Lecture 11: Non-linear dynamical systems: Part 3

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The application of non-linear systems analysis to understand the elementary response of *Drosophila* photoreceptor cells to light.

Henri Poincare
1854 - 1912

Edward Lorenz
1917-2008

Robert May
1936 -

Boris Shraiman
KITP, UCSB

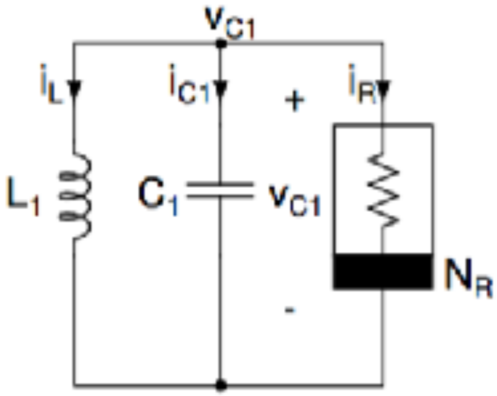
Alain Pumir
CNRS, ENS de Lyon

So, today we study a real case of a biological **non-linear dynamical system**.

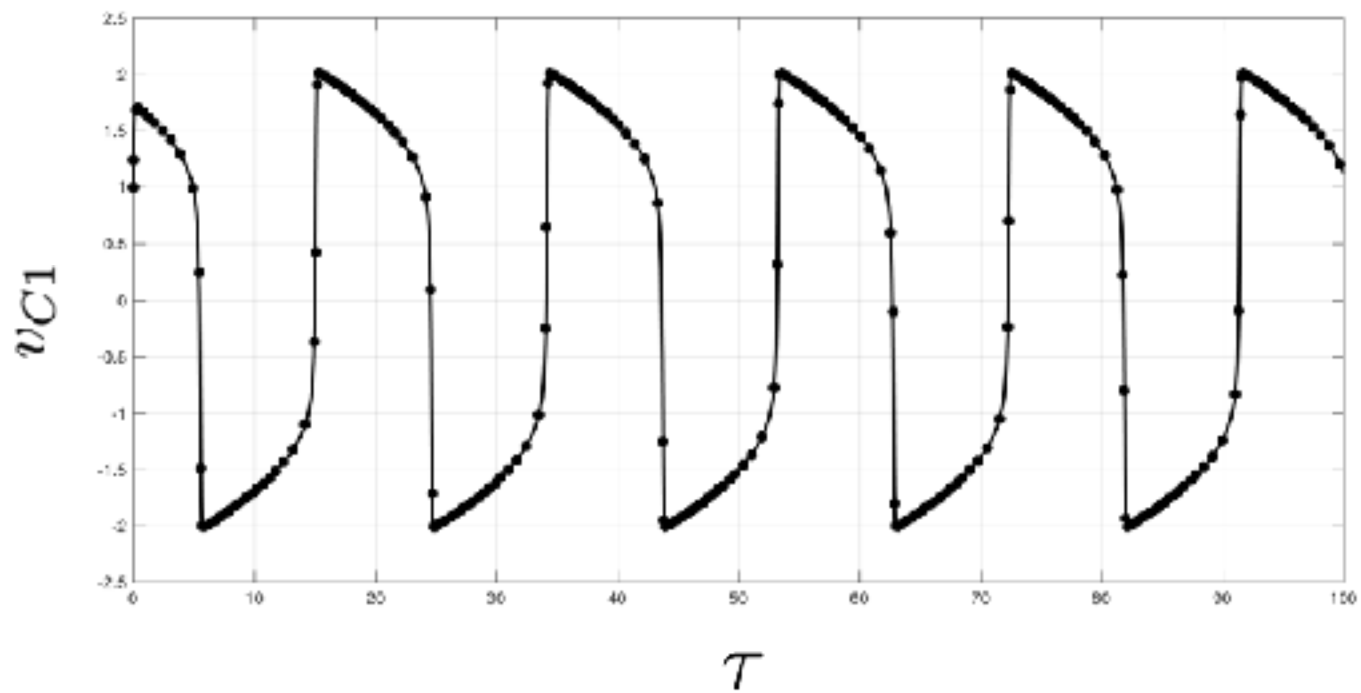
	n = 1	n = 2 or 3	n >> 1	continuum
Linear	exponential growth and decay single step conformational change fluorescence emission pseudo first order kinetics	second order reaction kinetics linear harmonic oscillators simple feedback control sequences of conformational change	electrical circuits molecular dynamics systems of coupled harmonic oscillators equilibrium thermodynamics diffraction, Fourier transforms	Diffusion Wave propagation quantum mechanics viscoelastic systems
Nonlinear	fixed points bifurcations, multi stability irreversible hysteresis overdamped oscillators	anharmomic oscillators relaxation oscillations predator-prey models van der Pol systems Chaotic systems	systems of non-linear oscillators non-equilibrium thermodynamics protein structure/function neural networks the cell ecosystems	Nonlinear wave propagation Reaction-diffusion in dissipative systems Turbulent/chaotic flows

adapted from S. Strogatz

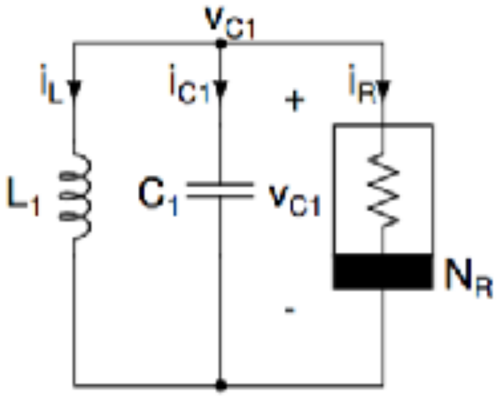
The van der Pol **non-linear oscillator...**



$$\ddot{v}_{C1} - \epsilon(1 - v_{C1}^2)\dot{v}_{C1} + v_{C1} = 0$$, where… $\epsilon = \frac{1}{R}\sqrt{\frac{L_1}{C_1}}$



The van der Pol **non-linear oscillator...**



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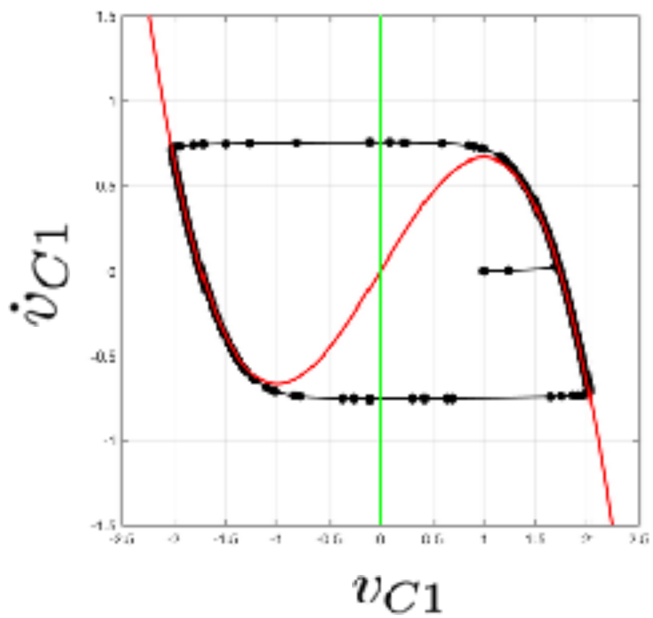
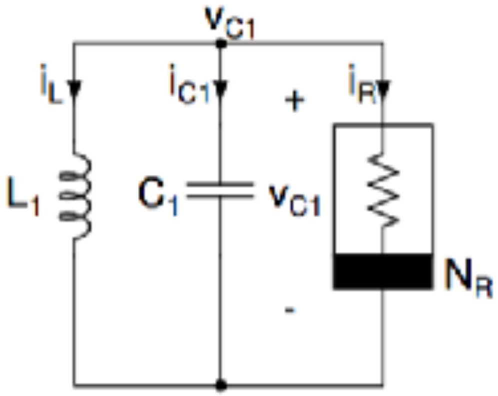


an unstable fixed point at the origin,
and a **stable limit cycle oscillation**

The van der Pol **non-linear oscillator...**



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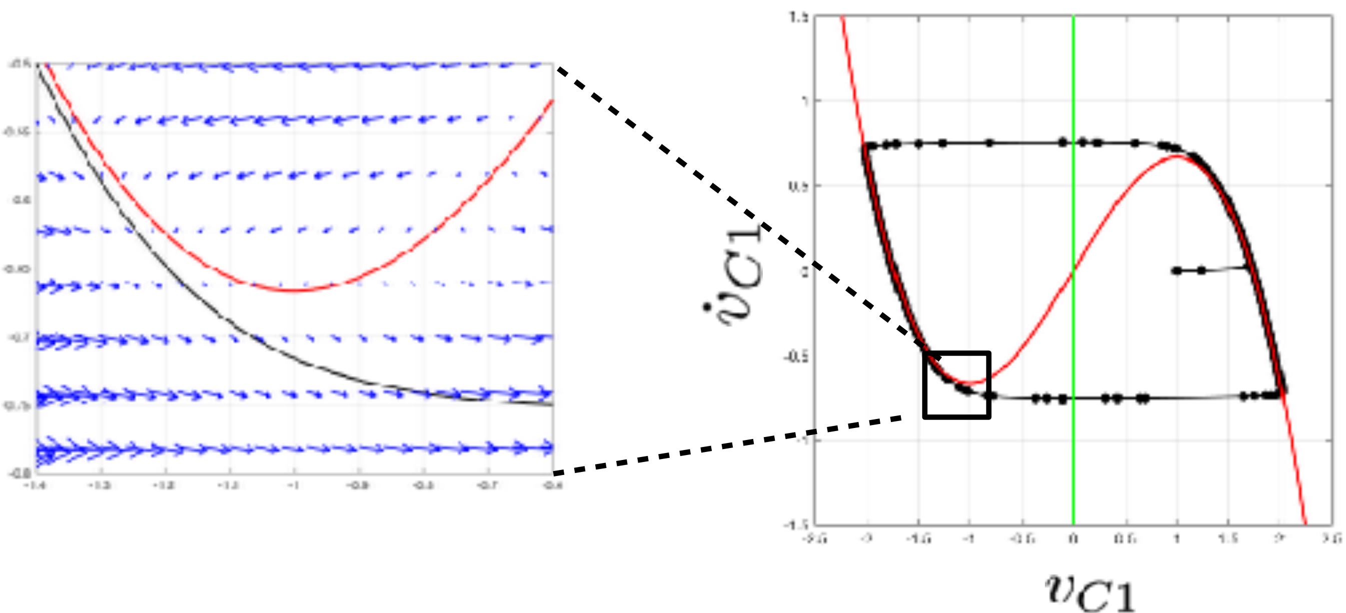
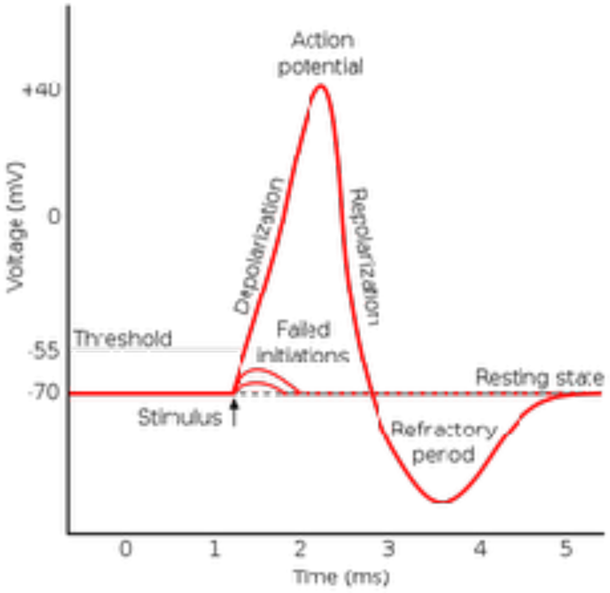


the **switch** from slow to fast flow…

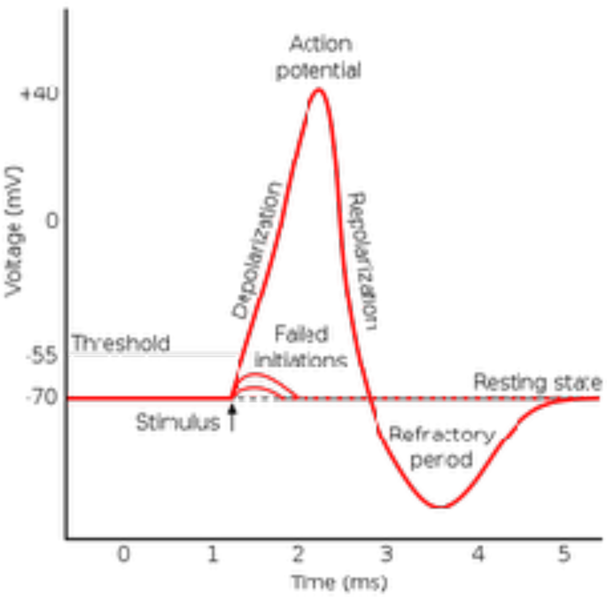
A **non-linear oscillator...**

The **neuronal action potential…**a slight variation on the van der Pol oscillator…



A **non-linear oscillator...**

Fitzhugh-Nagumo (1962)



membrane pot $$\frac{dv}{dt} = v - \frac{v^3}{3} - w + I$$

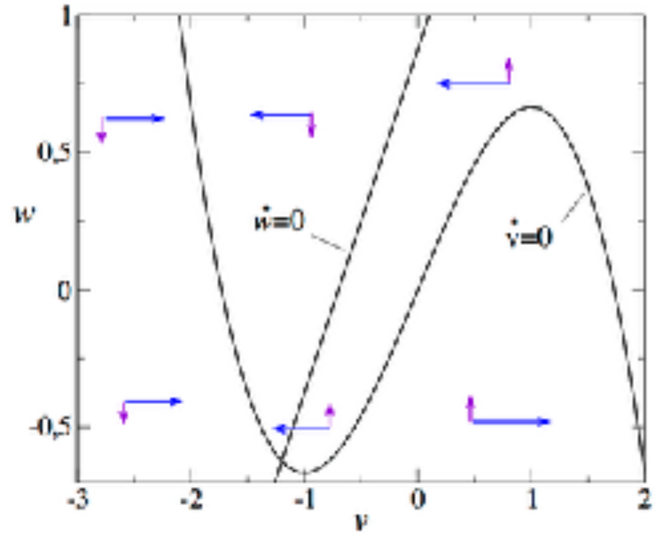
slow K+ flux $$\frac{dw}{dt} = \frac{1}{\tau}(v + a - bw)$$

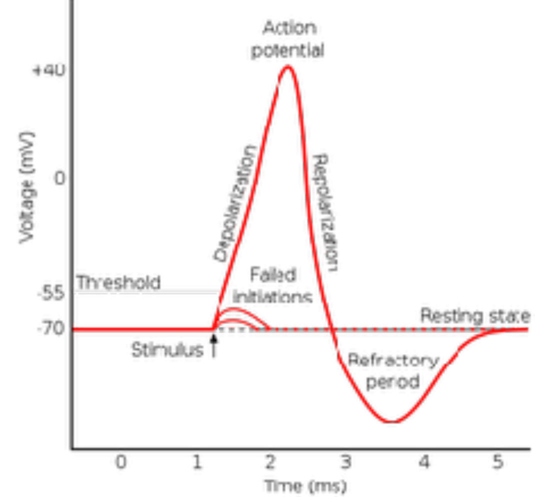
this is essentially the van der Pol oscillator, with **one difference**….

A **non-linear oscillator...**

membrane pot
$$\frac{dv}{dt} = v - \frac{v^3}{3} - w + I$$

slow K+ flux
$$\frac{dw}{dt} = \frac{1}{\tau}(v + a - bw)$$



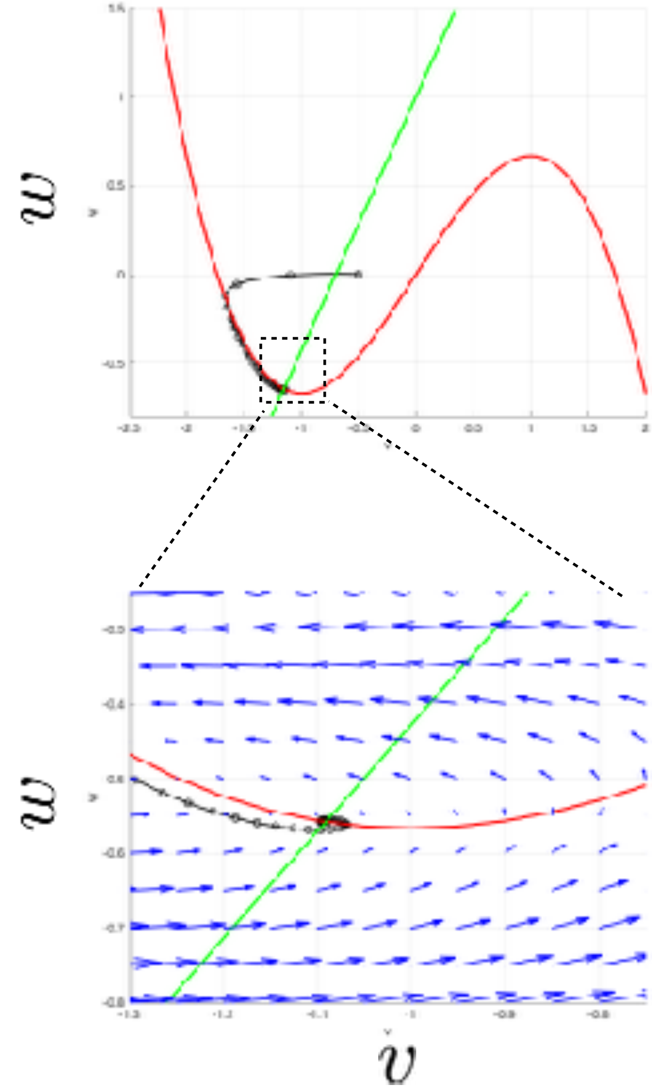


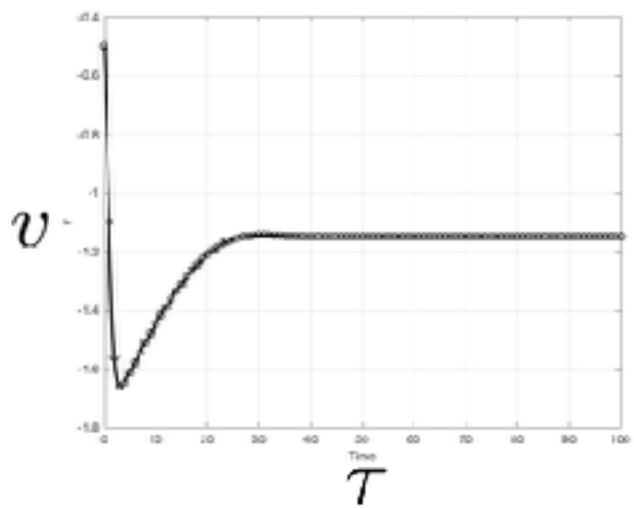
the linear term to the w nullcline provides for **thresholded oscillation**….

