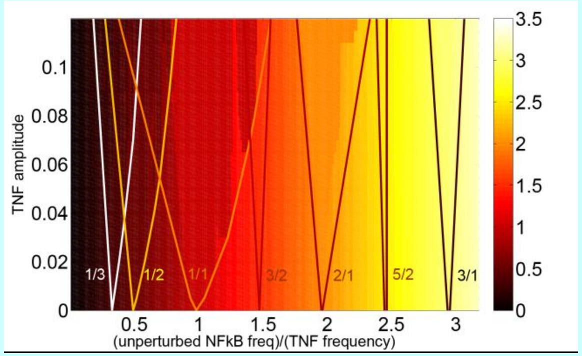
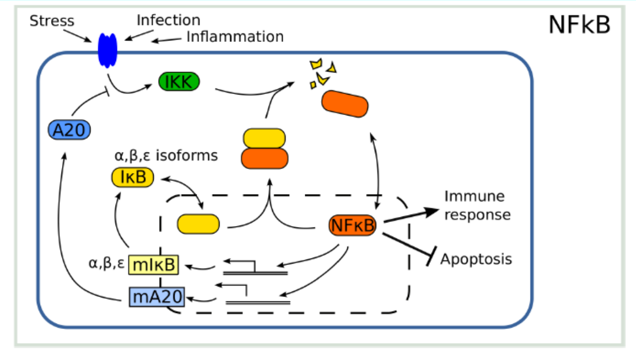
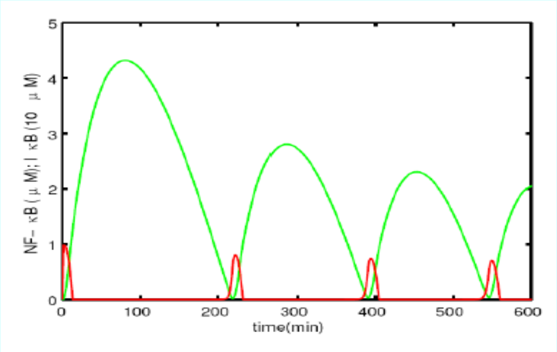
Time Correlations in Cell Dynamics

KITP, 16 January 2018
Mogens H. Jensen, Niels Bohr Institute







1. **Two oscillators couple:**

   One internal to one external:

   Arnold tongues or entrainment !

2. **Biological oscillations: Cell cycle, circadian, calcium, embryos, proteins (DNA damage)**

3. Oscillations of a protein density inside a cell: regulated by negative feed-back loops (NF-κB, p53, Wnt proteins):

DNA damage, inflammation, embryo segmentation.

4. An external (cytokine or protein) oscillation coupled to internal oscillation: The cell 'learns' and get memory, it synchronizes (entrain)

Arnold tongues → Overlap → Mode hopping

5. Pulsatile extracellular signaling in experiments (Chicago):

When memory is short: Observe mode hopping.

A way to control cell dynamics ? Jump between genes?

Chaotic motion !

6. Understand time correlations: One tongue dominates → stronger time correlations and memory (Poincare section).

Collaborators:

- Sandeep Krishna, Leo Kadanoff, Savas Tay, Mathias Heltberg, Ryan Kellogg, Namiko Mitarai, Uri Alon

M. Heltberg, R. Kellogg, S. Krishna, S. Tay and M.H. Jensen, "Chaos and stochasticity in NF-kB oscillations manifest as mode hopping between entrained states", Cell Systems 3, 532-539 (2016)

M.H. Jensen and S. Krishna, "Inducing phase-locking and chaos in cellular oscillators by modulating the driving stimuli", FEBS Letters 586, 1664 (2012).

