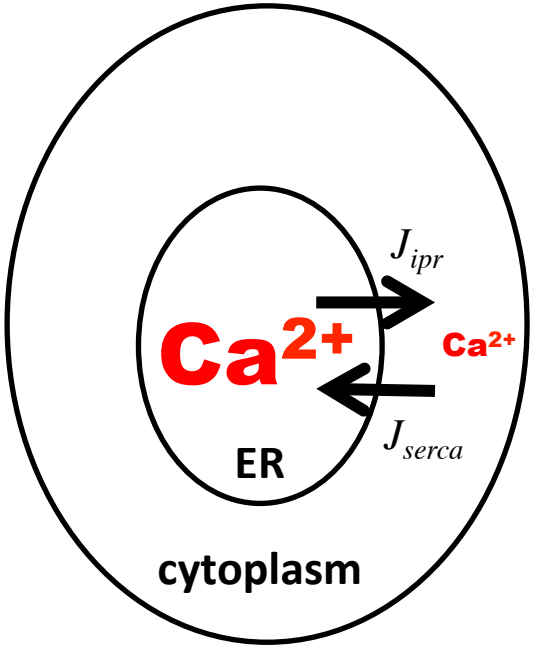


airway smooth muscle



HSY cells

The generic model



flux through IPR (J_{ipr})

flux through SERCA pump (J_{serca})

$$\frac{dc}{dt} = k_{\mathrm{ipr}}\phi_c(c)\phi_p(p)h(c_e - c) - \frac{V_s c^2}{K_s^2 + c^2}$$