A **non-linear oscillator...**

membrane pot
$$\frac{dv}{dt} = v - \frac{v^3}{3} - w + I$$

slow K+ flux
$$\frac{dw}{dt} = \frac{1}{\tau}(v + a - bw)$$



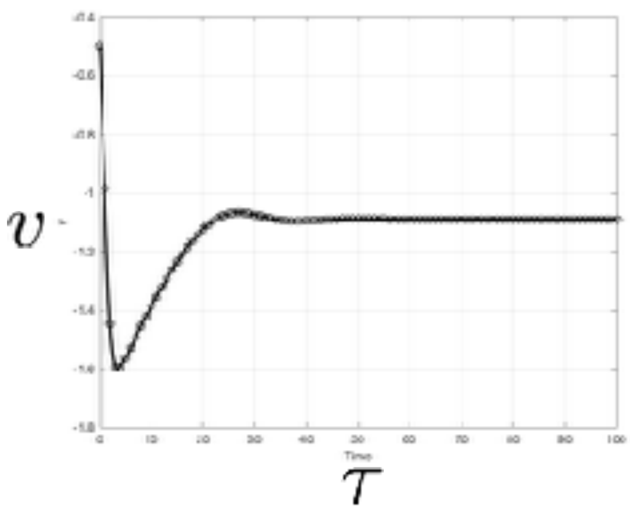


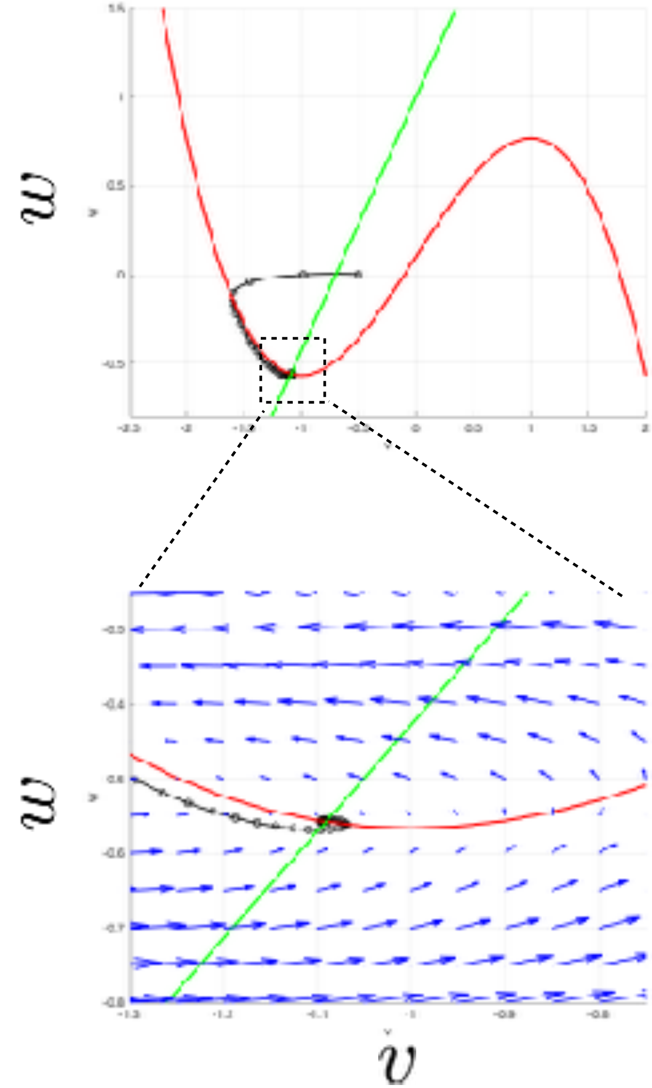
for **I = 0**…a stable fixed point

A **non-linear oscillator...**

membrane pot
$$\frac{dv}{dt} = v - \frac{v^3}{3} - w + I$$

slow K+ flux
$$\frac{dw}{dt} = \frac{1}{\tau}(v + a - bw)$$



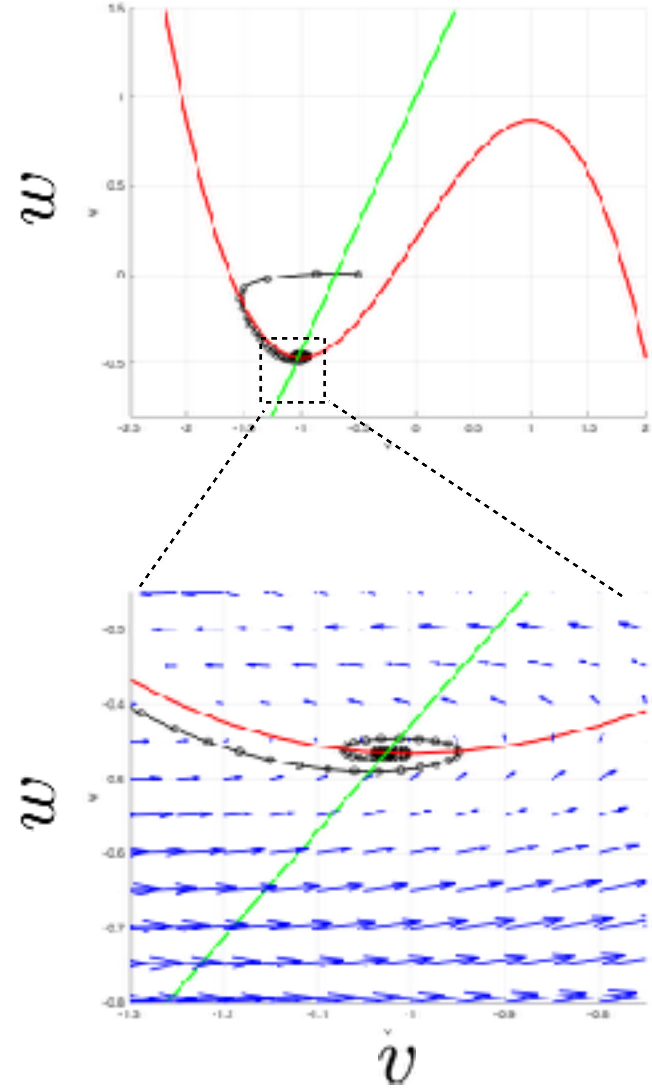


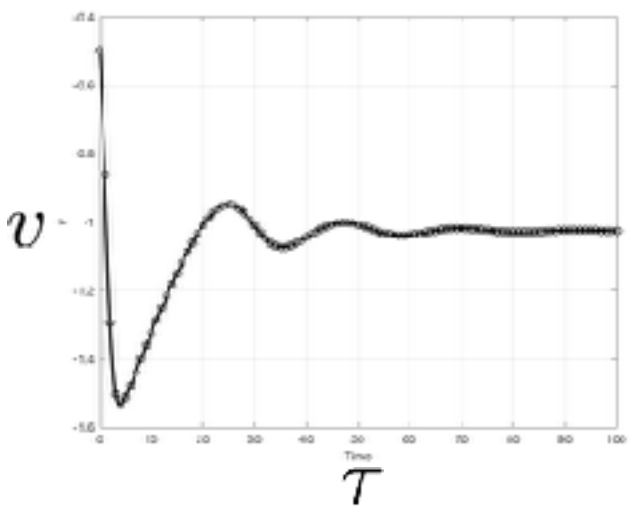
for **I = 0.1**…a stable fixed point, but a transient oscillation…

A **non-linear oscillator...**

membrane pot
$$\frac{\mathrm{d}v}{\mathrm{d}t} = v - \frac{v^3}{3} - w + I$$

slow K+ flux
$$\frac{\mathrm{d}w}{\mathrm{d}t} = \frac{1}{\tau}(v + a - bw)$$



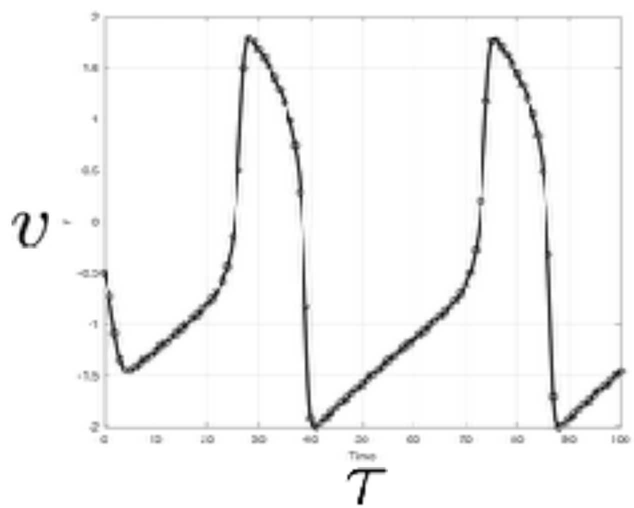


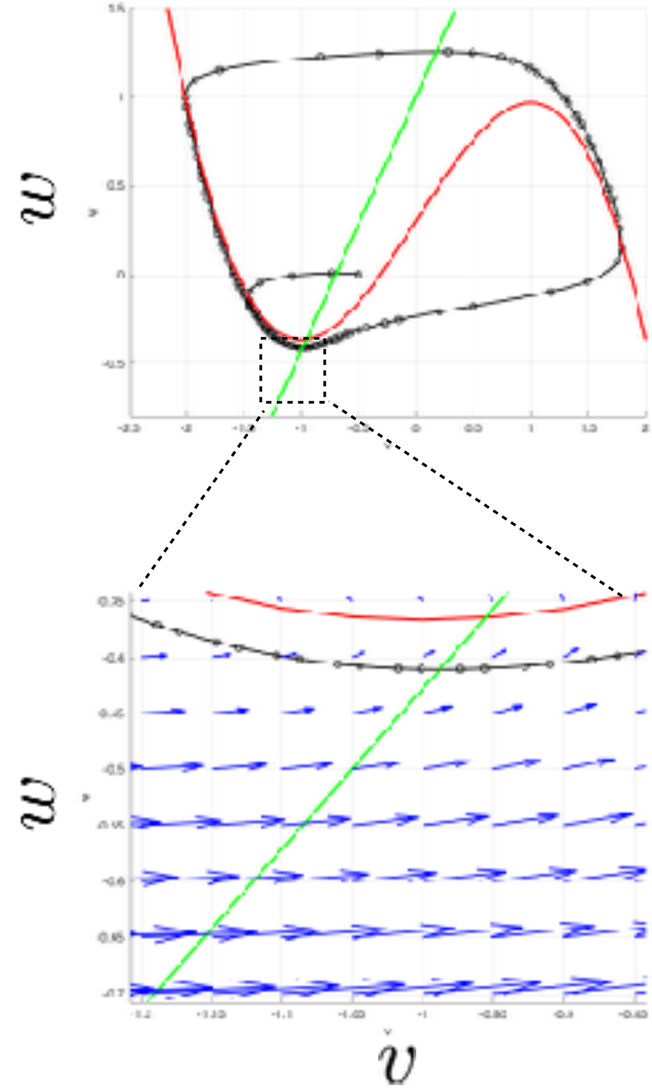
for **I = 0.2**…a stable fixed point, but a larger transient oscillation…

A **non-linear oscillator...**

membrane pot $$\frac{dv}{dt} = v - \frac{v^3}{3} - w + I$$

slow K+ flux $$\frac{dw}{dt} = \frac{1}{\tau}(v + a - bw)$$





for **I = 0.3**…the fixed point de-stabilizes via **Hopf bifurcation**

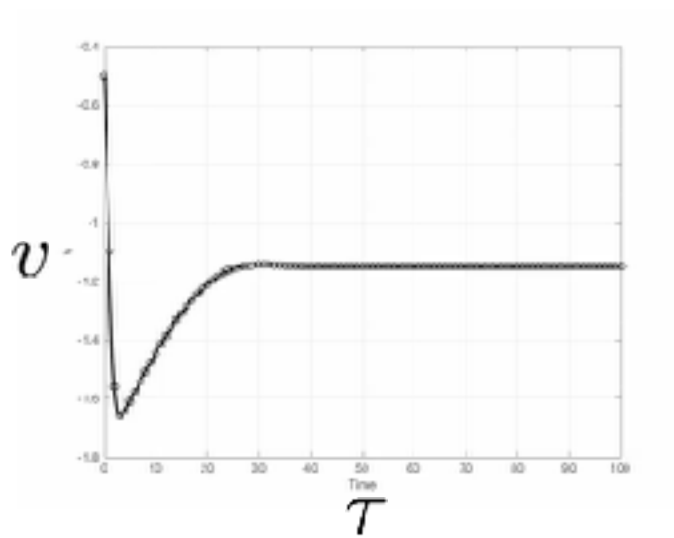
A **non-linear oscillator...**

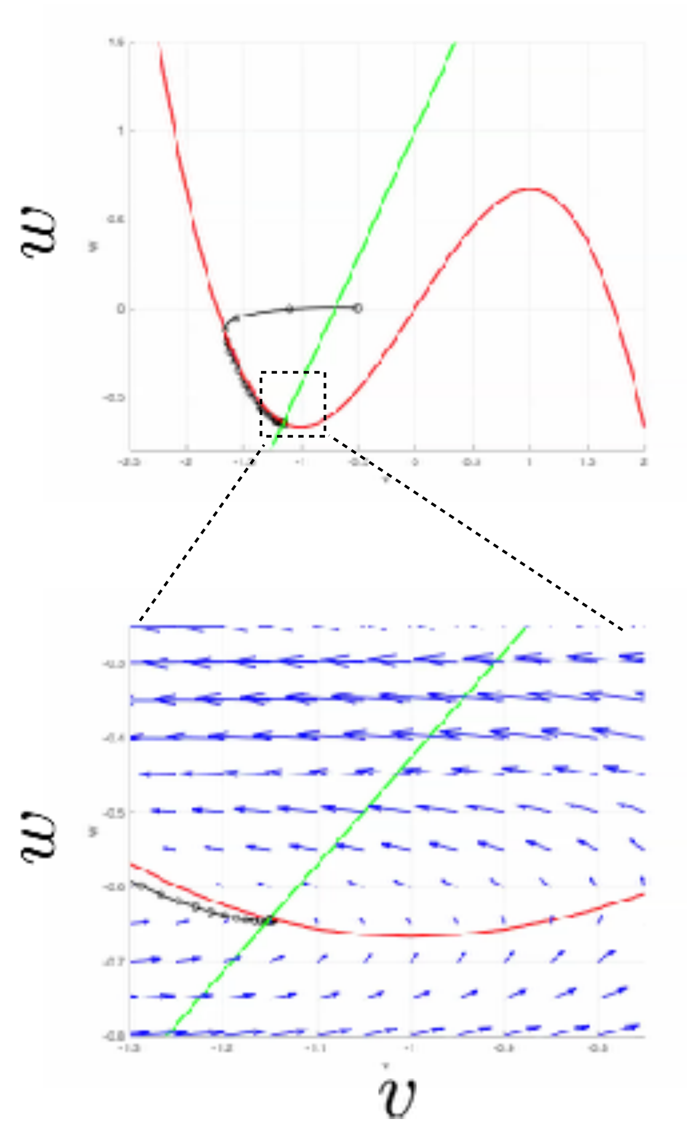
membrane pot

$$\frac{dv}{dt} = v - \frac{v^3}{3} - w + I$$

slow K+ flux

$$\frac{dw}{dt} = \frac{1}{\tau}(v + a - bw)$$



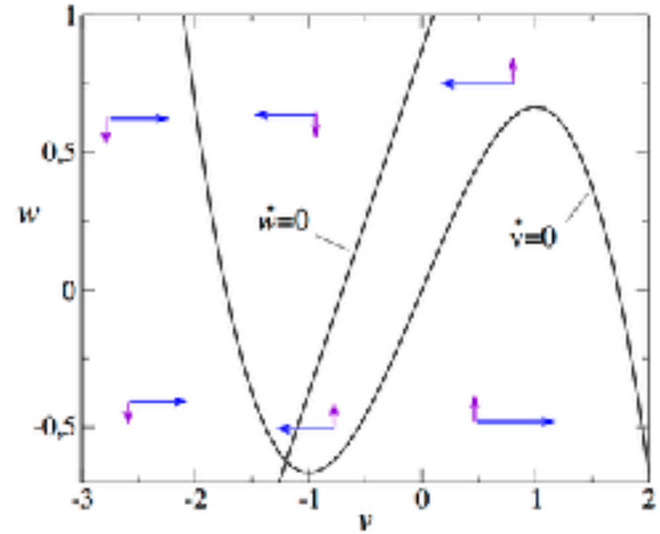


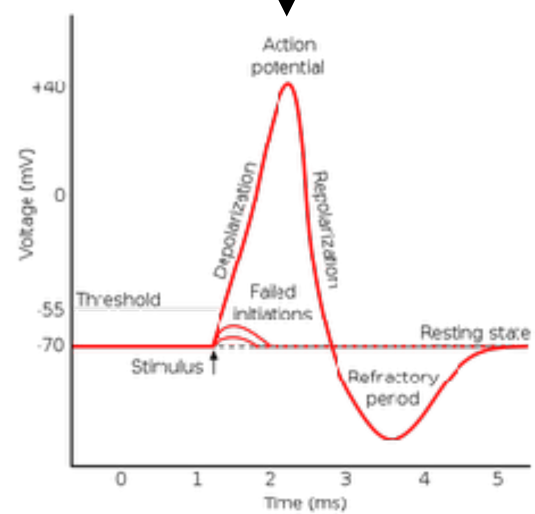
This provides for a **thresholded firing** of the action potential…

A **non-linear oscillator**...

membrane pot
$$\frac{dv}{dt} = v - \frac{v^3}{3} - w + I$$

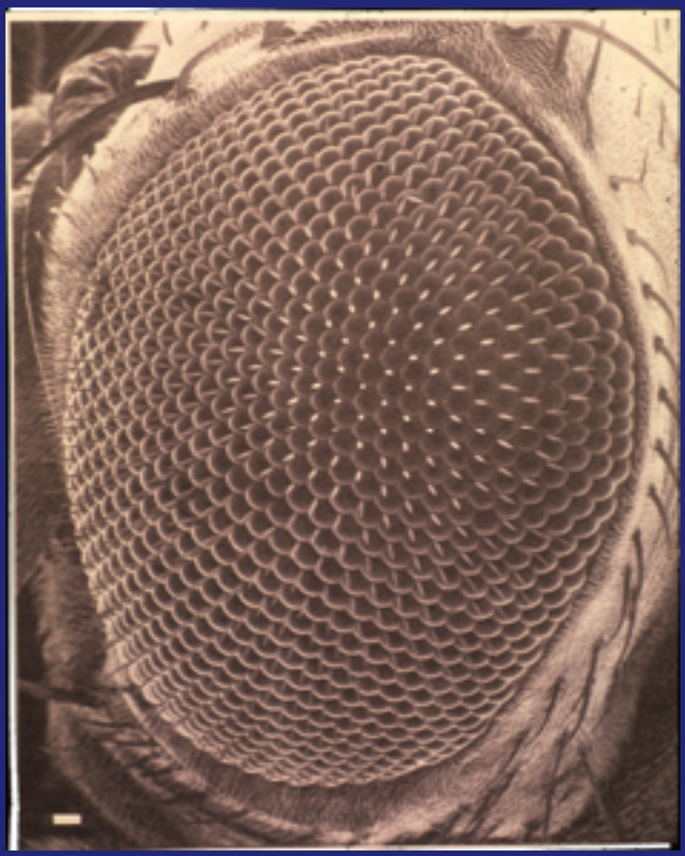
slow K+ flux
$$\frac{dw}{dt} = \frac{1}{\tau}(v + a - bw)$$

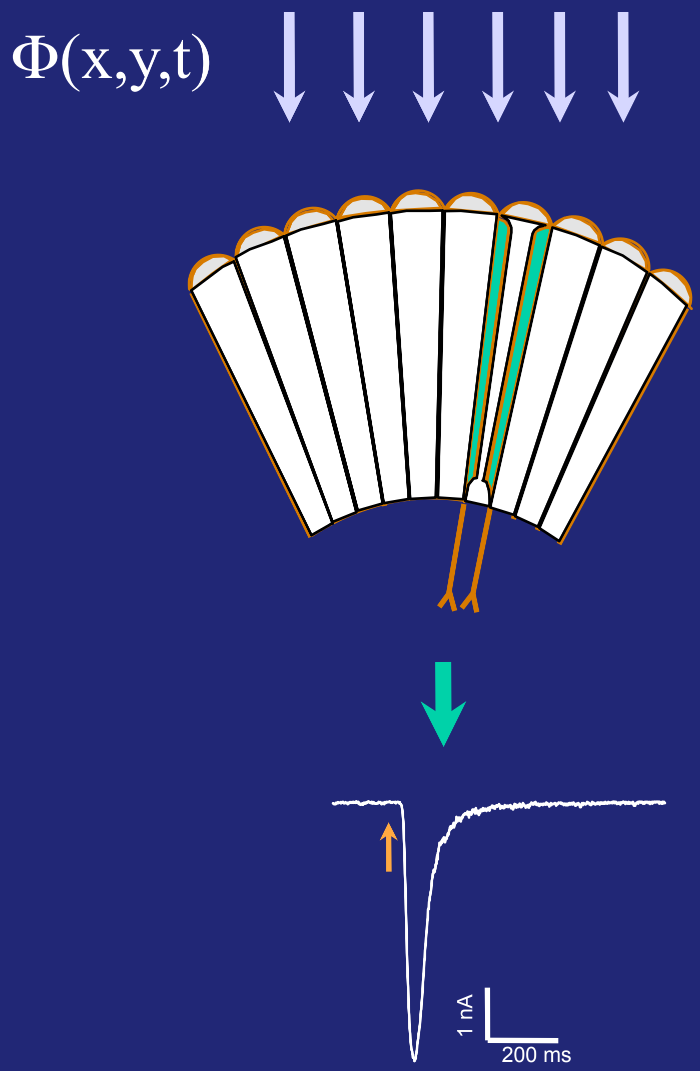




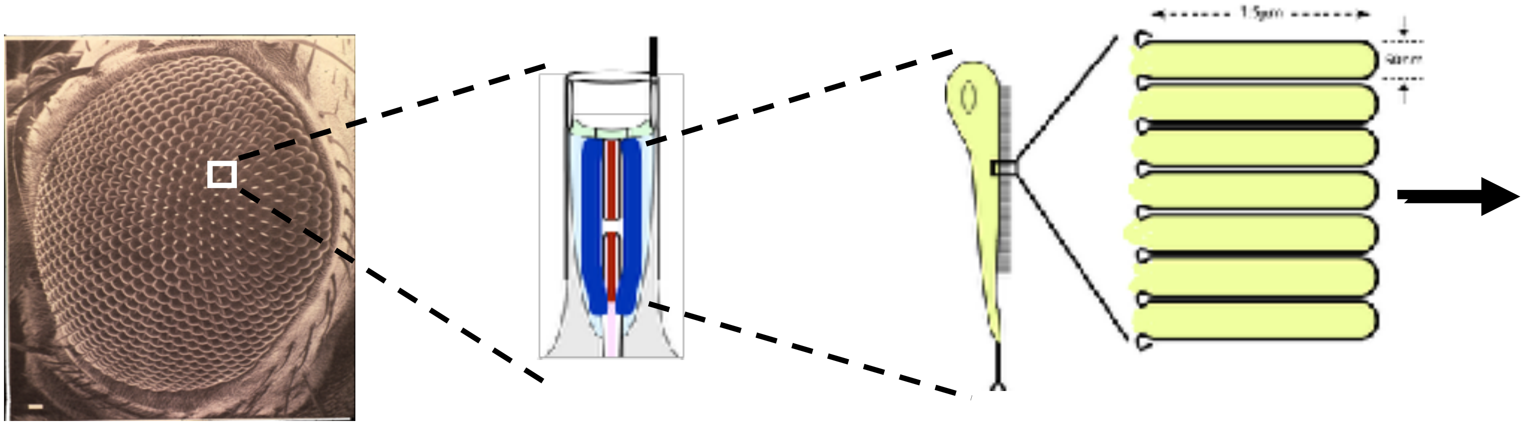
the linear term to the w nullcline provides for **thresholded oscillation**….