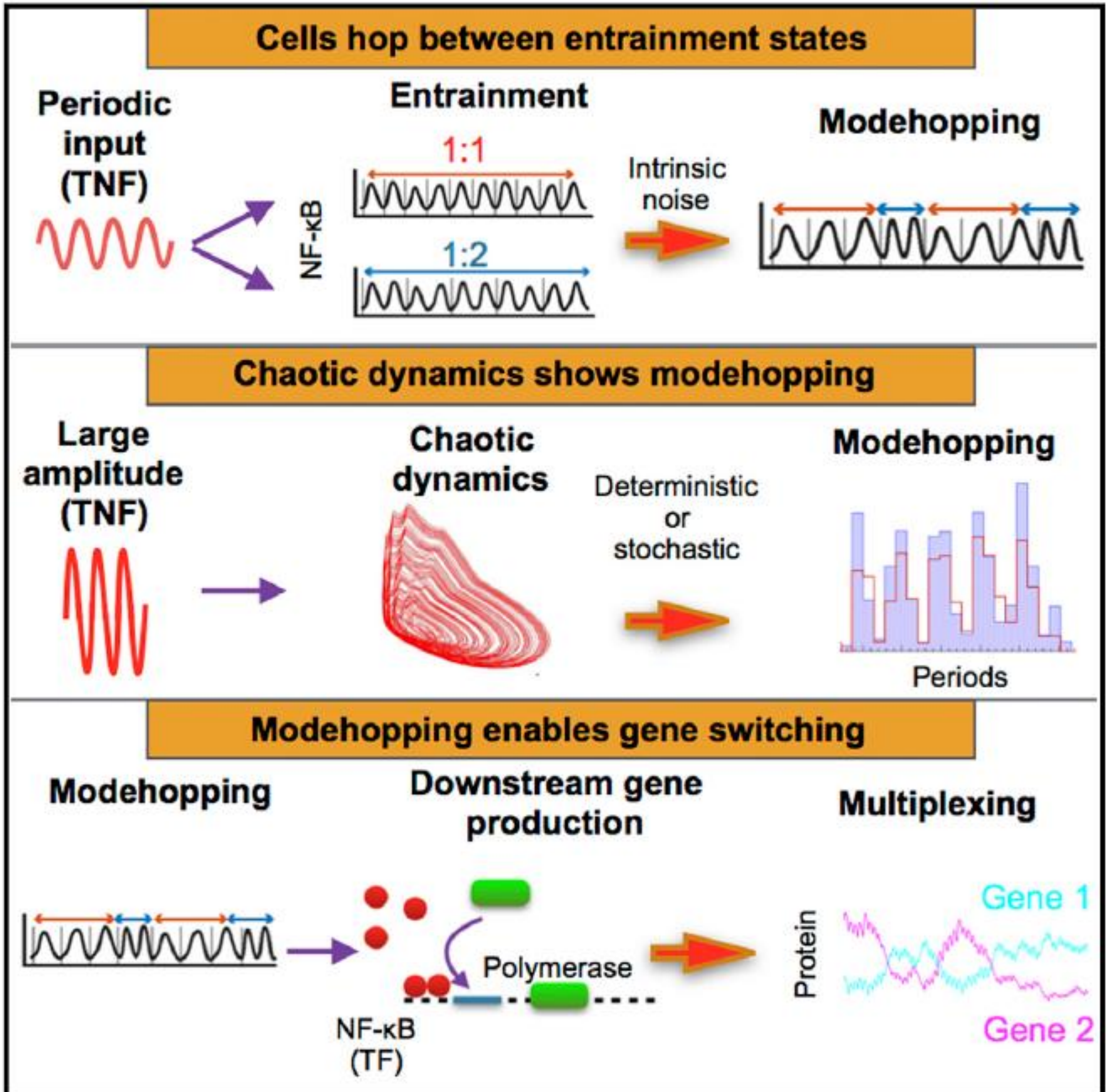
M. Heltberg, M.H. Jensen and S. Krishna, "Time orrelations in Mode Hopping of Coupled oscillators", J. Stat.Phys. 167, 792-805 (2017).