$$\tau_h \frac{dh}{dt} = 1 - \frac{h}{h_\infty(c)}$$

IPR inactivation

$$\frac{dp}{dt} = V_{\mathrm{plc}}(c) - V_{\mathrm{deg}}p$$

production and degradation of IP_3

$$\phi_c(c) = \frac{c^3}{K_c^3 + c^3}$$

fast positive feedback

$$h_\infty(c) = \frac{K_h^3}{K_h^3 + c^3}$$

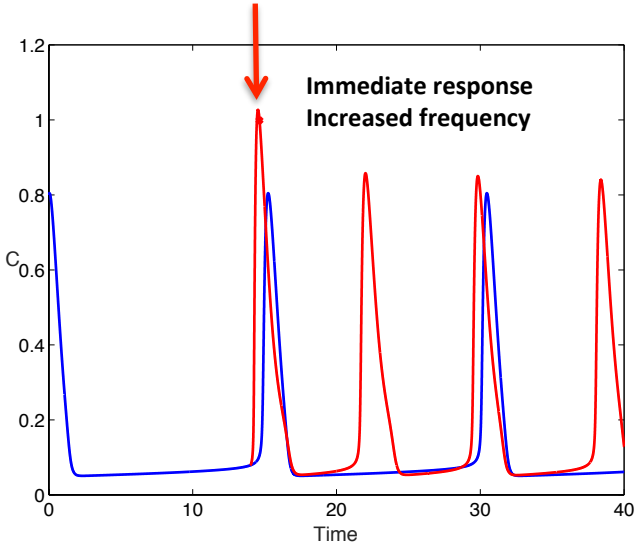
slower negative feedback

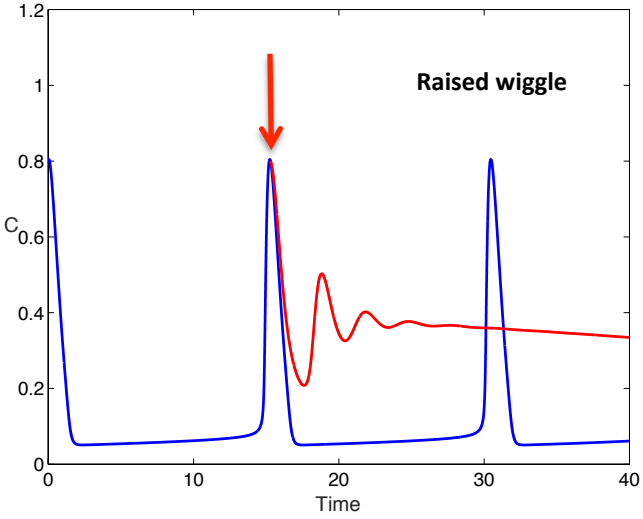
$$\phi_p(p) = \frac{p^3}{K_p^3 + p^3}$$

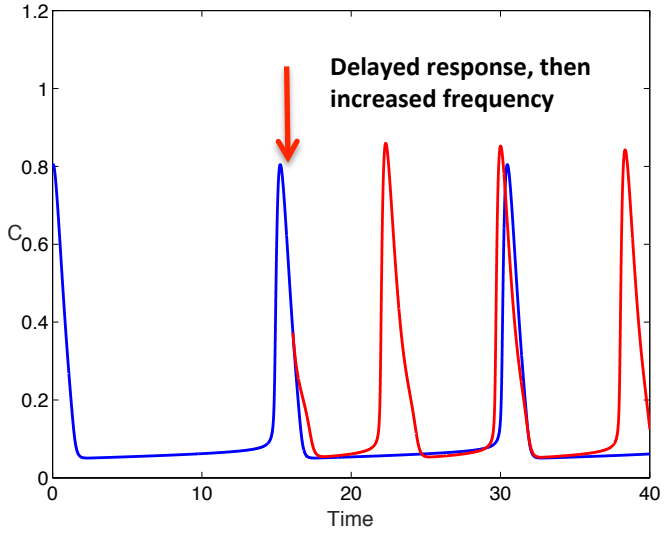
not important for now

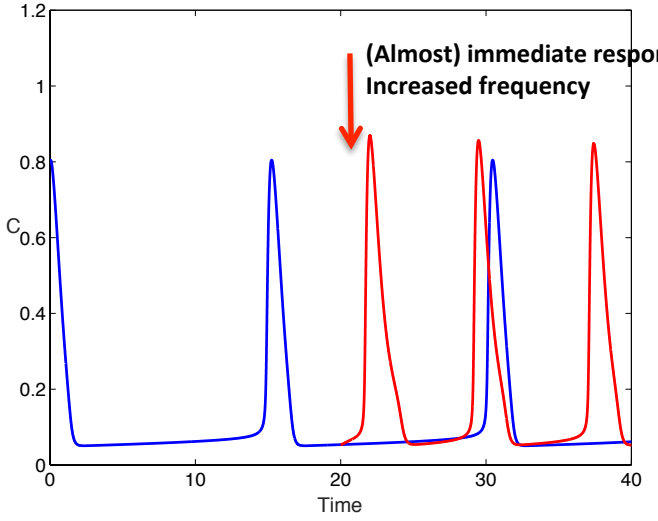
$$V_{\mathrm{plc}} = \text{not so important}$$