The *Drosophila* eye





Levels of structural organization…



The molecular machinery...

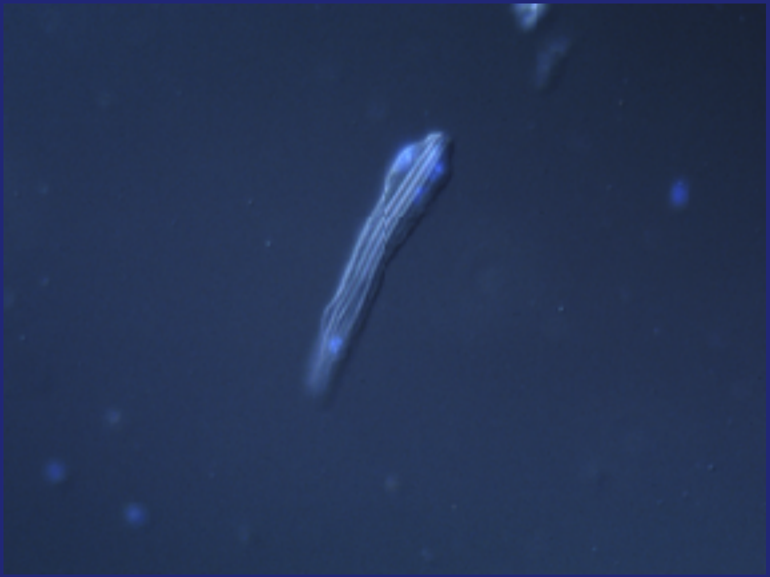
The compound eye...
~800 unit eyes

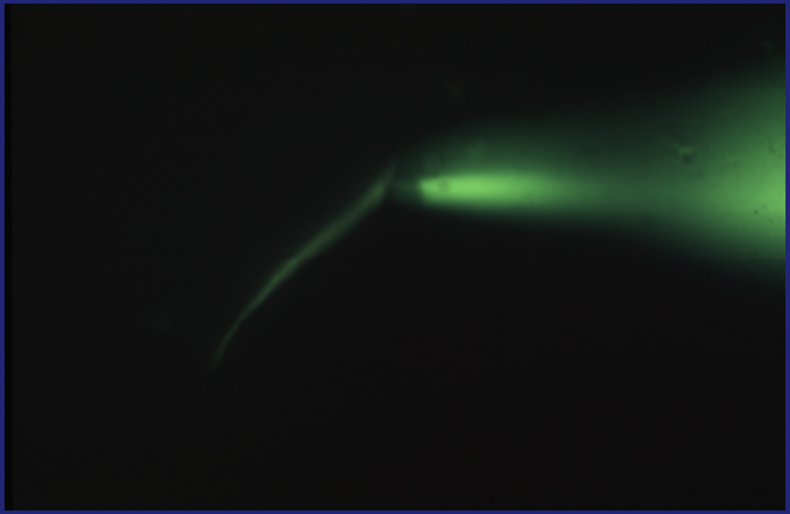
Each unit eye (an ommatidium)...
8 photoreceptor cells

Each cell...
~30,000 microvilli (the rhabdomere)

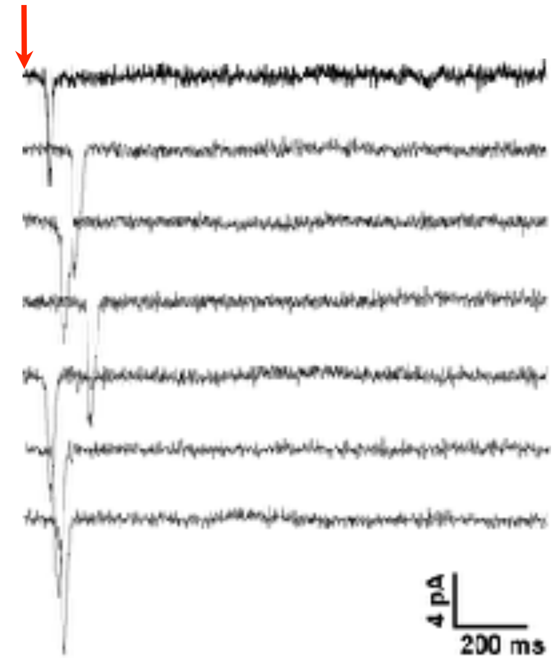
Each microvillus...
~10,000 rhodopsin molecules

Tsunoda et al., Nature (1997) 388, 244
Shieh and Niemeyer, Neuron (1995) 14, 201



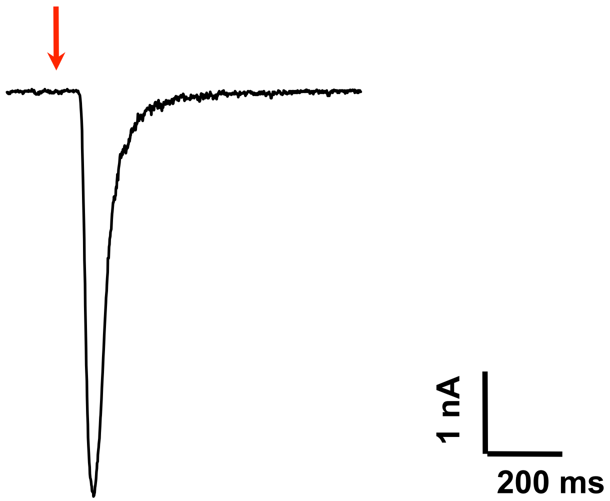


The Single Photon Response (Quantum Bump):



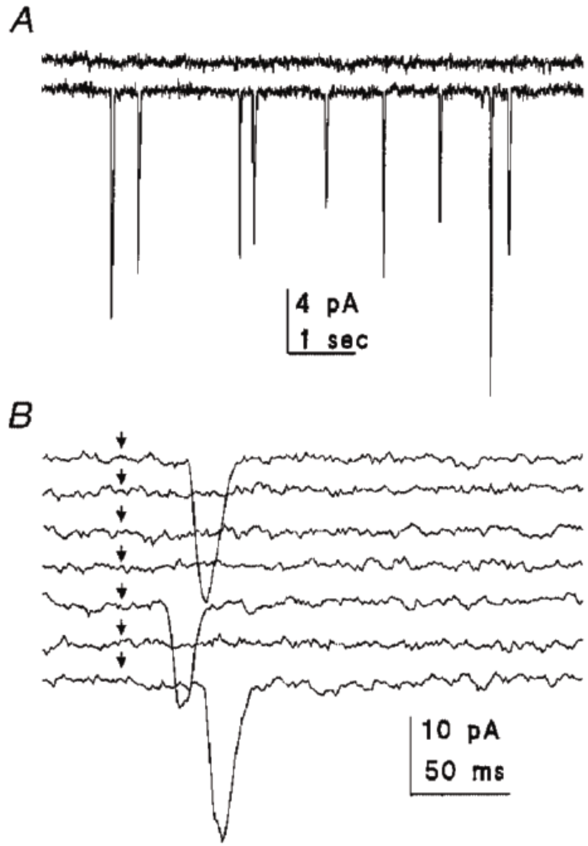
Stochastic electrical response to the absorption of a single photon. Parameters: size, shape, latency of occurrence, and a refractory period.

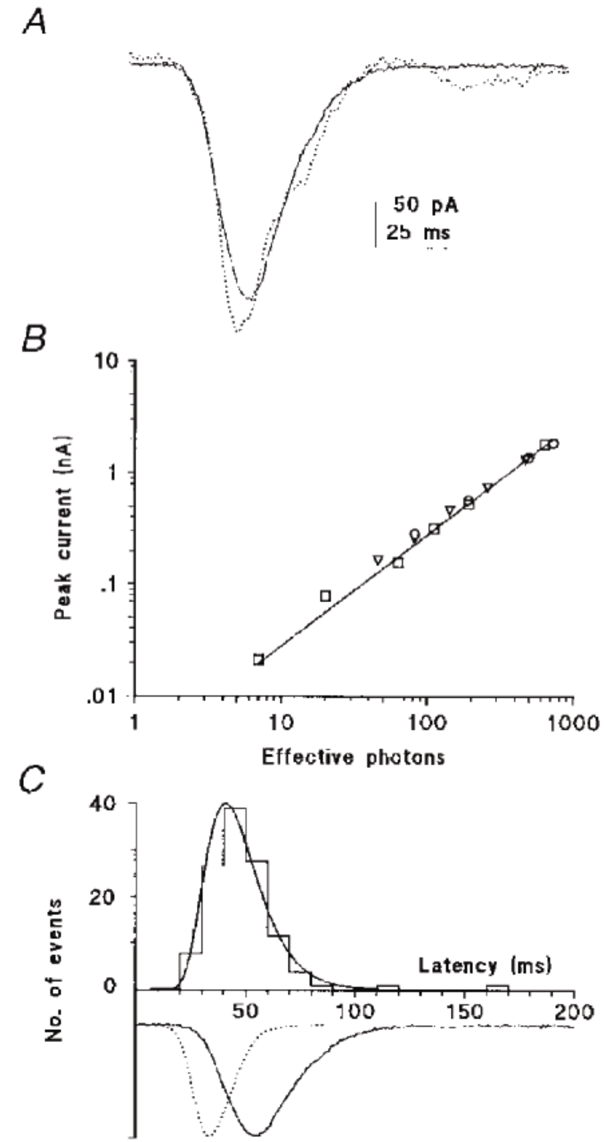
The Macroscopic Impulse Response:



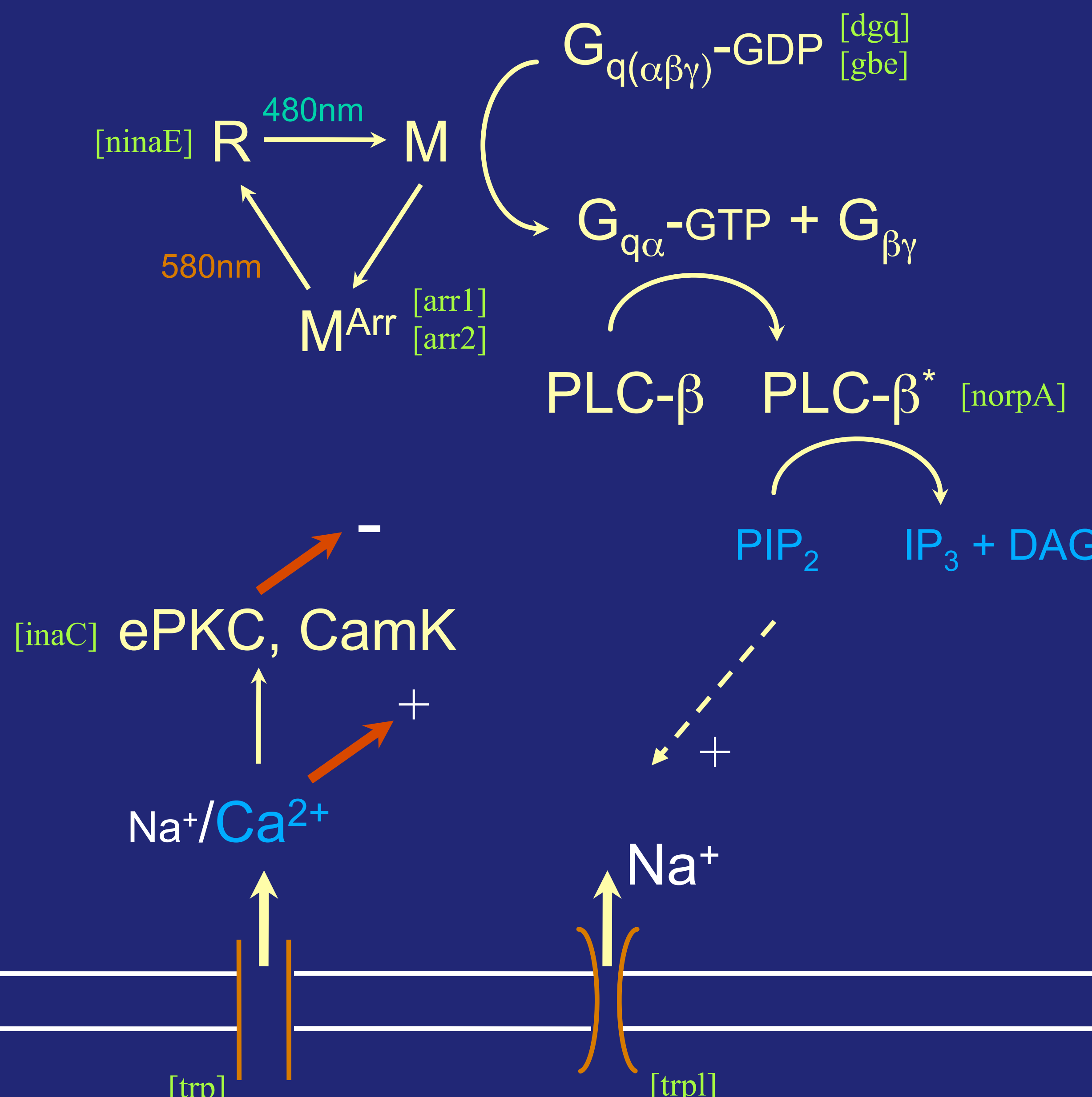
A statistical superposition of quantal responses. This response is the bump latency distribution convolved with the average bump size and shape.

Linearity at the **cellular level**...





Henderson and Hardie, J.Physiol. (2000) 524.1, 179


[ninaE] R
480nm
M
580nm
M^Arr
[arr1]
[arr2]
G q(αβγ) -GDP
[dgq]
[gbe]
G qα -GTP + G βγ
PLC-β
PLC-β*
[norpA]
PIP2
IP3 + DAG
-
[inaC] ePKC, CamK
+
+
Na+/Ca2+
Na+
[trp]
[trpl]

Calcium-dependence...

the macroscopic response..

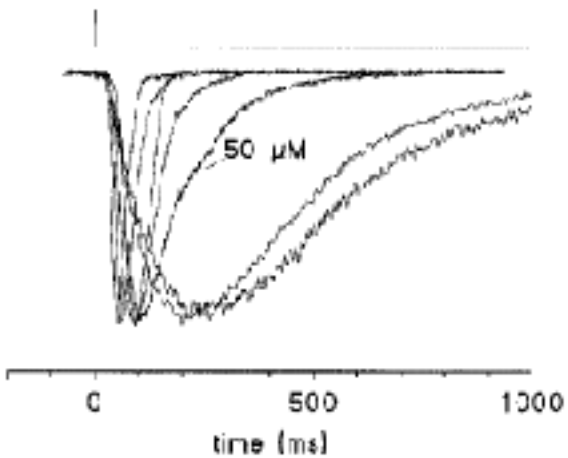
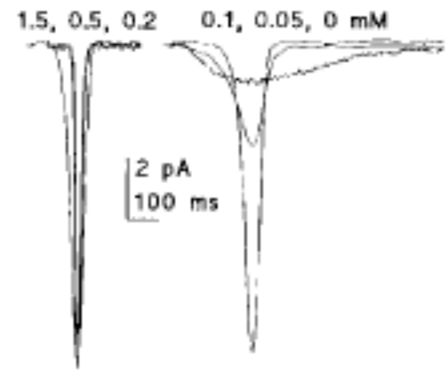


Figure 6. Impulse responses at different Ca^{2+} concentrations

Normalized responses to a brief (10 ms) flash of light containing ca 75 effective photons over the range of bath Ca^{2+} concentrations used in this study (1·5 and 0·5 mM, 200, 100, 50 and 25 µM and '0' Ca^{2+}). Response kinetics became progressively slower as Ca^{2+} was lowered. Note that responses in 25 µM and '0' Ca^{2+} were very similar

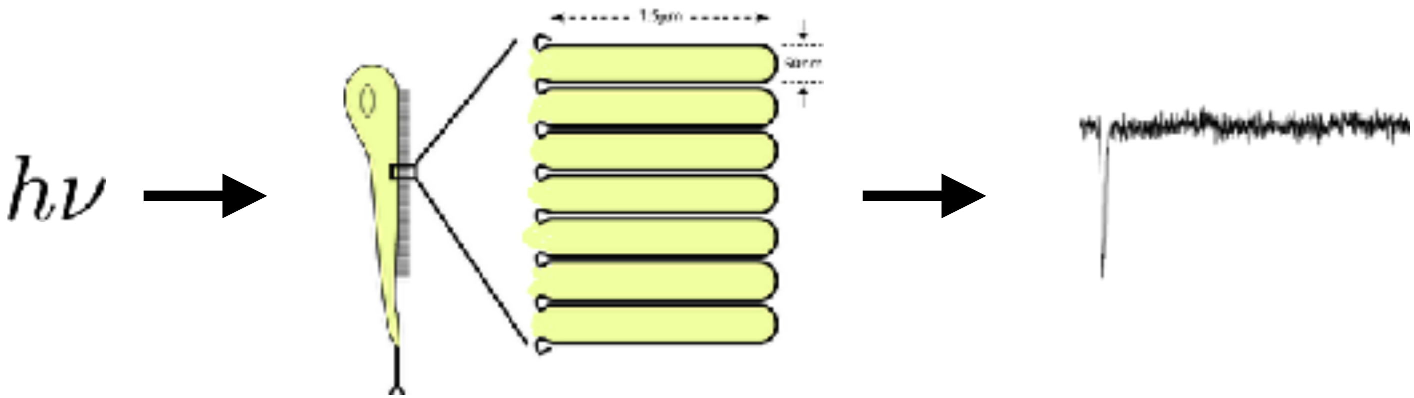
the quantum bump....



Henderson and Hardie, J. Physiol. (2000) 524, 179

Essentially all of the proteins and small molecules involved are identified, every state-of-the-art high-quality experiment (single/double knockouts, electrophysiology, calcium imaging, etc.) has been carried out…

BUT...yet we do not understand even the most basic response of this system – the quantum bump.