N. Mitarai, U. Alon and M.H. Jensen, "Entrainment of linear and non-linear system under noise", Chaos, 23, 023125 (2013)

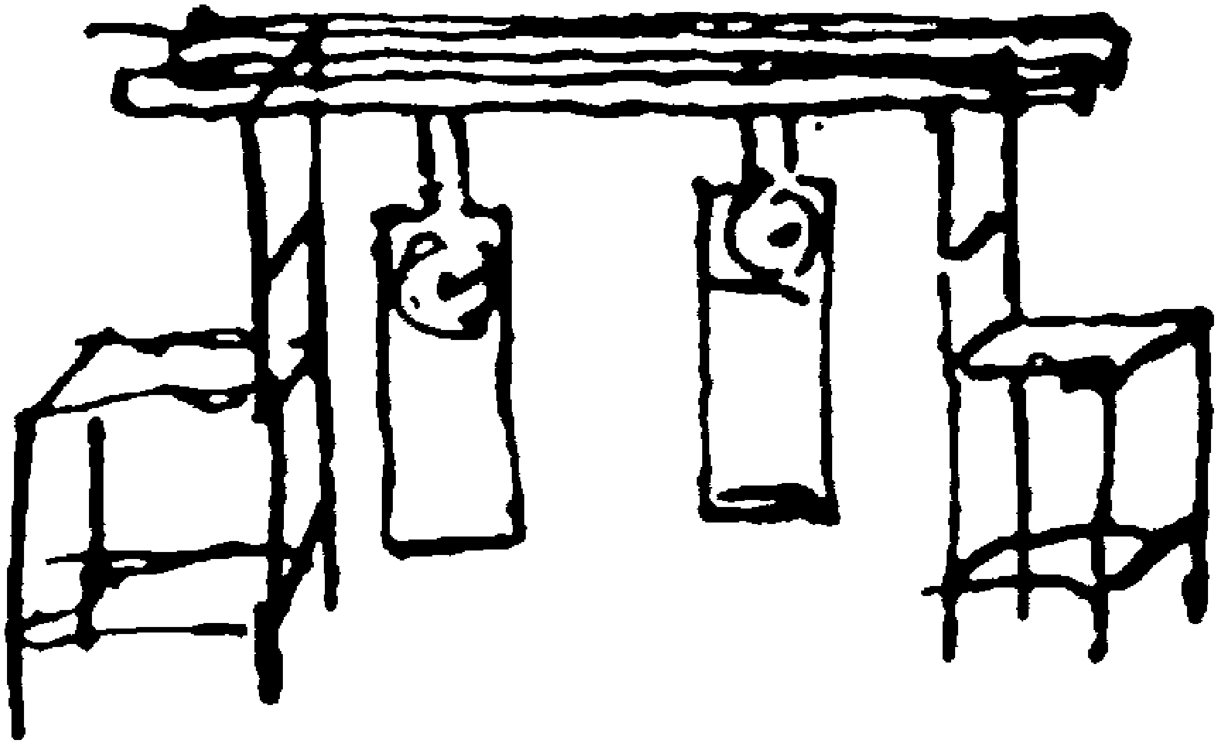
Leo Kadanoff and M.H. Jensen, "Global and Local: Synchronization and Emergence", Review (2014)

Oscillations: Many papers with K. Sneppen, S. Pigolotti, L. Pedersen, B. Mengel, A. Trusina, P. Jensen, P. Yde, S. Chakraborty, S. Semsey, A. Hunziker, K. Moss, J. Juul