Pulses of IP_3: model predictions



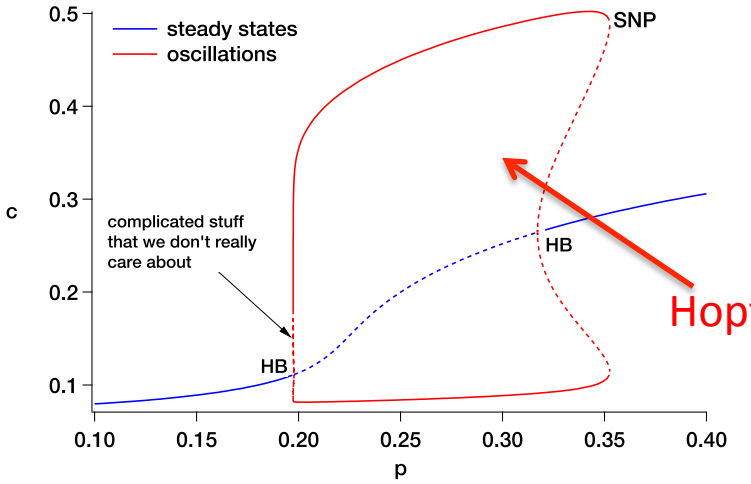




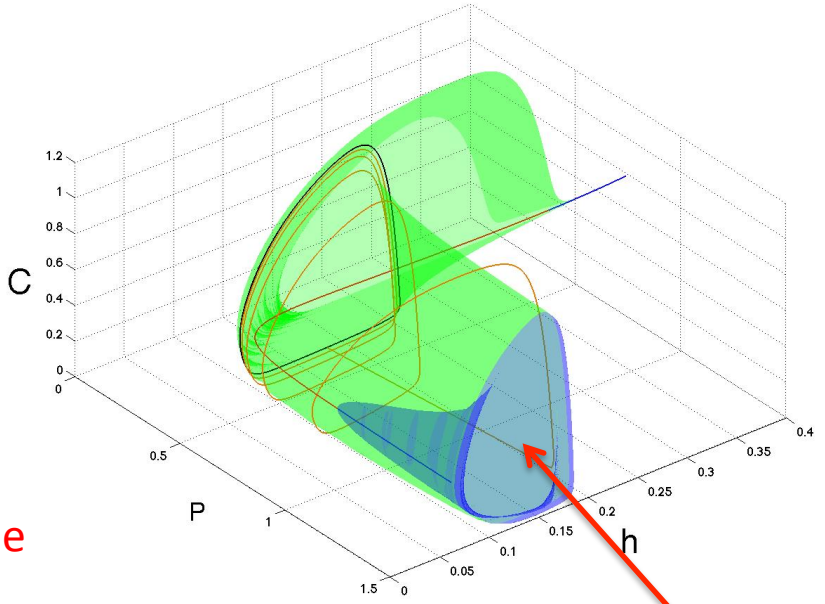


Computations from Sylvia (Jung Min) Han (NIH) and Susan Wang (Auckland), but I'll try to take the credit anyway