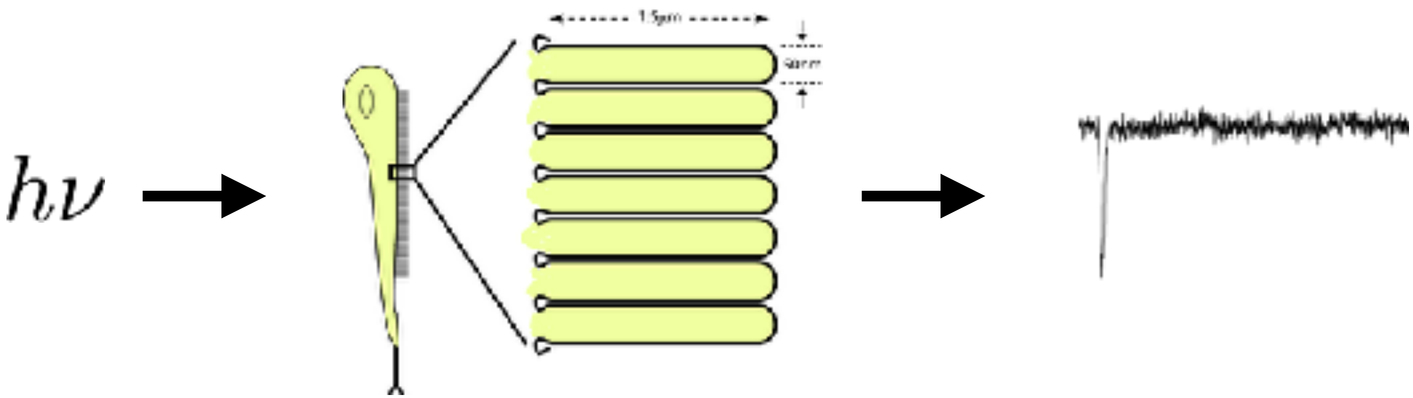


The basic questions

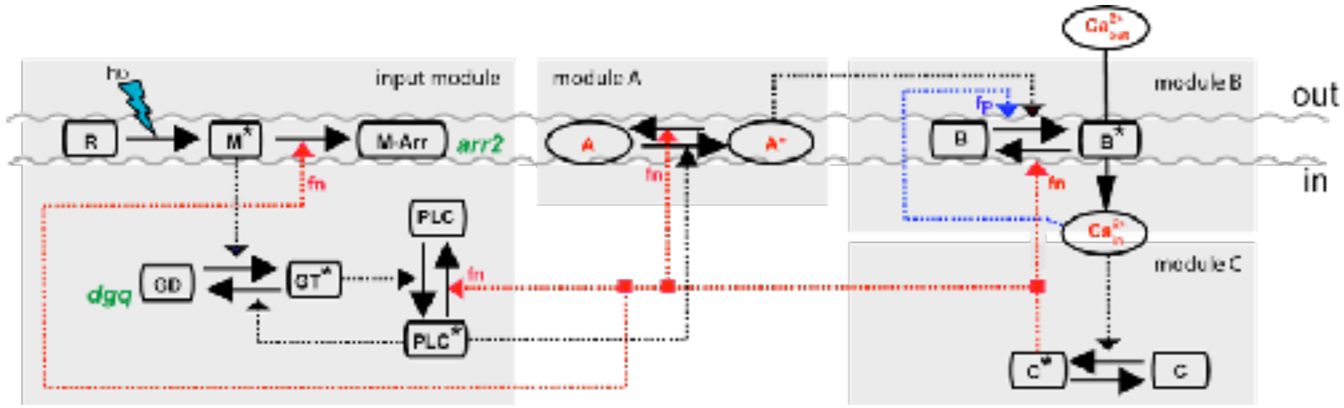
(1) What is the basis for the quantum bump...what determines latency, size/shape, and refraction? Why is it an all-or-nothing event?

(2) What makes it so reliable following light absorption and so improbable in the dark?

(3) Why do we get exactly one bump per photon, never two or more?



The model…

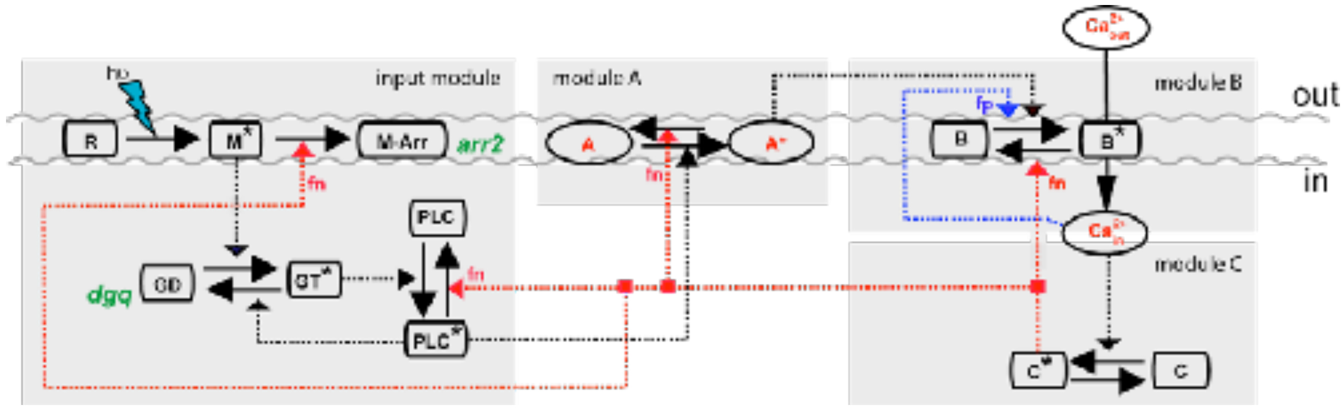


Concepts, simplifications, and an important feature…

(1) You can think of the model as comprising four conceptual "modules". An bump trigger (input), a bump initiator (A), a bump generator (B), and a negative feedback unit (C).

Pumir et al., PNAS (2008) 105, 10354

The model…



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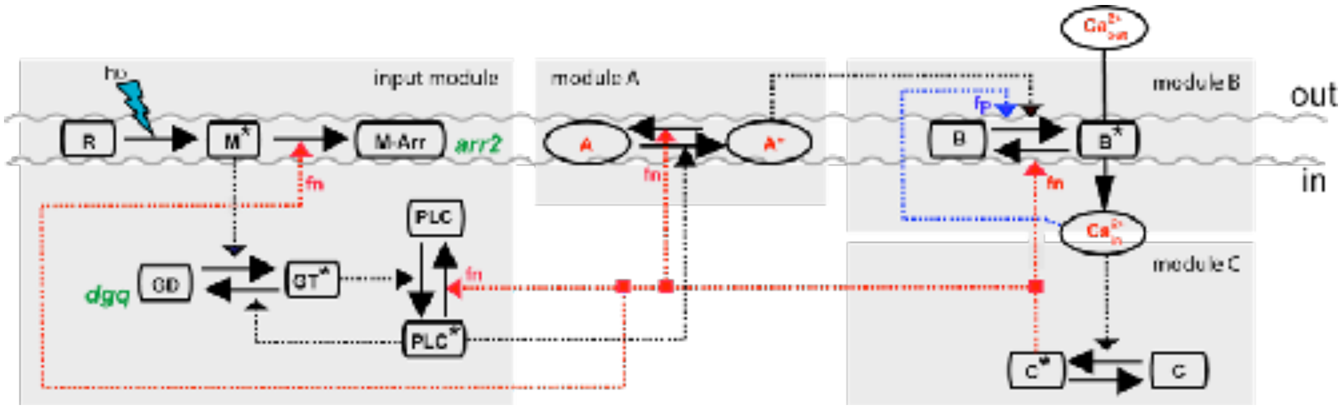
The model…



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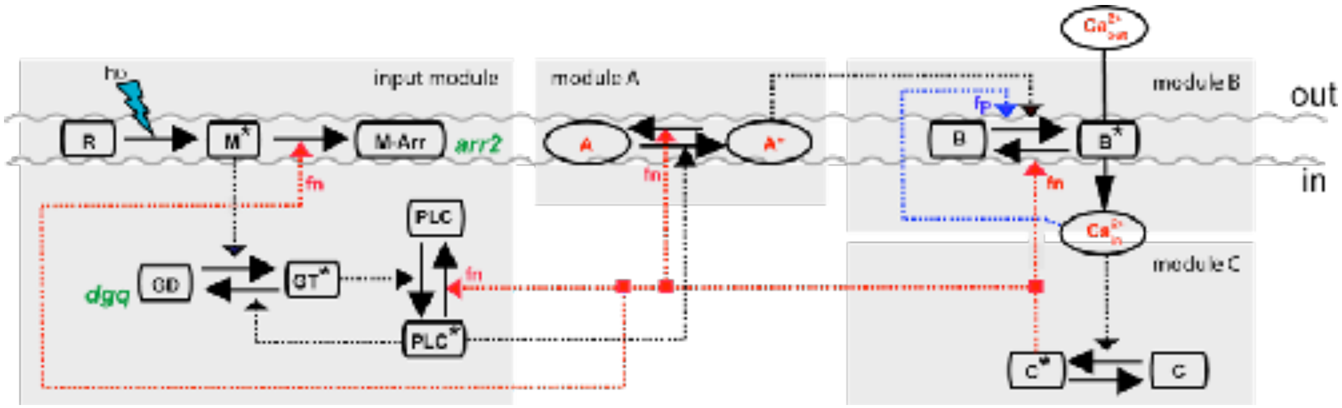
(2) Some known molecules (e.g. M* inactivation, and InaD) are represented implicitly in the model.

Pumir et al., PNAS (2008) 105, 10354

The model…



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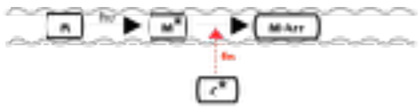
(2) Some known molecules (e.g. M* inactivation, and InaD) are represented implicitly in the model.

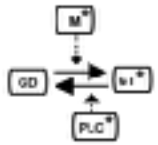
(3) System operates at the stochastic limit (1 M*, 1-5 G*, 1-5 PLC*…15-25 B*), so requires stochastic simulation methods (numbers, not concentrations of species). We will describe the method for computational simulation of the reaction dynamics shortly...

Pumir et al., PNAS (2008) 105, 10354

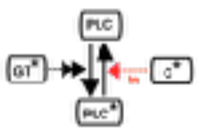
The model…mathematically:



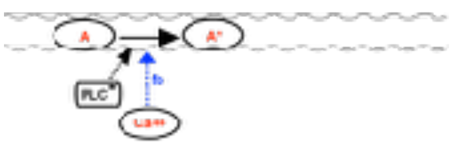
$$\frac{dM^*}{dt} = -\gamma_{rh}(1 + g_{rh}f_n)M^*$$



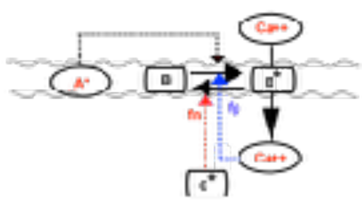
$$\frac{dG^*}{dt} = k_g G M^* - k_{plc}PLC_t G^* - a_g G^*$$



$$\frac{dPLC^*}{dt} = k_{plc}PLC_t G * -\gamma_{plc}(1 + g_{plc}f_n)PLC^*$$

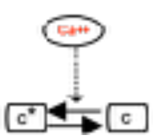


$$\frac{dA^*}{dt} = k_a PLC^* - \gamma_a(1 + g_a f_n)A^*$$



$$\frac{dB^*}{dt} = k_b(1 + g_{bp}f_p)(A^*/k_a)^m(B_t - B^*) - \gamma_b(1 + g_{bn}f_n)B^*$$

$$\frac{dCa}{dt} = \sigma B^*([Ca]_{ext} - [Ca]) - \gamma_{Ca}([Ca] - [Ca]_0) - (k_c[Ca] - \gamma_c C^*)$$



$$\frac{dC^*}{dt} = k_c[Ca] - \gamma_c C^*$$

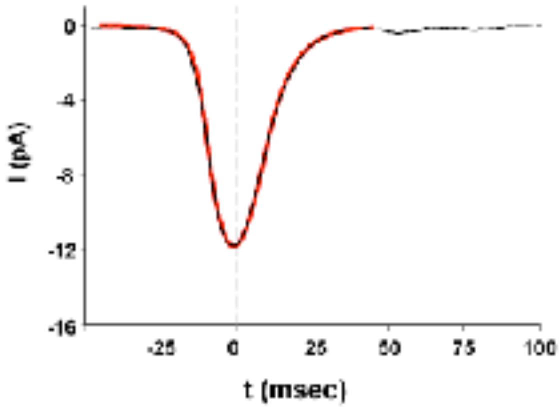
$$f_n(C^*) = \frac{([C^*]/K_n)^{m_n}}{1 + ([C^*]/K_n)^{m_n}}$$

$$f_p(Ca) = \frac{([Ca]/K_p)^{m_p}}{1 + ([Ca]/K_p)^{m_p}}$$

Parameter estimation:

Free parameters fit to average quantum bump size and shape, and average latency.

And...



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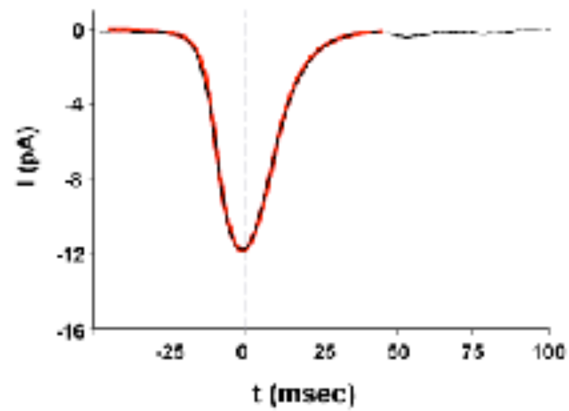
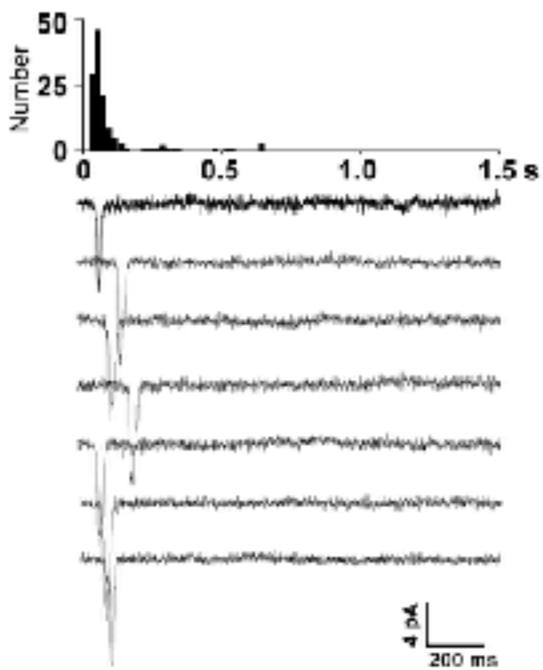
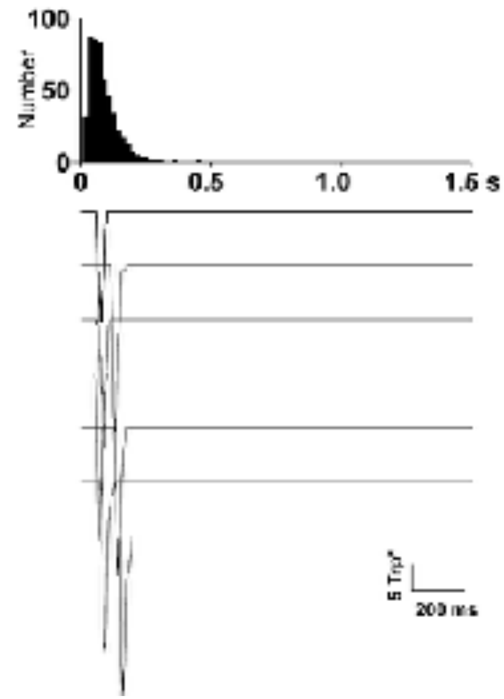


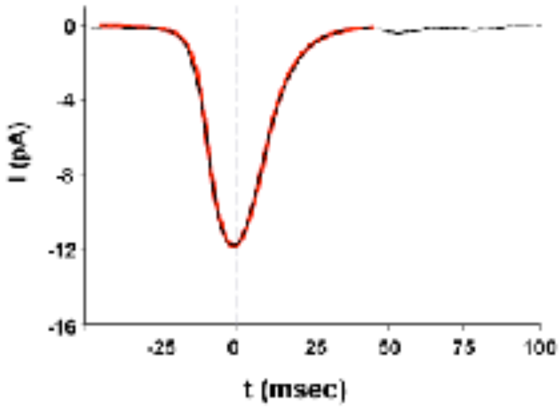
And...as you will see soon, the system generates nice looking quantum bumps upon stochastic numerical simulation...





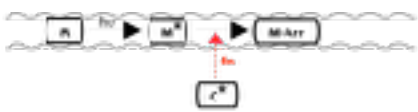
Parameter estimation:

Free parameters fit to average quantum bump size and shape, and average latency.

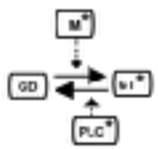


Results in a "solution manifold", but basic mechanism of bump generation is independent of specific parameter values.

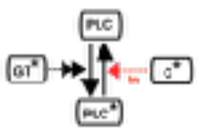
How can we “see” the system dynamics in some intuitive way? And...what about the stochasticity?



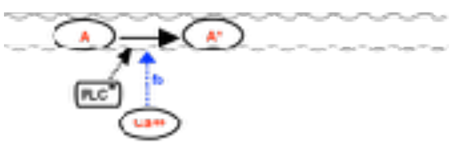
$$\frac{dM^*}{dt} = -\gamma_{rh}(1 + g_{rh} f_n) M^*$$



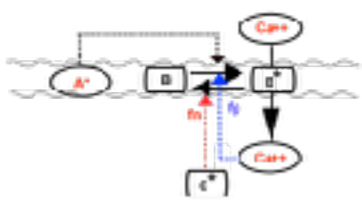
$$\frac{dG^*}{dt} = k_g G M^* - k_{plc} PLC_t G^* - a_g G^*$$



$$\frac{dPLC^*}{dt} = k_{plc} PLC_t G * -\gamma_{plc}(1 + g_{plc} f_n) PLC^*$$

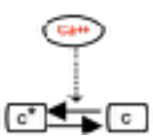


$$\frac{dA^*}{dt} = k_a PLC^* - \gamma_a (1 + g_a f_n) A^*$$



$$\frac{dB^*}{dt} = k_b (1 + g_{bp} f_p)(A^*/k_a)^m (B_t - B^*) - \gamma_b (1 + g_{bn} f_n) B^*$$

$$\frac{dCa}{dt} = \sigma B^*([Ca]_{ext} - [Ca]) - \gamma_{Ca}([Ca] - [Ca]_0) - (k_c[Ca] - \gamma_c C^*)$$



$$\frac{dC^*}{dt} = k_c[Ca] - \gamma_c C^*$$

$$f_n(C^*) = \frac{([C^*]/K_n)^{m_n}}{1 + ([C^*]/K_n)^{m_n}}$$

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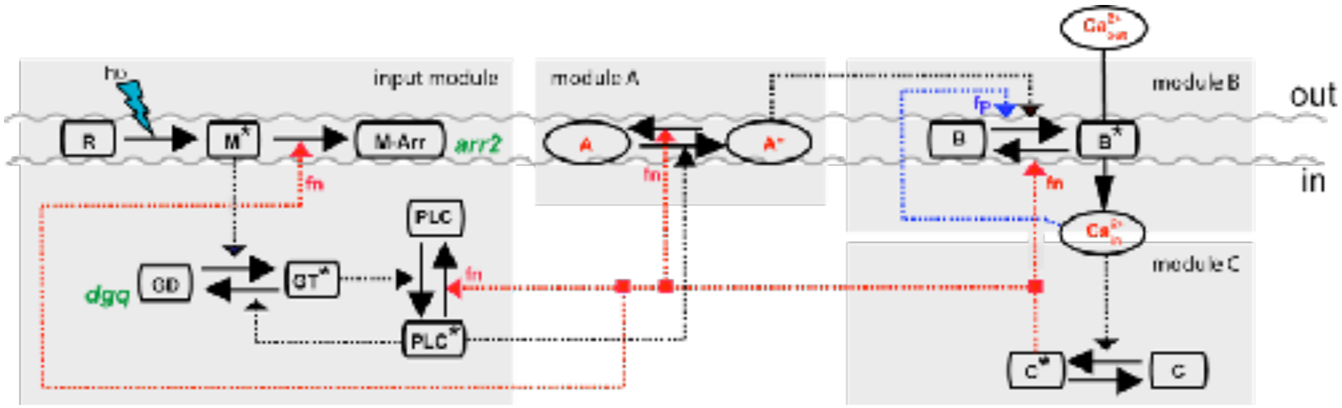


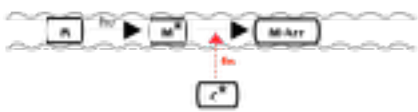
(1) We want to “see” the **system dynamics** in some intuitive way...and...

(2) System operates at the stochastic limit (1 M*, 1-5 G*, 1-5 PLC*…15-25 B*), so requires stochastic simulation methods (numbers, not concentrations of species).

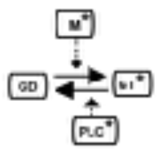
Let’s deal with item 2 first....the Gillespie method (another interlude).