Graphical Abstract

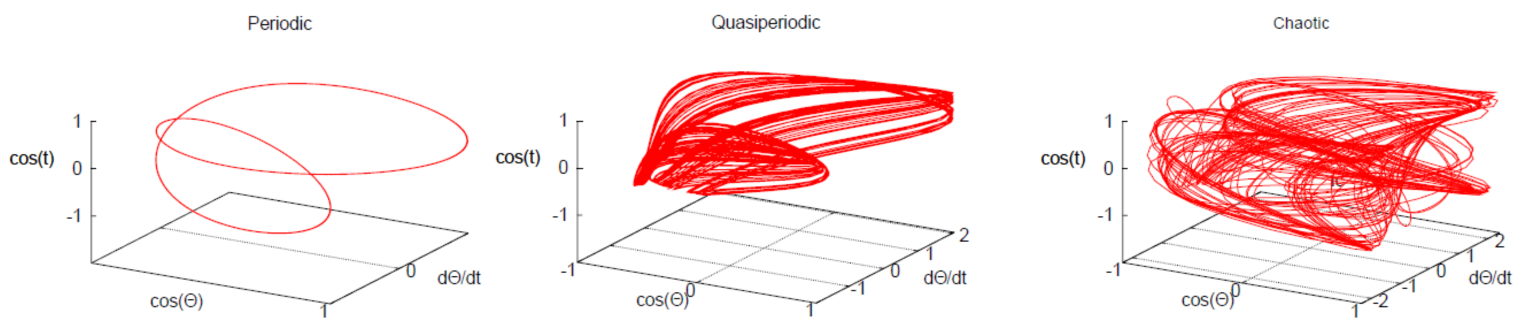


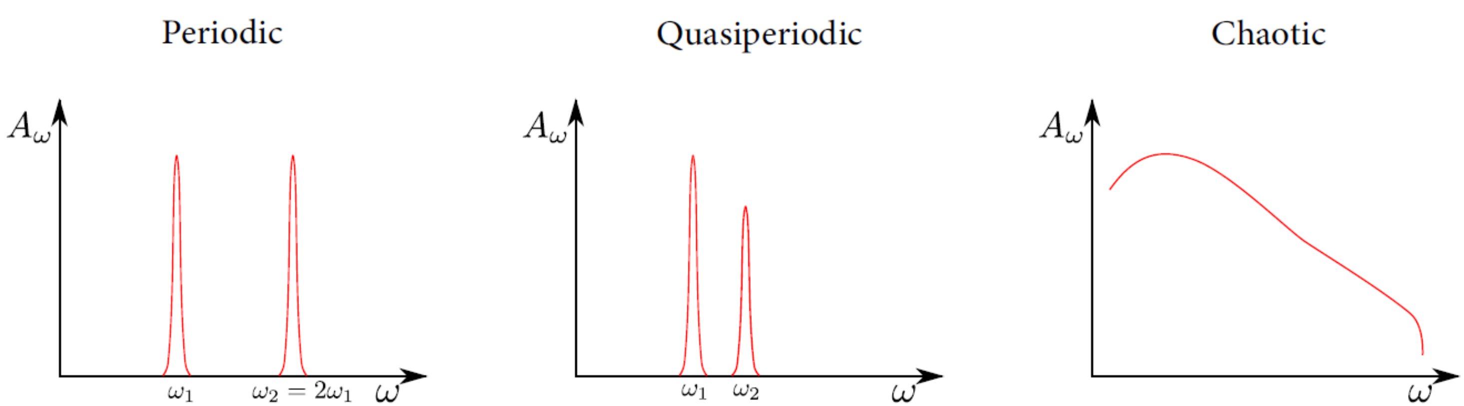
Synchronization of two oscillators



Huygens' clocks 1665