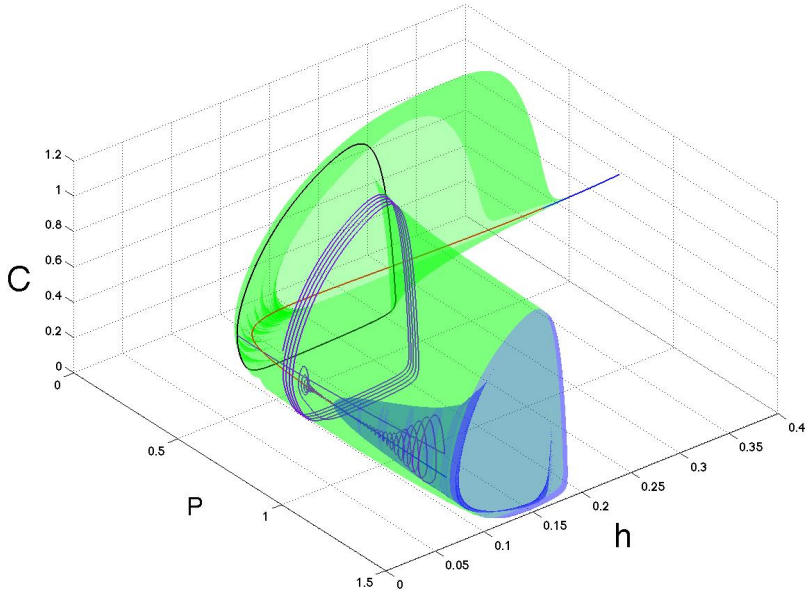
Bifurcations in 2-d and 3-d

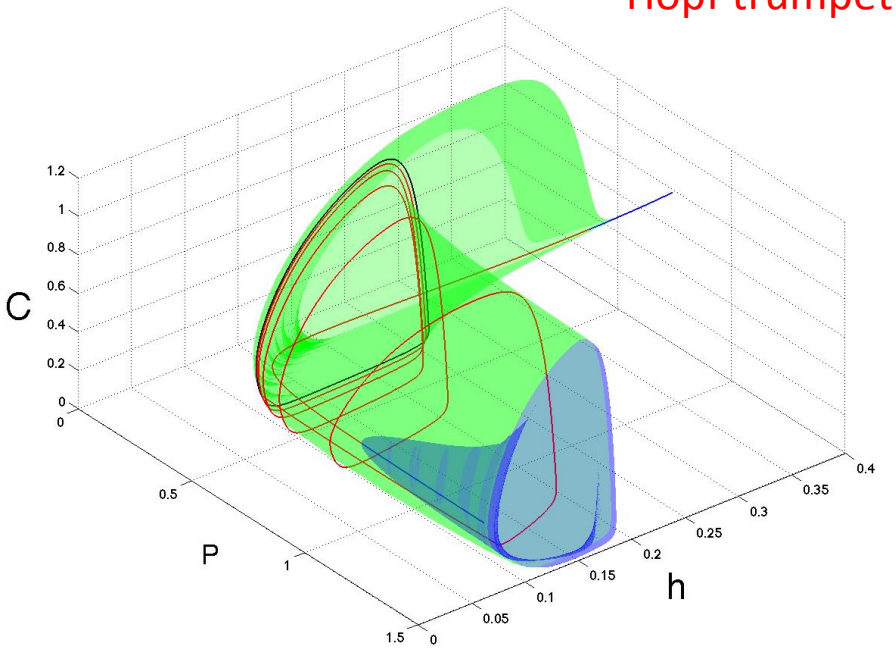


Hopf bubble



Hopf trumpet

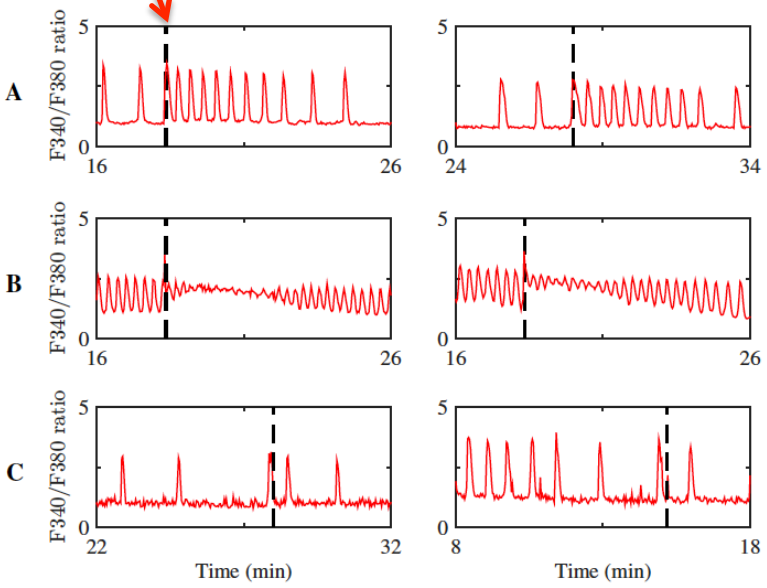




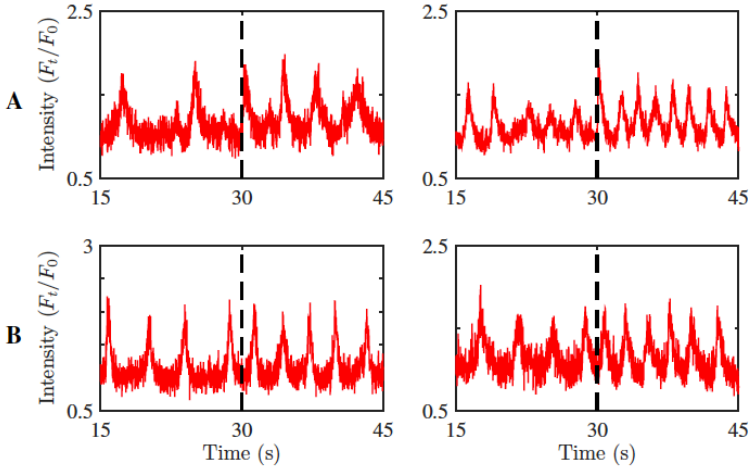
Testing the model predictions

pulse of IP_3

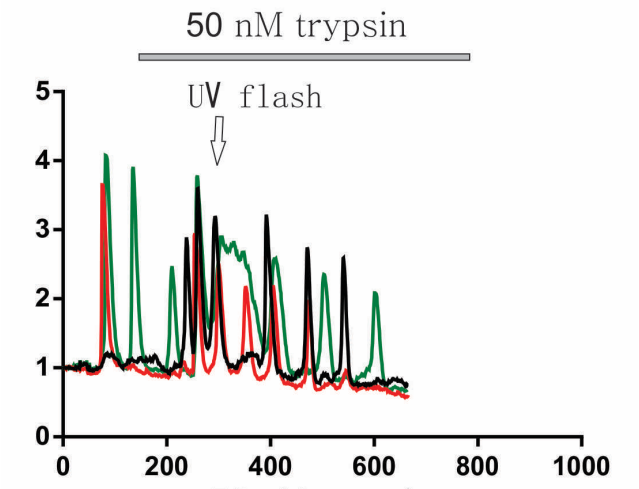
HSY cells. Akihiko Tanimura



Airway smooth muscle cells. Michael Sanderson



Note the widely differing time scales

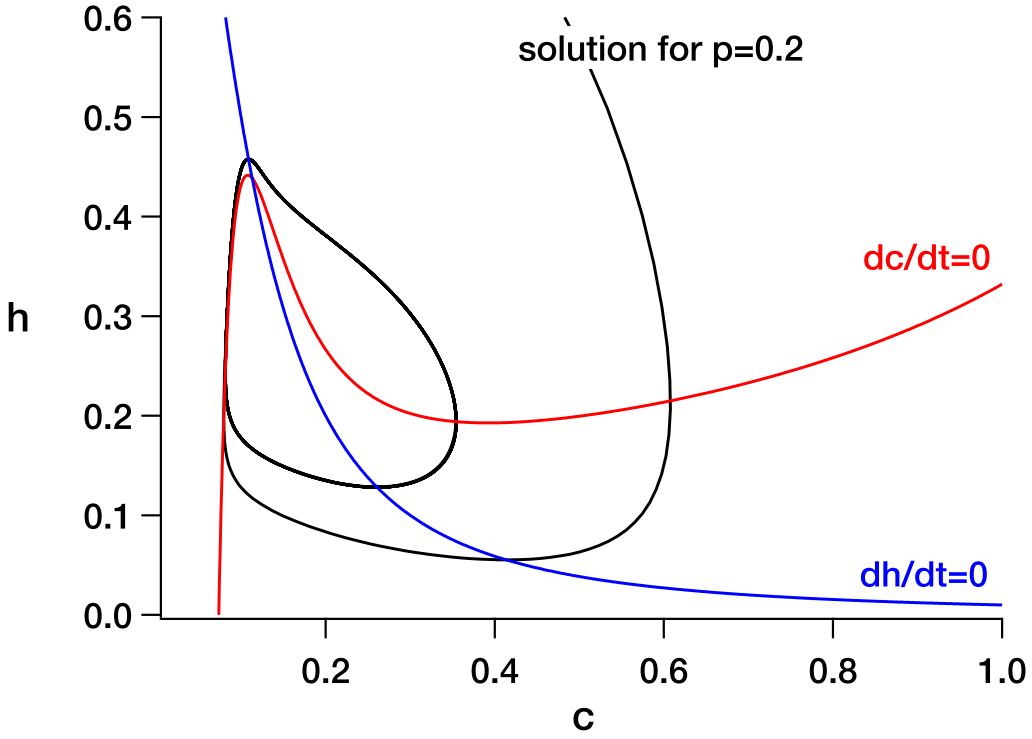


DT40 3KO (R2WT) cells. David Yule

We get the predicted dynamic behaviour, and in three completely different cell types. Cheer, and have a cup of tea.

Is this just FitzHugh-Nagumo?

No. Not really. But it's close.



- **N-shaped nullcline and a "straight" one.**
- **Time-scale separation, but ONLY for low c.**
- **When c is large, the distinction between fast and slow variables is lost.**
- **This is mandated by the physiological properties of the IPR.**
- **Basically, it's FHN with a very shallow nullcline and an ε that depends on c.**

Conclusions?

- **Not entirely sure yet.**
- **But the evidence suggests that there is a unifying dynamical structure underlying a large range of calcium oscillations.**
- **This dynamical structure seems to be independent of the time scale.**
- **Thus, cells generate the underlying structure, and then move around on it as fast as they have to.**