Pumir et al., PNAS (2008) 105, 10354

Stochastic simulation...the Gillespie method.



$$\frac{dM^*}{dt} = -\gamma_{rh}(1 + g_{rh}f_n)M^*$$



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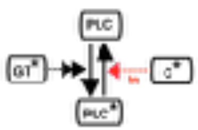
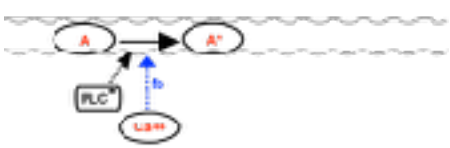
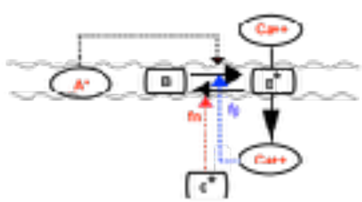


$$\frac{dPLC^*}{dt} = k_{plc}PLC_tG * -\gamma_{plc}(1 + g_{plc}f_n)PLC^*$$



$$\frac{dA^*}{dt} = k_aPLC^* - \gamma_a(1 + g_af_n)A^*$$



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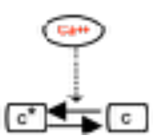

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<u>Now to deal with stochastic fluctuations</u>…the Gillespie Method

<u>Step 1:</u> $[X_i(t)] = [M^*(t), G^*(t), PLC^*(t), A^*(t), B^*(t), Ca(t), C^*(t)]$ The current “state” of the system

↓

Now to deal with stochastic fluctuations…the Gillespie Method

Step 1: $[X_i(t)] = [M^*(t), G^*(t), PLC^*(t), A^*(t), B^*(t), Ca(t), C^*(t)]$ The current "state" of the system

↓

Step 2: $\frac{d[X_i^f]}{dt} = \left[\frac{dM_f^*}{dt}, \frac{dG_f^*}{dt}, \frac{dPLC_f^*}{dt}, \frac{dA_f^*}{dt}, \frac{dB_f^*}{dt}, \frac{dCa_f^*}{dt}, \frac{dC_f^*}{dt}\right]$ Calculate forward and reverse rates for time t

$$\frac{d[X_i^r]}{dt} = \left[\frac{dM_r^*}{dt}, \frac{dG_r^*}{dt}, \frac{dPLC_r^*}{dt}, \frac{dA_r^*}{dt}, \frac{dB_r^*}{dt}, \frac{dCa_r^*}{dt}, \frac{dC_r^*}{dt}\right]$$

↓

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Calculate forward and reverse rates

Step 3: $0 \le r_1, r_2 \le 1$

Generate two random numbers

Now to deal with stochastic fluctuations…the Gillespie Method

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Generate two random numbers

Step 4:

$$t_{new} = t_{old} + \frac{\ln\left(\frac{1}{r_1}\right)}{\sum_i \frac{d[X_i^f]}{dt} + \sum_i \frac{d[X_i^r]}{dt}}$$

Update time…so that time steps are a function of how fast the system dynamics are evolving

Now to deal with stochastic fluctuations…the Gillespie Method

Step 1: $[X_i(t)] = [M^*(t), G^*(t), PLC^*(t), A^*(t), B^*(t), Ca(t), C^*(t)]$

The current "state" of the system

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Calculate forward and reverse rates

Step 3: $0 \le r_1, r_2 \le 1$

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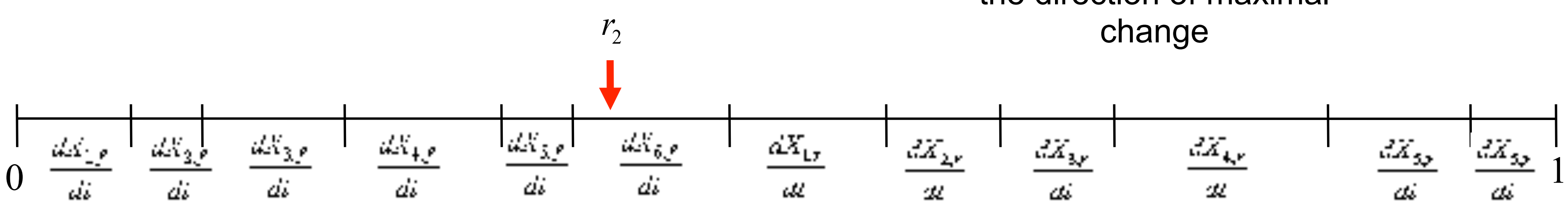
$$t_{new} = t_{old} + \frac{\ln\left(1/r_1\right)}{\sum_i \frac{d[X_i^f]}{dt} + \sum_i \frac{d[X_i^r]}{dt}}$$

Update time

Step 5: $X_6(t_{new}) = X_6(t_{old}) + 1$

Update state of system…so that the system statistically moves in the direction of maximal change



Now to deal with stochastic fluctuations…the Gillespie Method

Step 1: $[X_i(t)] = [M^*(t), G^*(t), PLC^*(t), A^*(t), B^*(t), Ca(t), C^*(t)]$

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Calculate forward and reverse rates

Step 3: $0 \le r_1, r_2 \le 1$

Generate two random numbers

Step 4:

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Update time

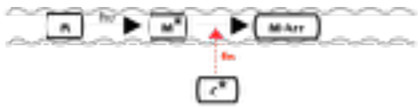
Step 5: $X_6(t_{new}) = X_6(t_{old}) + 1$

Update state of system

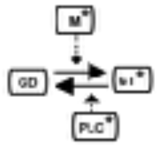
Step 6:

Repeat

Stochastic simulation...the Gillespie method.



$$\frac{dM^*}{dt} = -\gamma_{rh}(1 + g_{rh} f_n)M^*$$



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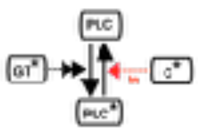
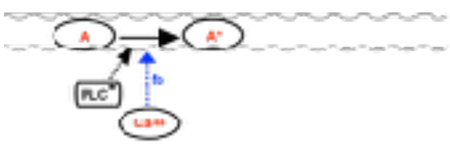
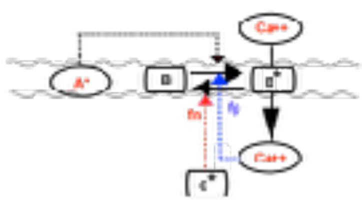


$$\frac{dPLC^*}{dt} = k_{plc} PLC_t G * - \gamma_{plc}(1 + g_{plc} f_n) PLC^*$$



$$\frac{dA^*}{dt} = k_a PLC^* - \gamma_a (1 + g_a f_n) A^*$$



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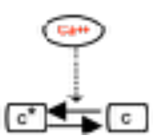

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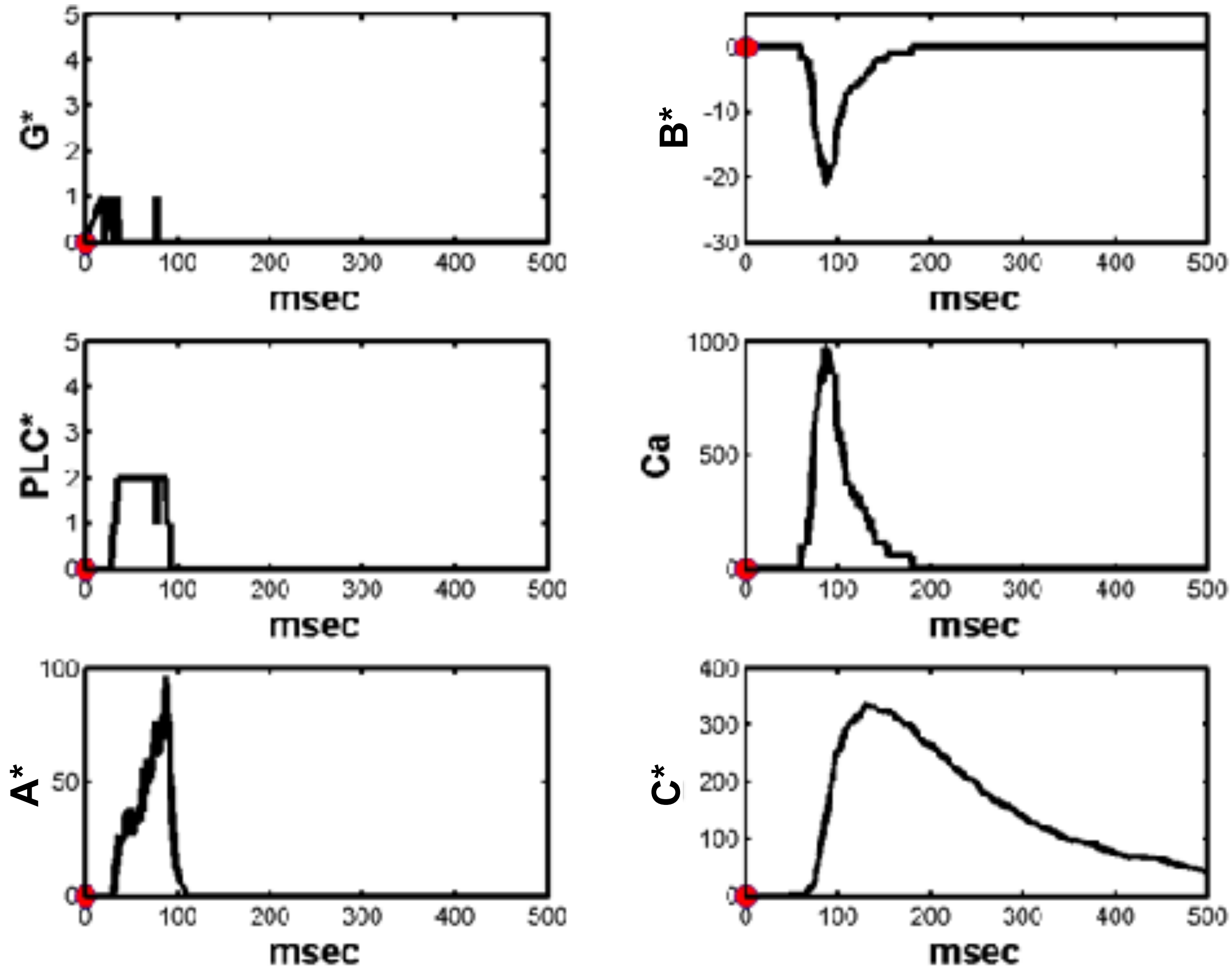
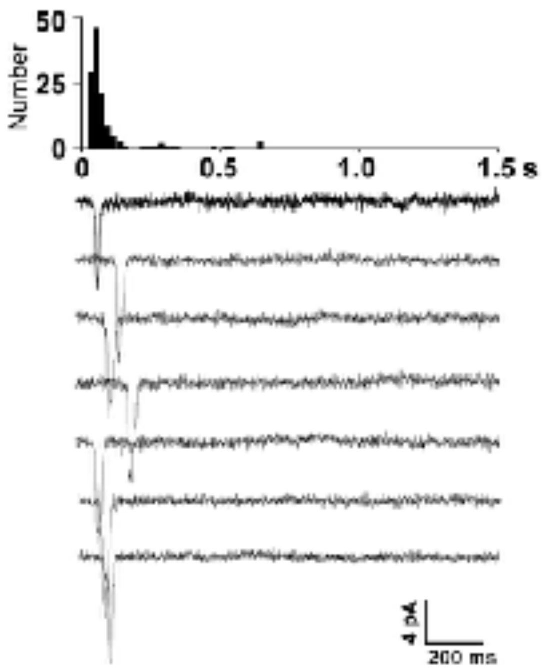
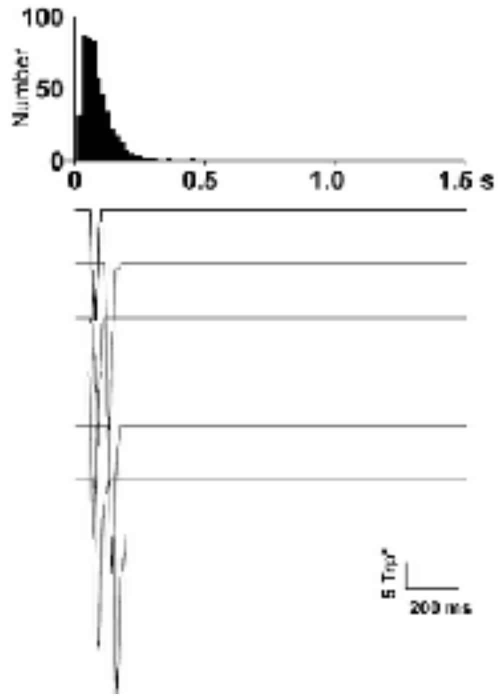
$$f_p(Ca) = \frac{([Ca]/K_p)^{m_p}}{1 + ([Ca]/K_p)^{m_p}}$$

The result of one trial of Gillespie simulation of this system. “Light stimulation” amounts to creating one active rhodopsin molecule instantly at t=0.

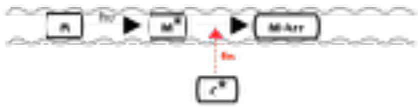


Several quantum bump trials (1M* made at t=0):





How can we "see" the system dynamics in some more intuitive way? This is a seven-dimensional dynamic!!



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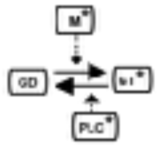

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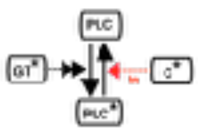
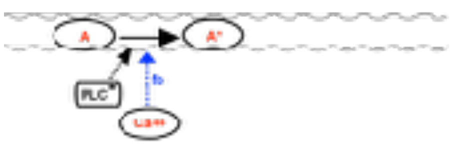


$$\frac{dPLC^*}{dt} = k_{plc} PLC_t G * -\gamma_{plc}(1 + g_{plc} f_n) PLC^*$$



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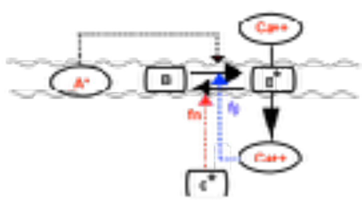

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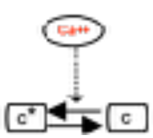

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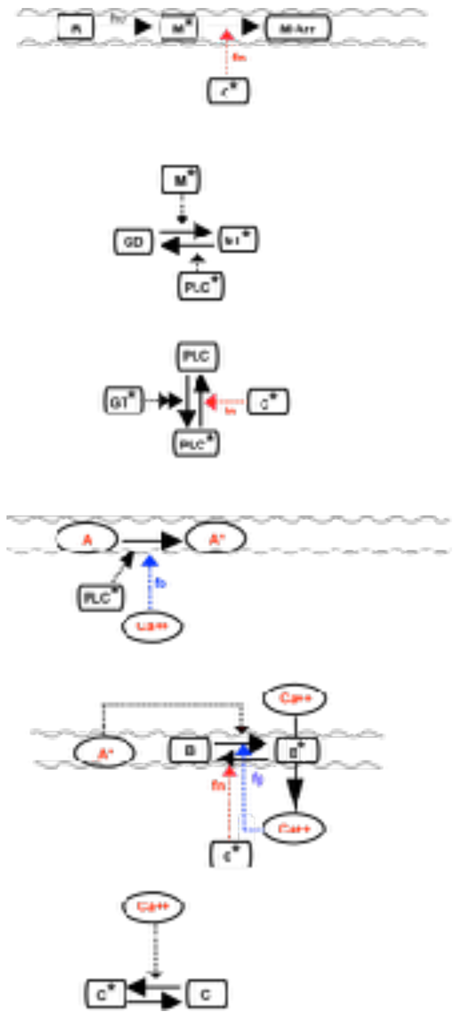
How can we “see” the system dynamics in some intuitive way? This is a seven-dimensional dynamic!!

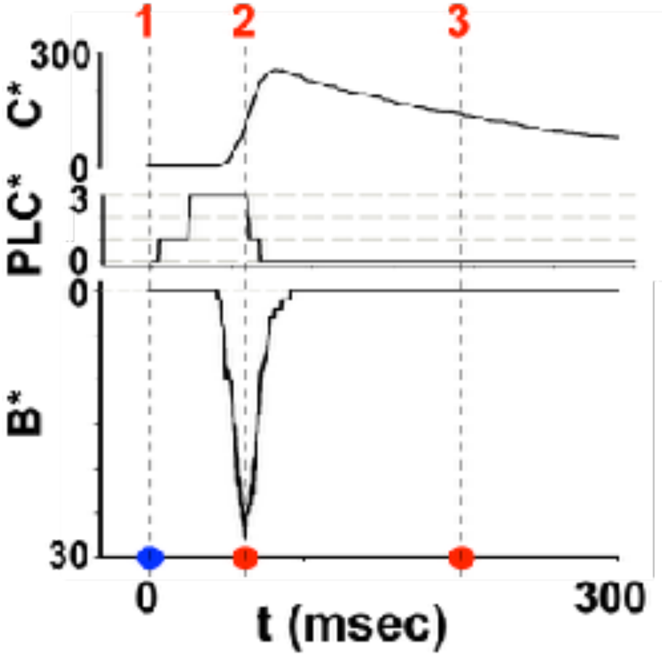


But, it turns out that all the reactions except for B* (the channels) and C* (the negative feedback) equilibrate fast. All the relevant dynamics are effectively in a two-dimensional subspace of the overall dynamics!

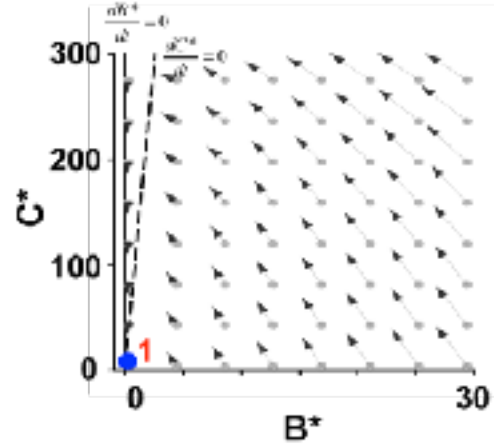
$$\frac{dB^*}{dt} = k_b(1 + g_{bp} f_p)(A^*/k_a)^m (B_t - B^*) - \gamma_b(1 + g_{bn} f_n) B^*$$

$$\frac{dC^*}{dt} = k_c[Ca] - \gamma_c C^*$$

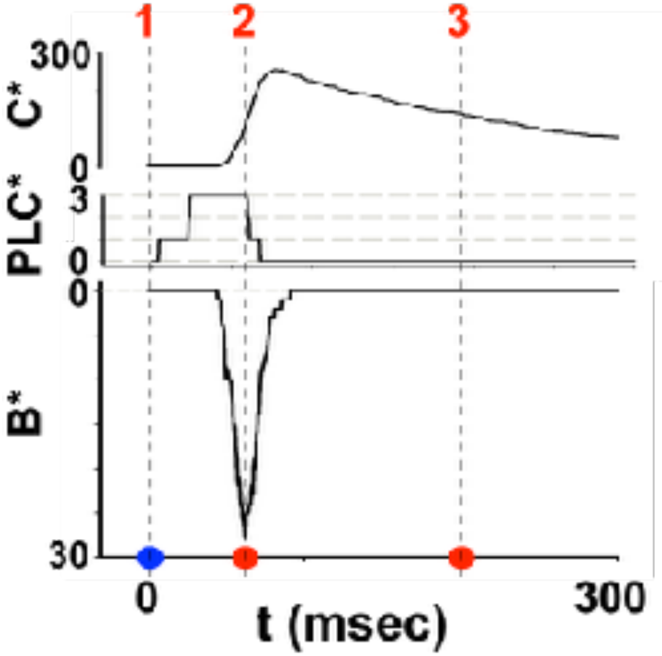
System dynamics in the B* - C* plane:



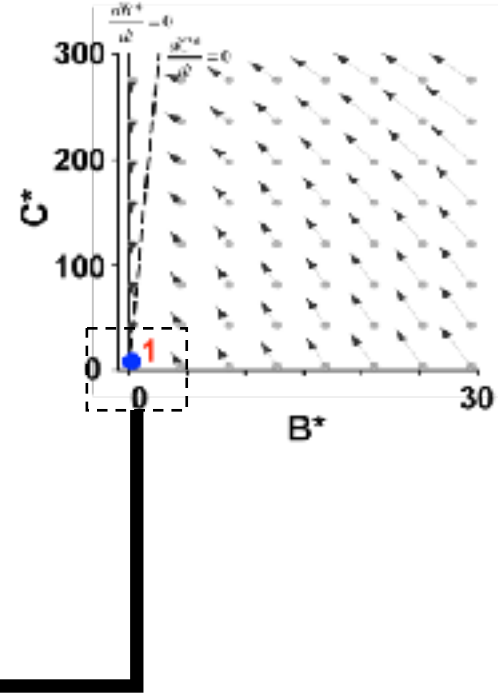
System dynamics in the B* - C* plane:



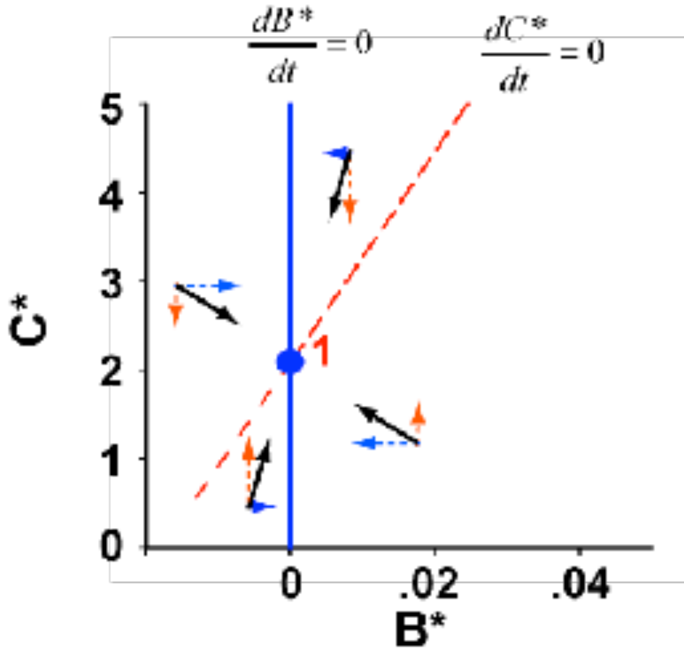
PLC*=0



<u>System dynamics in the B* - C* plane:</u>

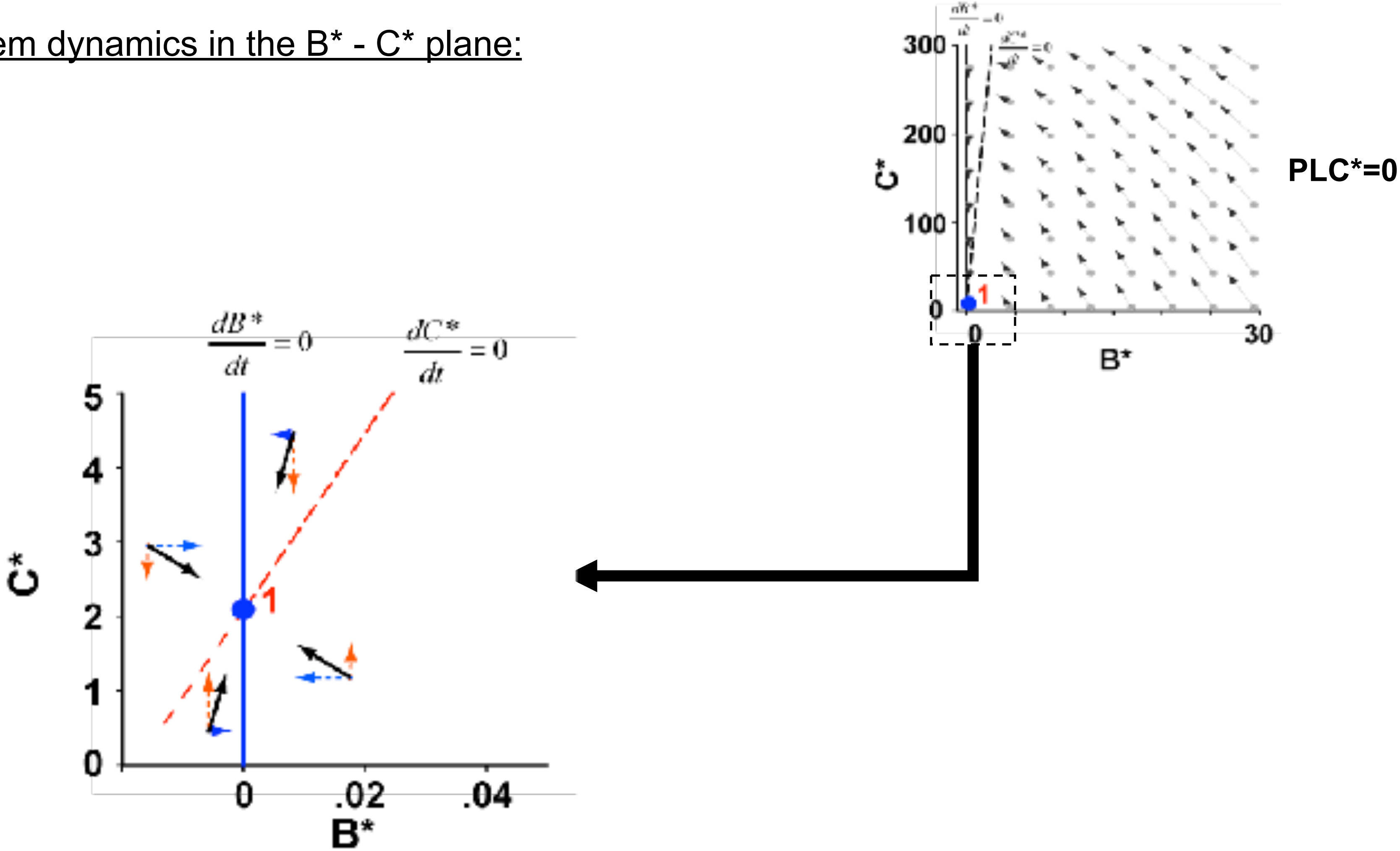


PLC*=0



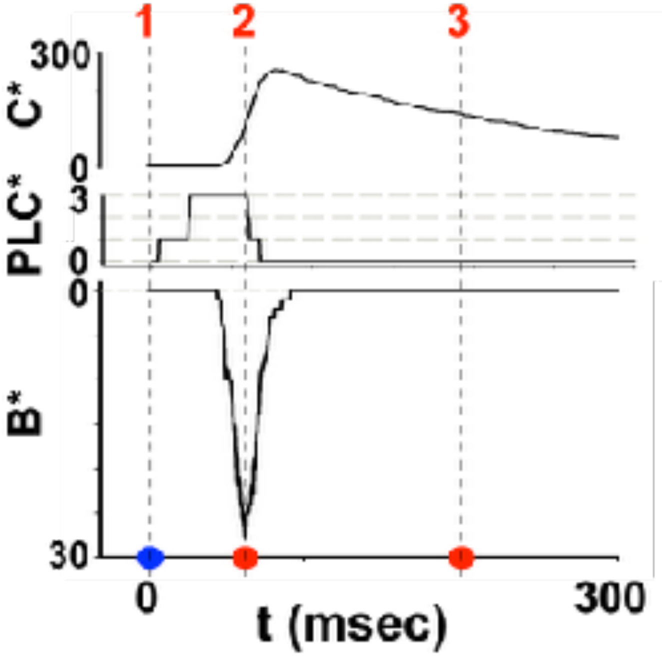
…fixed point stable?

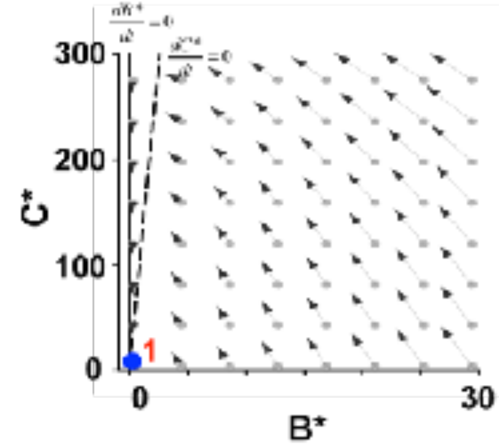
System dynamics in the B* - C* plane:



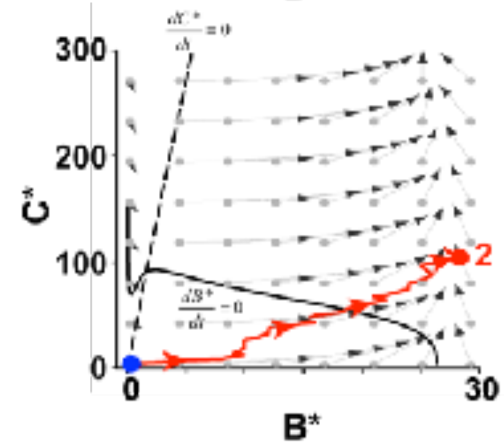
…a stable fixed point in the dark

System dynamics in the B* - C* plane:



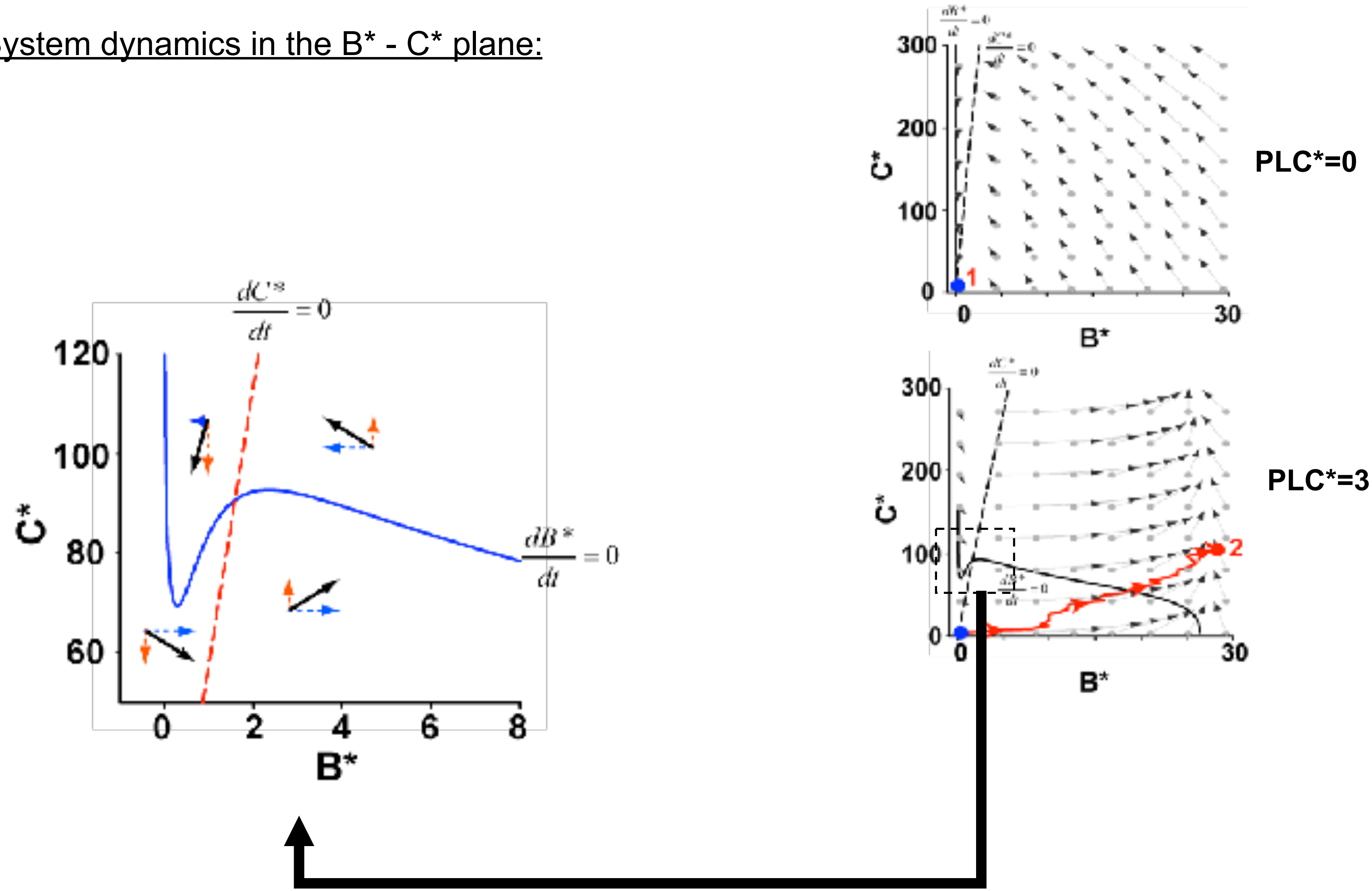


PLC*=0



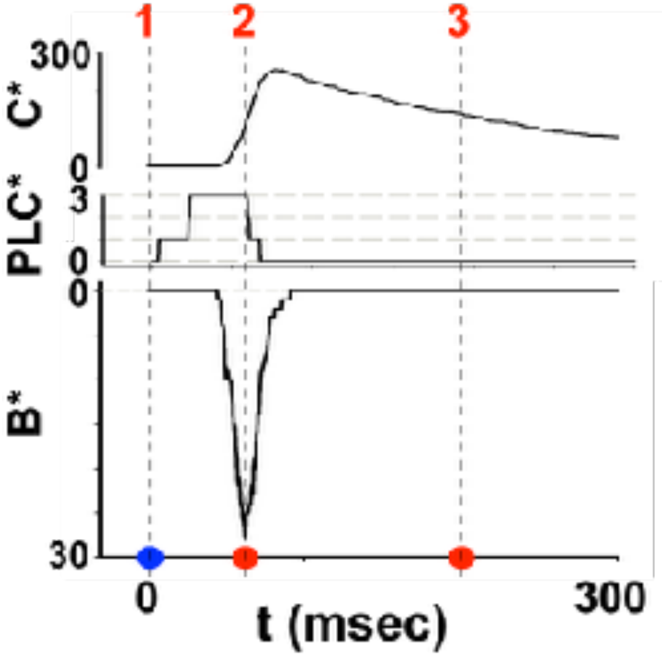
PLC*=3

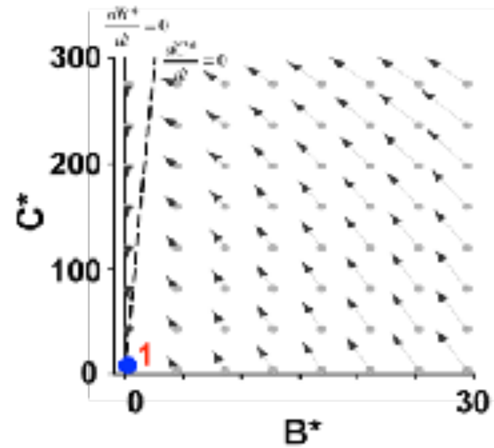
System dynamics in the B* - C* plane:



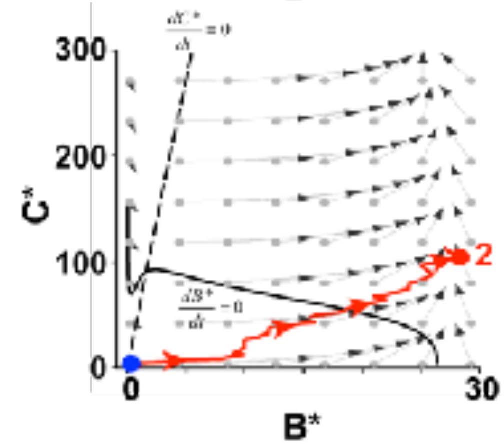
…fixed point destabilizes (via Hopf bifurcation)

System dynamics in the B* - C* plane:





PLC*=0



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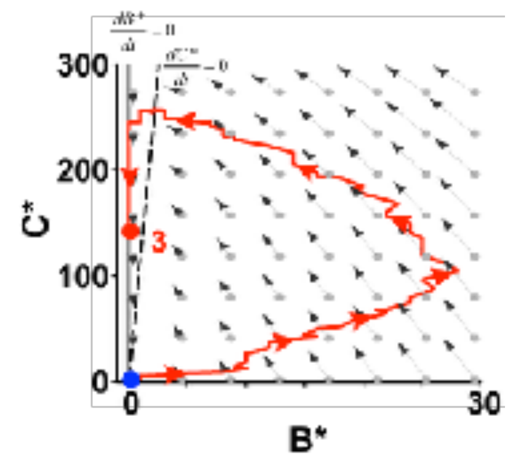
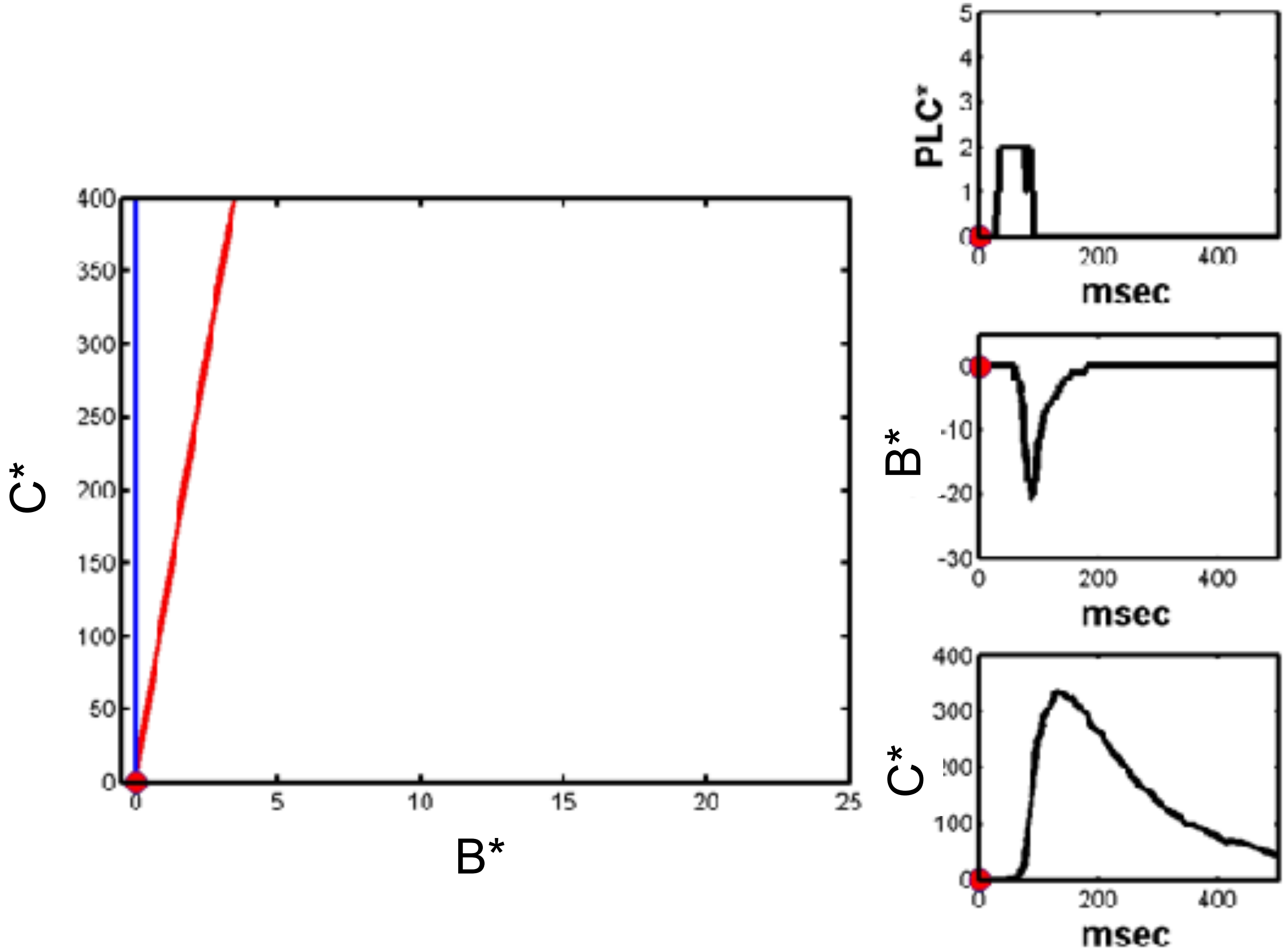


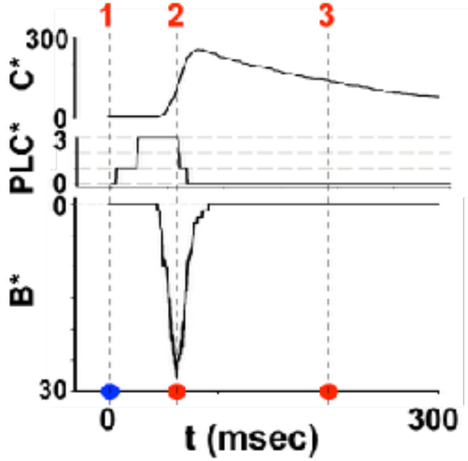
PLC*=0

<u>System dynamics in the Trp* - B* plane:</u>

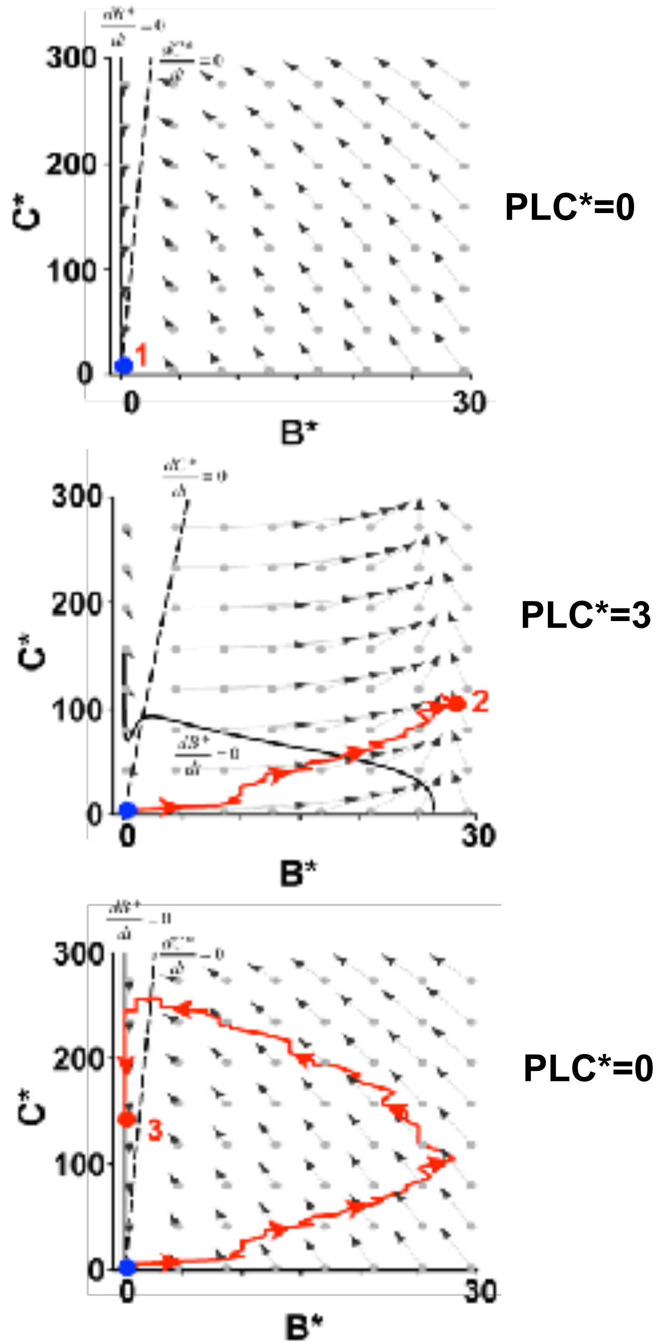
Again, one trial of stochastic simulation of this system. “Light stimulation” amounts to creating one active rhodopsin molecule instantly at t=0.