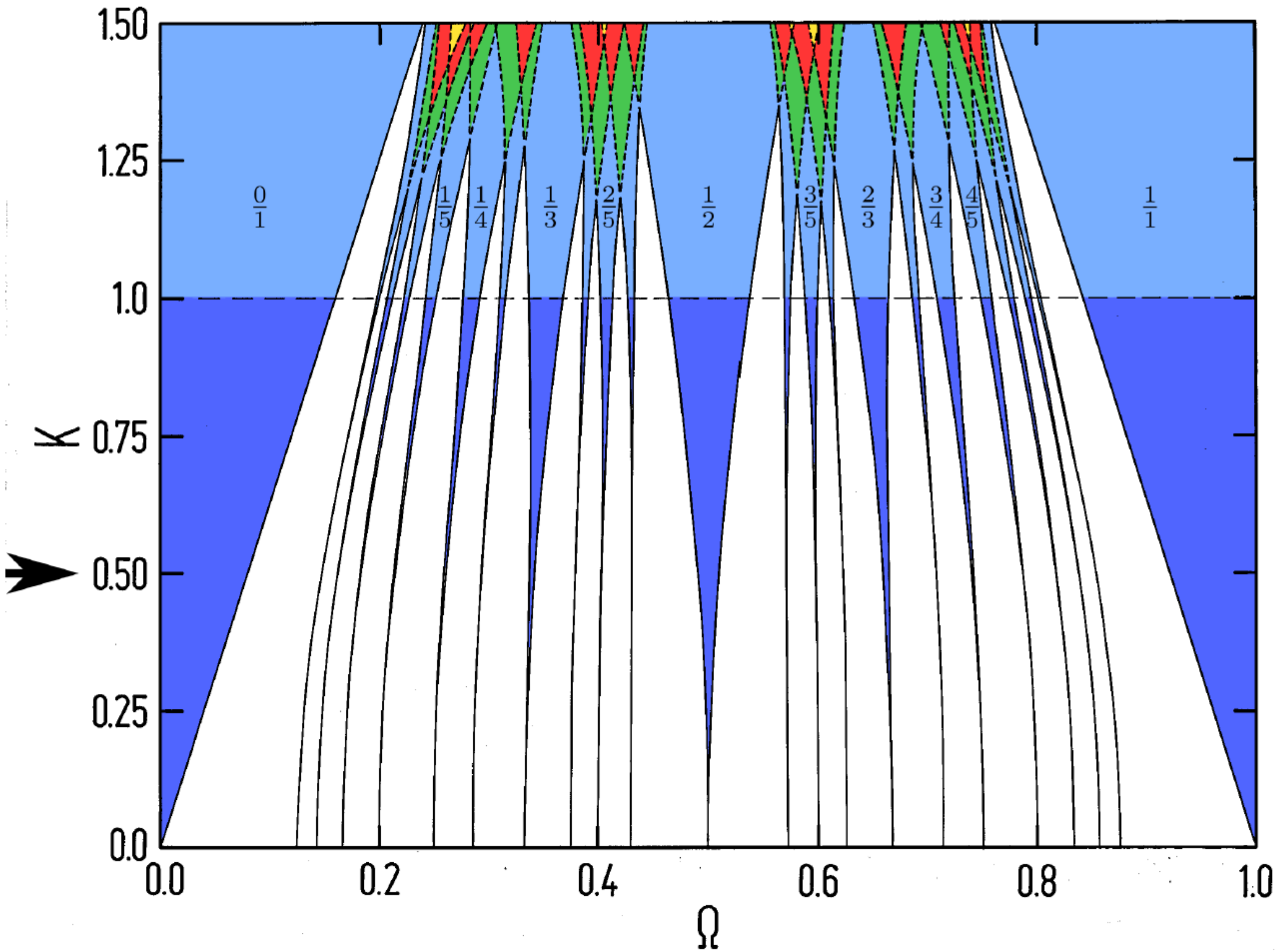
Three different non-linear dynamics



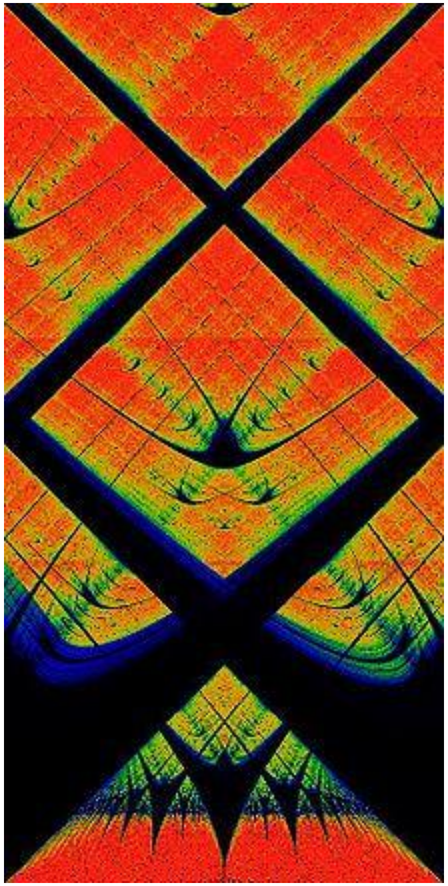


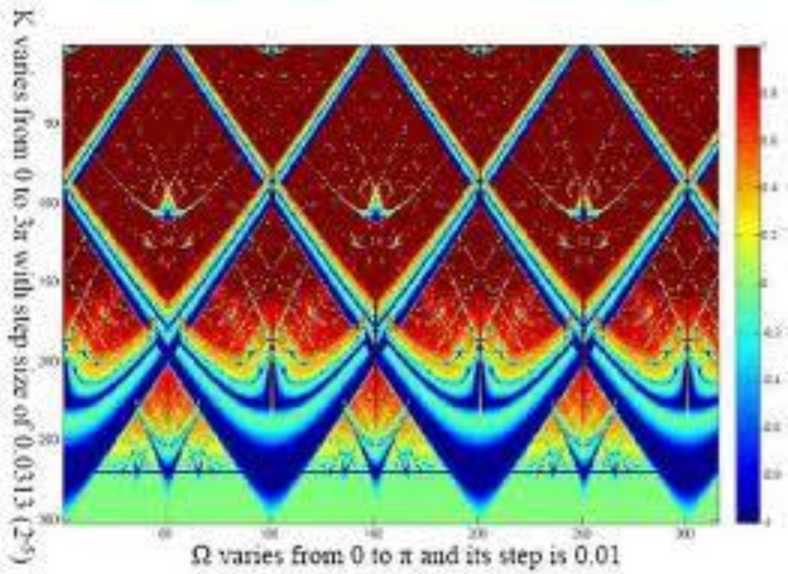
Two coupled oscillators: Arnold tongues

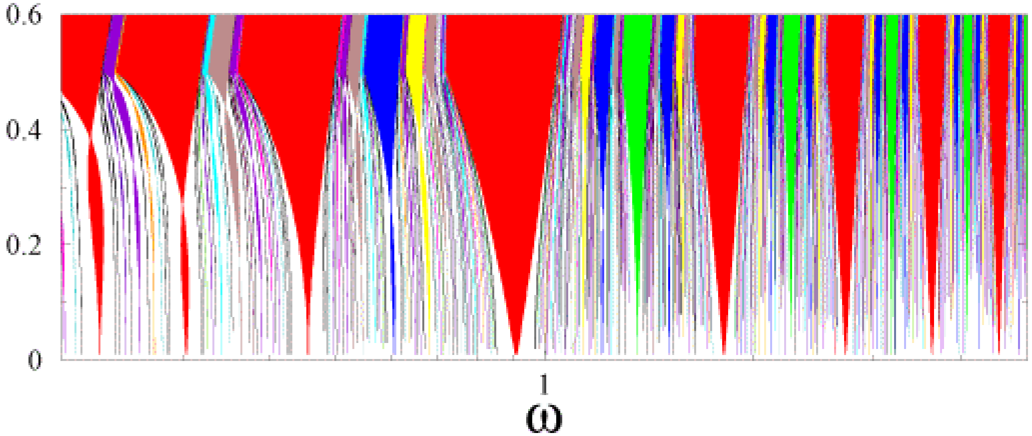
$$\omega/\Omega = P/Q$$



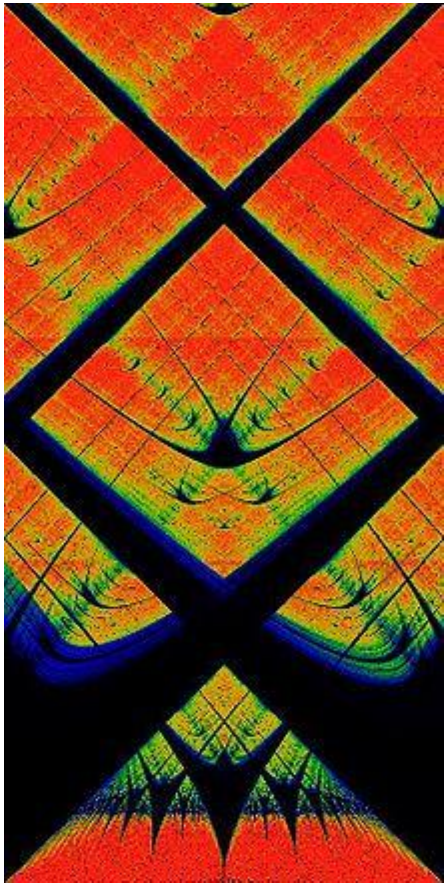
Examples of Arnold tongues !