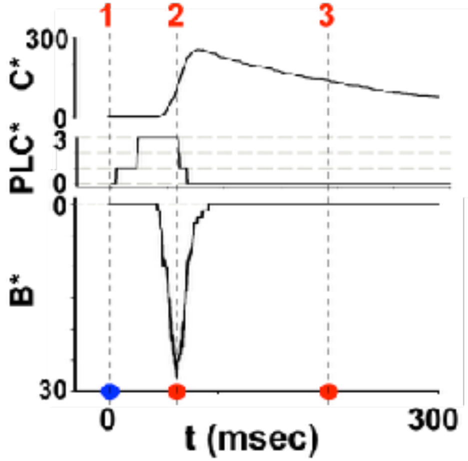
System dynamics in the B* - C* plane:

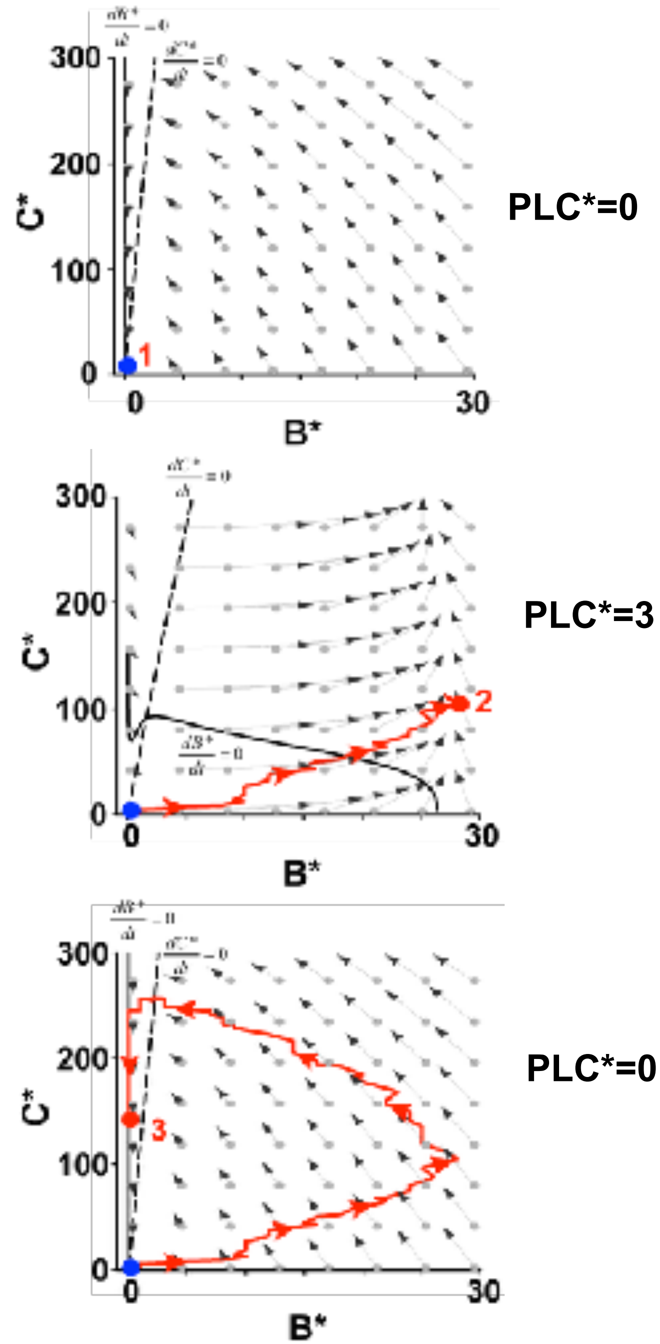


(1) In the dark, the system has a stable fixed point at B*=0. Per the model, a quantum bump is impossible from thermal activations of Trp channels.



System dynamics in the B* - C* plane:





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(2) But, upon activation of PLC*, the system dynamics causes the cascade to work as a stochastic relaxation oscillator… building up DAG to where calcium influx through Trp* ignites the positive feedback. This destabilizes the fixed point, triggers a regenerative opening of Trp channels, and causes the system to go through a “limit-cycle oscillation”.

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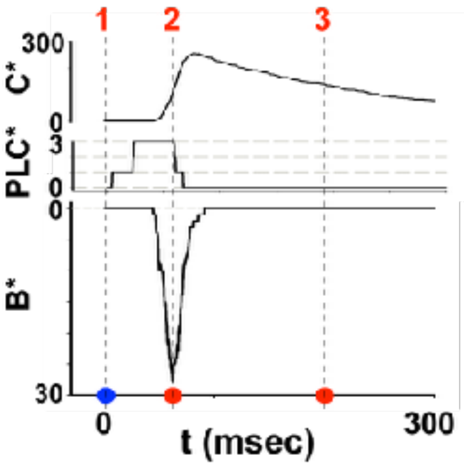

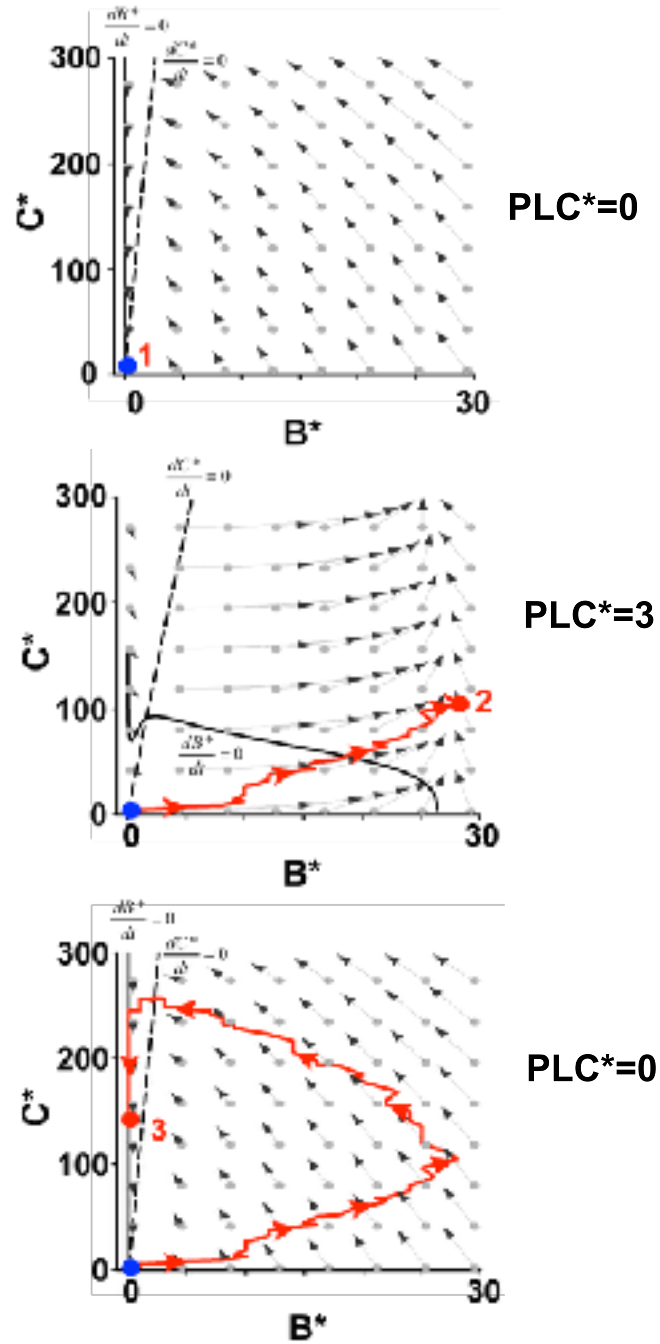

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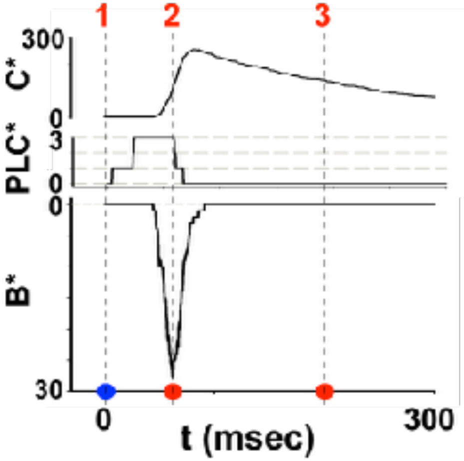
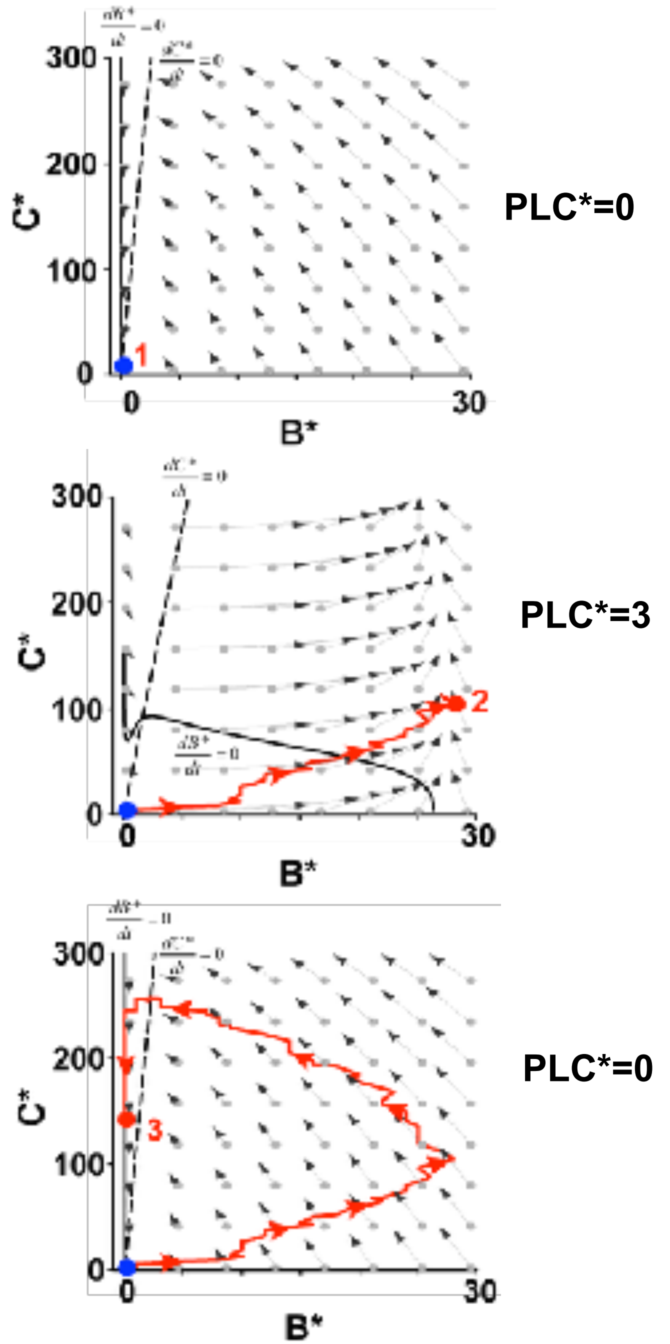
(3) Deactivation of PLC* and build-up of C* shuts-off the bump and causes the system to go into a refractory phase until C* itself deactivates.

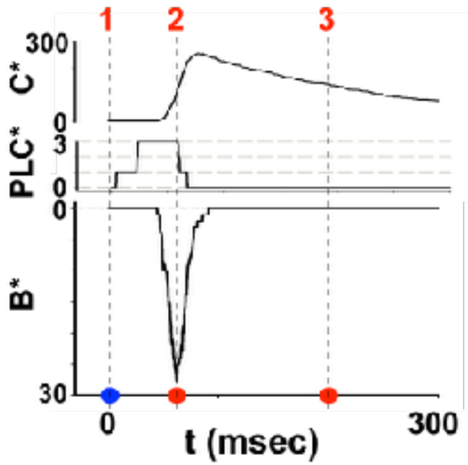
System dynamics in the B* - C* plane:

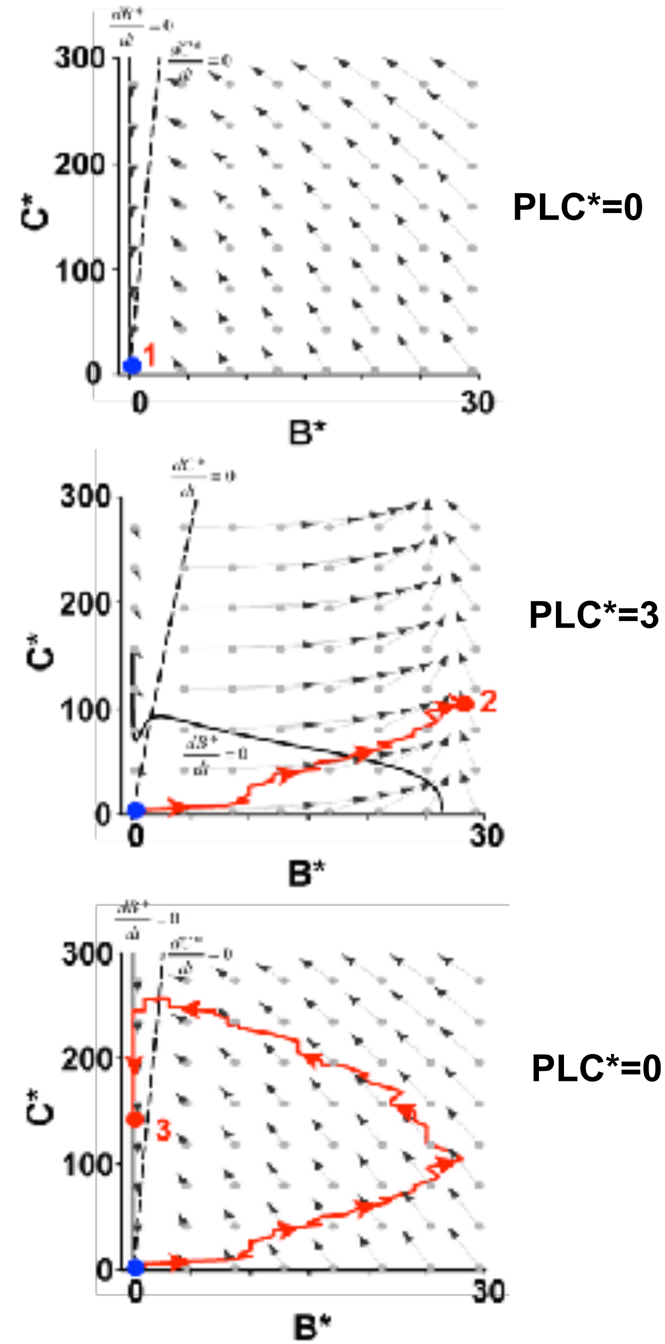




An oscillator that lives for one oscillation!

System dynamics in the B* - C* plane:

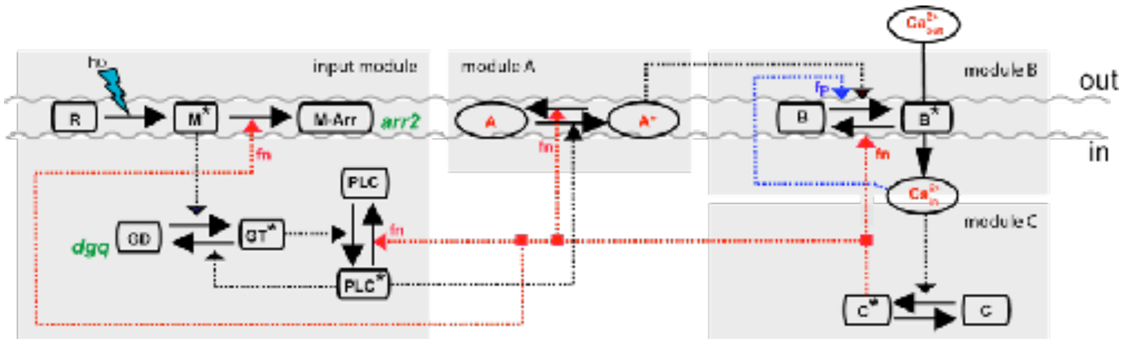




An oscillator that lives for one oscillation!

What kind of oscillator is that? One that makes exactly one QB per photon...a light-induced single cycle oscillator.

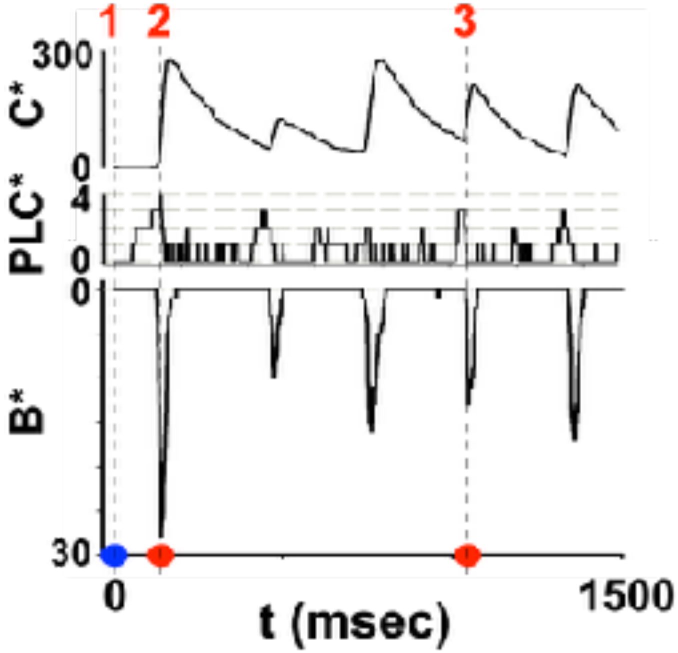
A test of the model…what if we don't let M* deactivate?