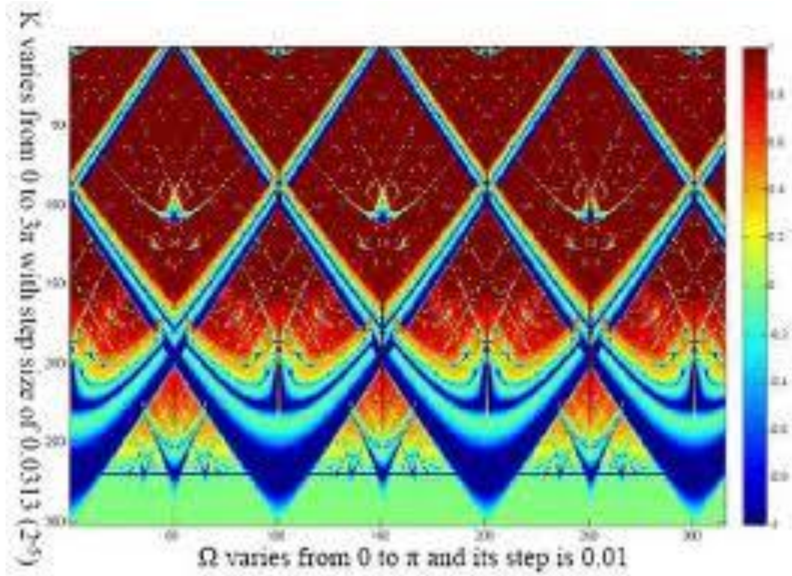


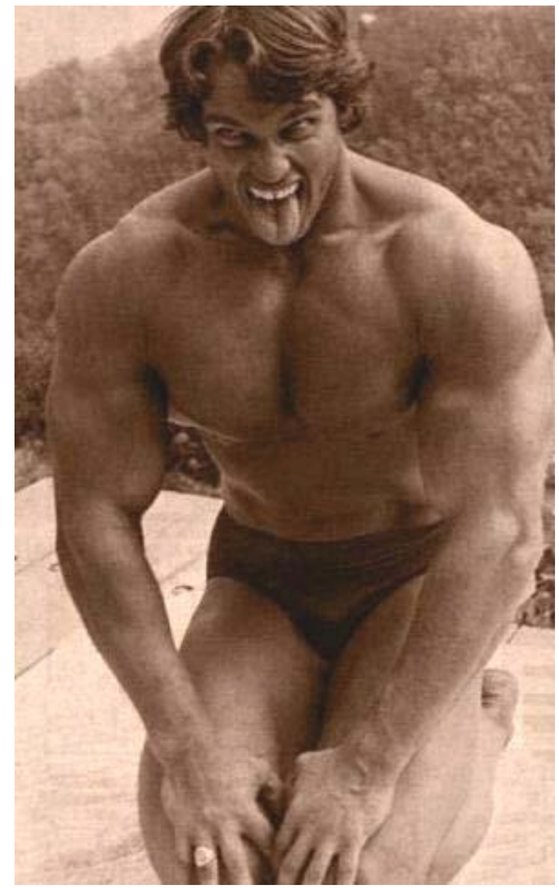


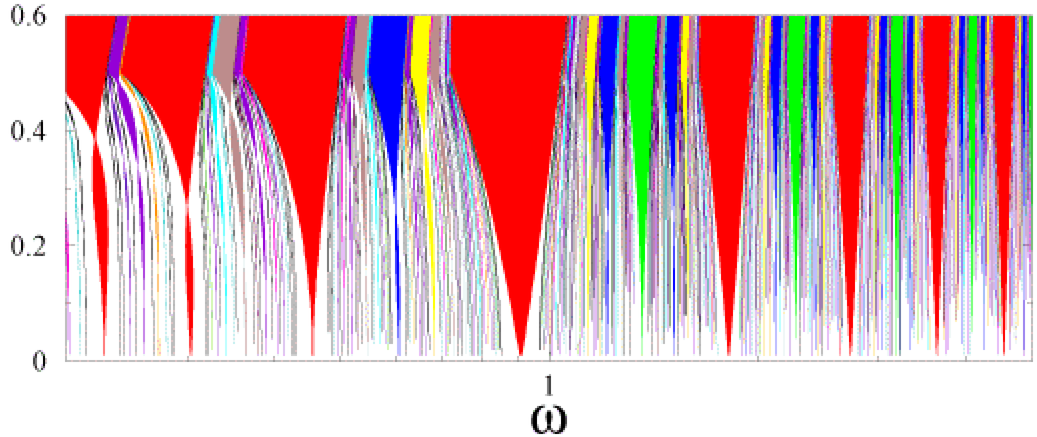


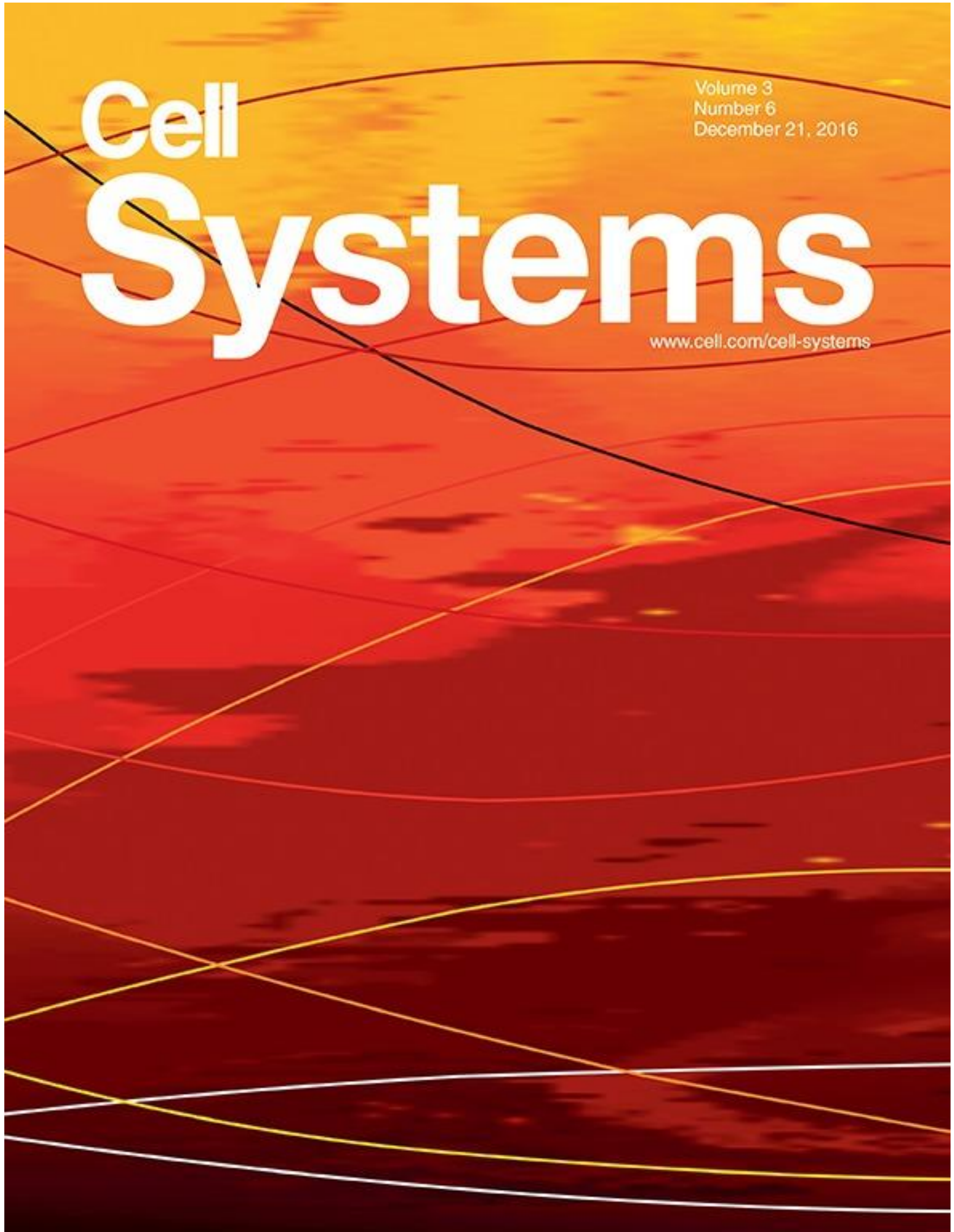
Examples of Arnold tongues !