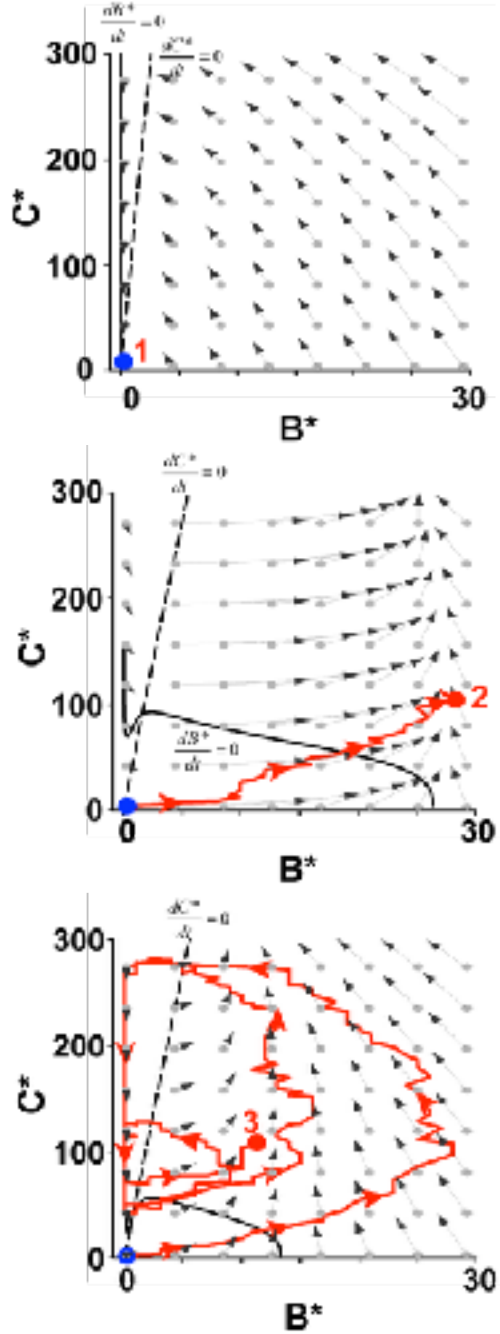


Computationally…by setting $\gamma_{rh} = 0$

$$\frac{dM^*}{dt} = -\gamma_{rh}(1 + g_{rh} f_n) M^*$$

<u>A test of the prediction of oscillation</u>…what if we don't let M* deactivate?





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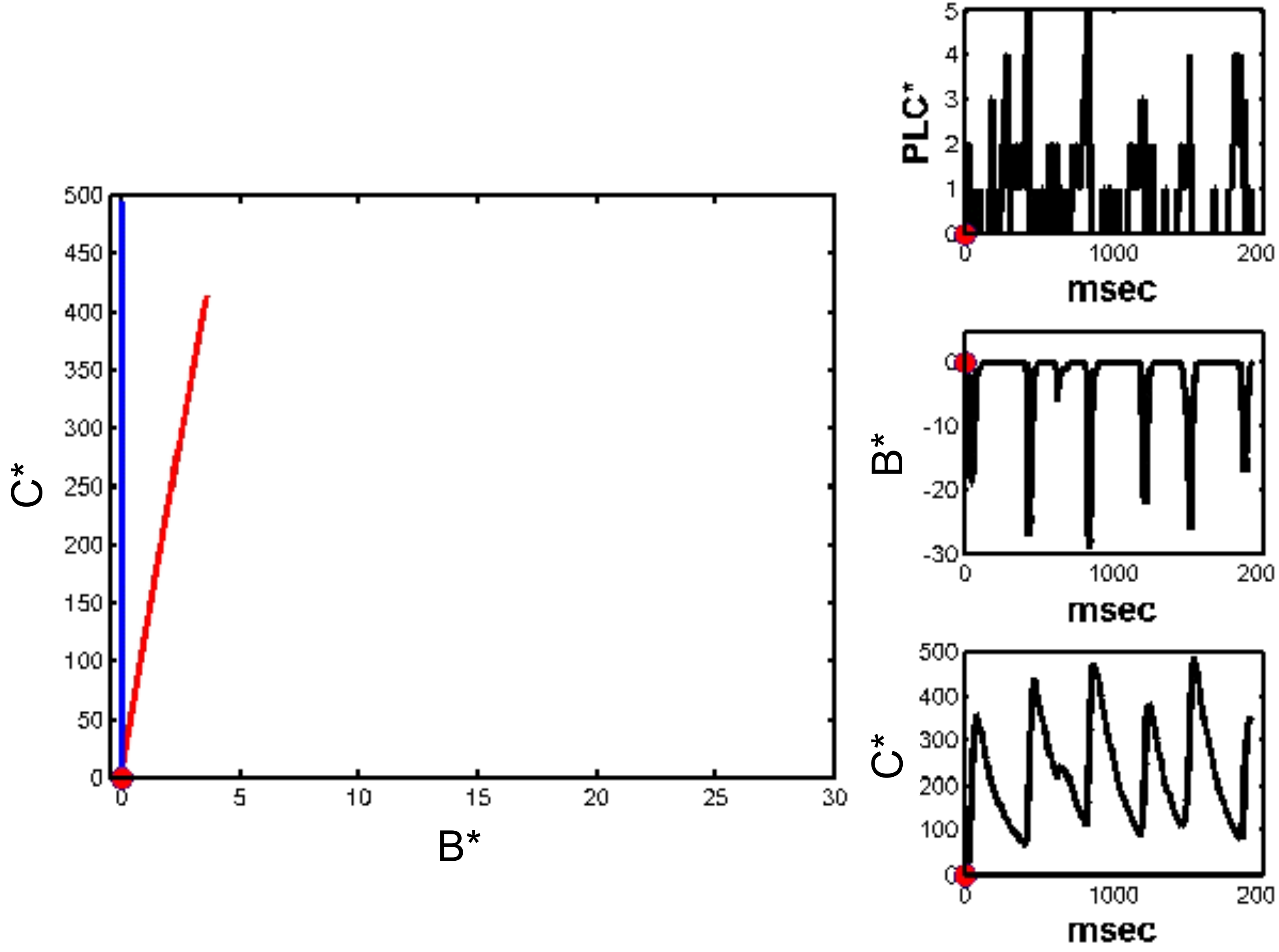
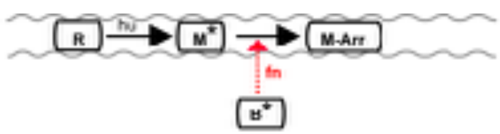


<u>A test of the model</u>…what if we don't let M* deactivate?

<u>Computationally</u>…by setting $\gamma_{rh} = 0$

$$\frac{dM^*}{dt} = -\gamma_{rh}(1 + g_{rh} f_n) M^*$$

<u>Experimentally</u>…by arrestin knockout



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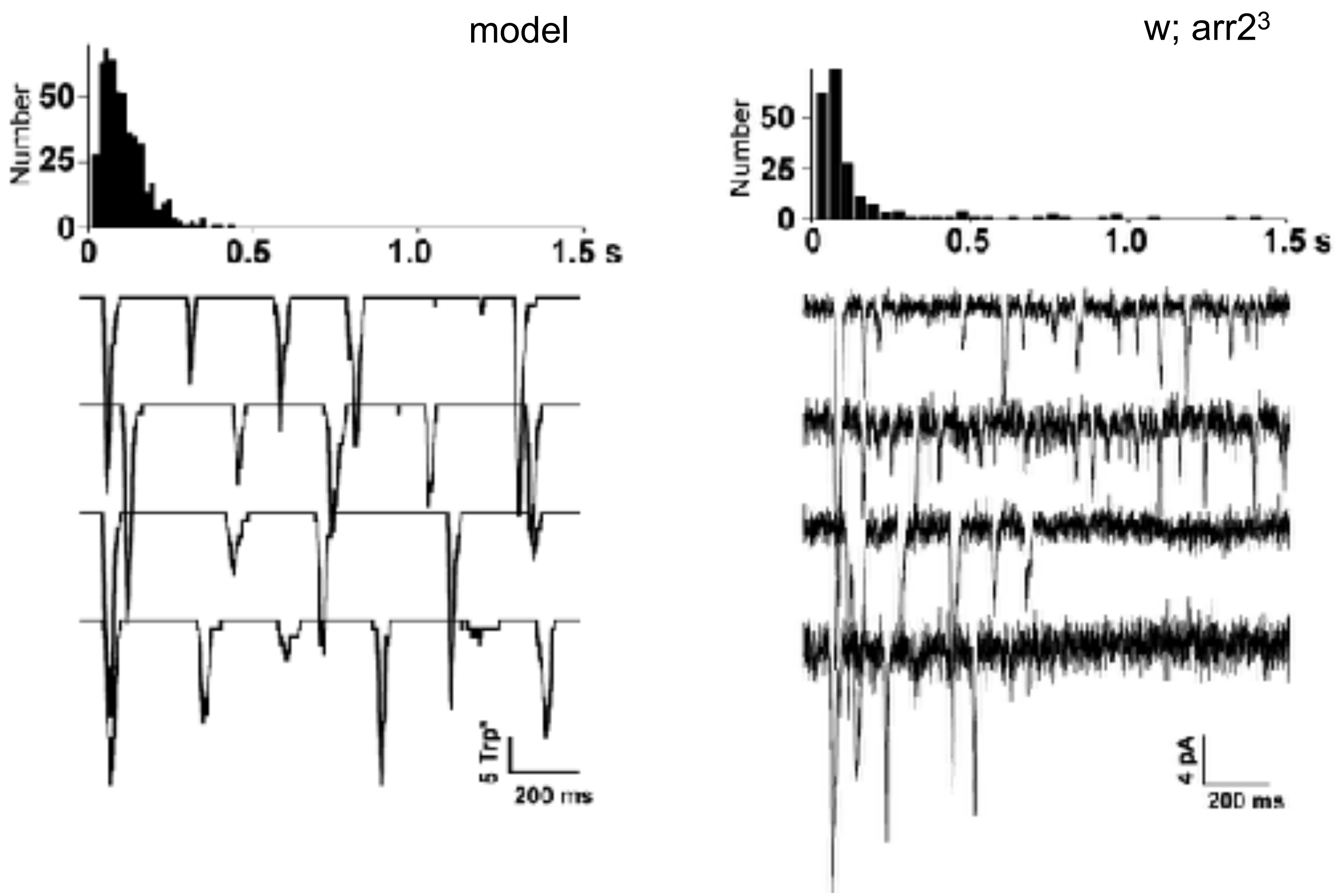
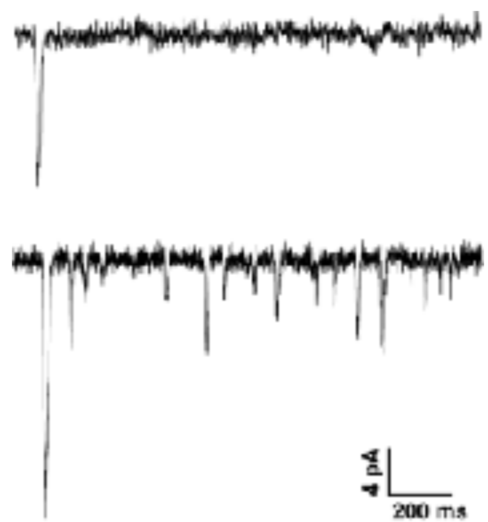


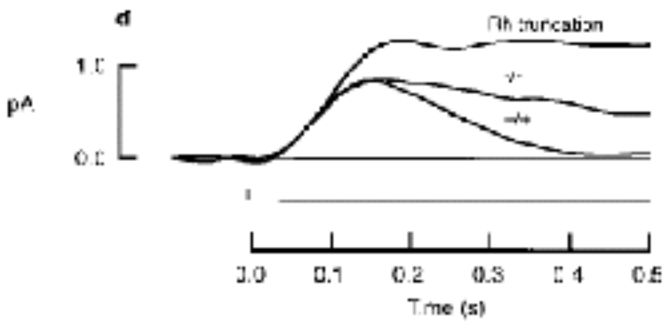
So, an explanation for why we get just one bump per photon....

In wild-type

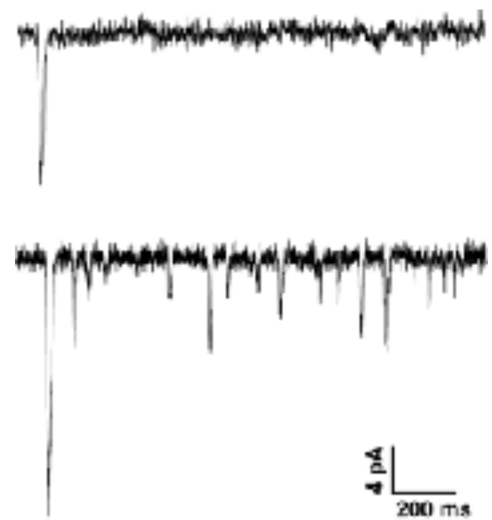
In arrestin knockout



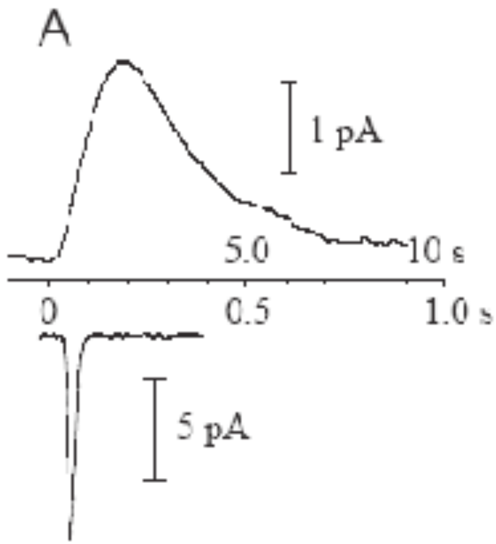
Fundamentally different from the vertebrate rod cell…



D.A. Baylor (1996) PNAS. 93, 560-6



Vertebrate and Invertebrate photoreceptors…comparative physiology

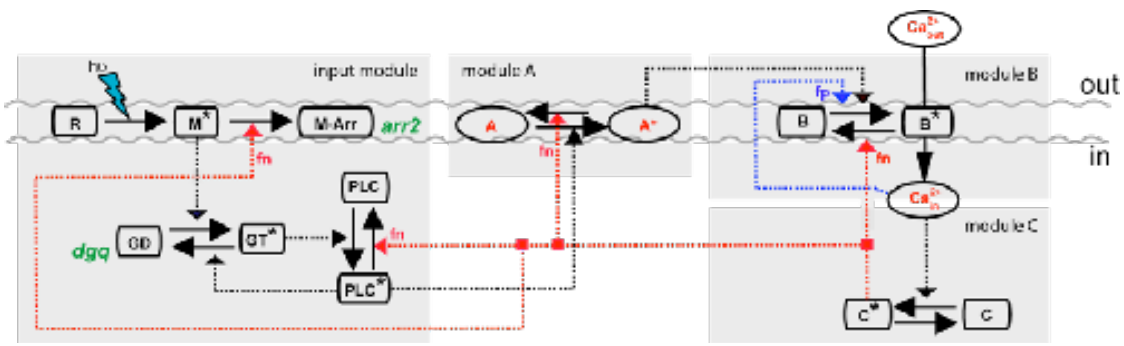


R.C. Hardie (2001) J. Exp. Biol. 204, 3403-9

Vertebrate (rod)	Invertebrate (fly photoreceptor)
G_t, cGMP cascade	**G_q, PLC-β pathway**
Hyperpolarizes	**Depolarizes**
Slow (~1-10 sec)	**fast (~50 msec)**
Consistent latency	**Randomly distributed latency**
Sterotyped size/shape	**Variable size**
Saturation at ~500 phot/sec	**Saturation at ~10^6 phot/sec**

<u>Conclusions</u>

1. The quantum bump is the result of a light-induced non-linear (relaxation) oscillator, converting photons into a fast, all-or-nothing opening of 25-30 ion channels.



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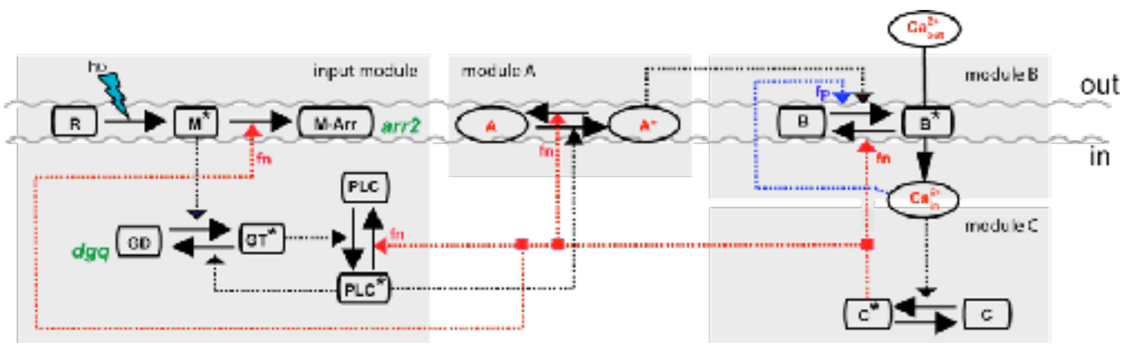
2. Variable latency comes from the stochasticity of igniting positive feedback and size/shape come from Ca^{2+}-dependent dynamics of positive and negative feedback.

A first explanation of the basic system behaviors....and can drive further experimentation...or...



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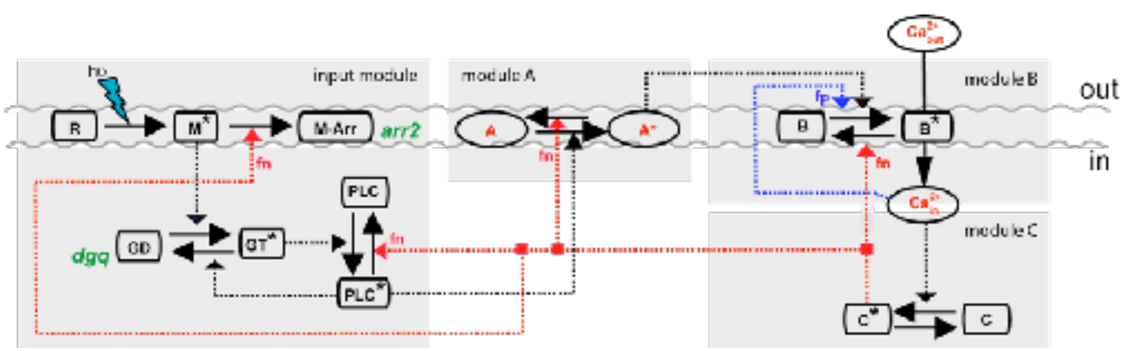

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3. Single bump per photon is guaranteed by deactivating the relaxation oscillator within one oscillation by shutting off early intermediates in signaling.

4. The reliability of the bump upon photon absorption and the absence of the bump in the dark is explained by the sharp threshold for igniting Ca^{2+}-mediated positive feedback. Below this, vanishingly low bump probability....above this, bumps with probability approaching one.

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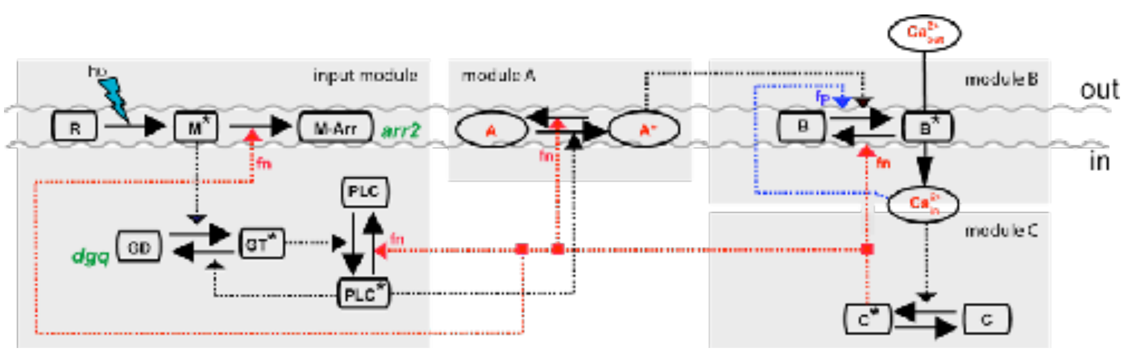

Next, we will use everything we have learned up to now to take on the problem of **protein function and evolution**….a non-linear dynamical system comprised of many parts.

	n = 1	n = 2 or 3	n >> 1	continuum
Linear	exponential growth and decay single step conformational change fluorescence emission pseudo first order kinetics	second order reaction kinetics linear harmonic oscillators simple feedback control sequences of conformational change	electrical circuits molecular dynamics systems of coupled harmonic oscillators equilibrium thermodynamics diffraction, Fourier transforms	Diffusion Wave propagation quantum mechanics viscoelastic systems
Nonlinear	fixed points bifurcations, multi stability irreversible hysteresis overdamped oscillators	anharmonic oscillators relaxation oscillations predator-prey models van der Pol systems Chaotic systems	systems of non-linear oscillators non-equilibrium thermodynamics protein structure/ function neural networks the cell ecosystems	Nonlinear wave propagation Reaction-diffusion in dissipative systems Turbulent/chaotic flows

adapted from S. Strogatz