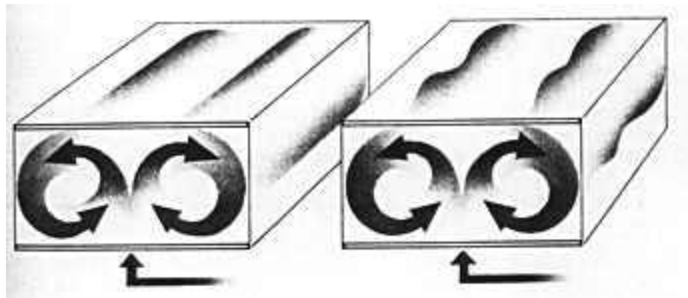







Cell
Systems
Volume 3
Number 6
December 21, 2016
www.cell.com/cell-systems

Chicago basement convection !



Libchaber, Stavans, Glazier:
External oscillating current !

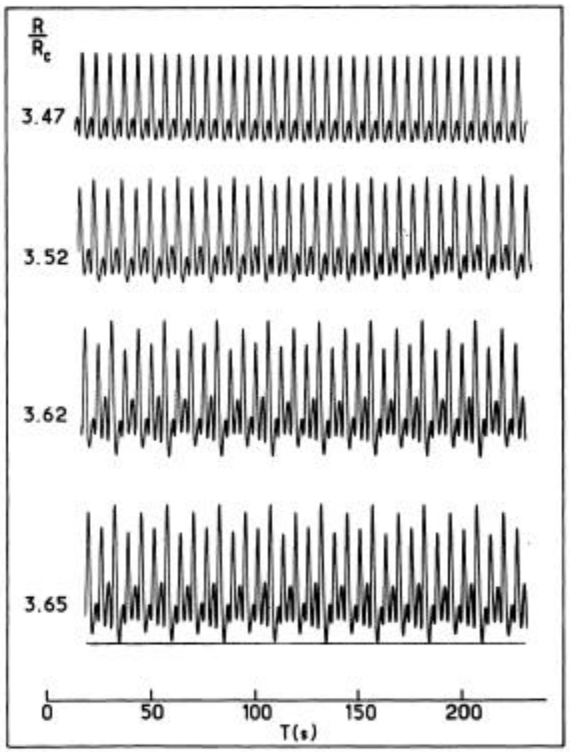


Fig. 2. — Direct time recordings of temperature for various stages of the period doubling cascade showing the onset of $f/4$ ($R/R_c = 3.52$), $f/8$ ($R/R_c = 3.62$), $f/16$ ($R/R_c = 3.65$).

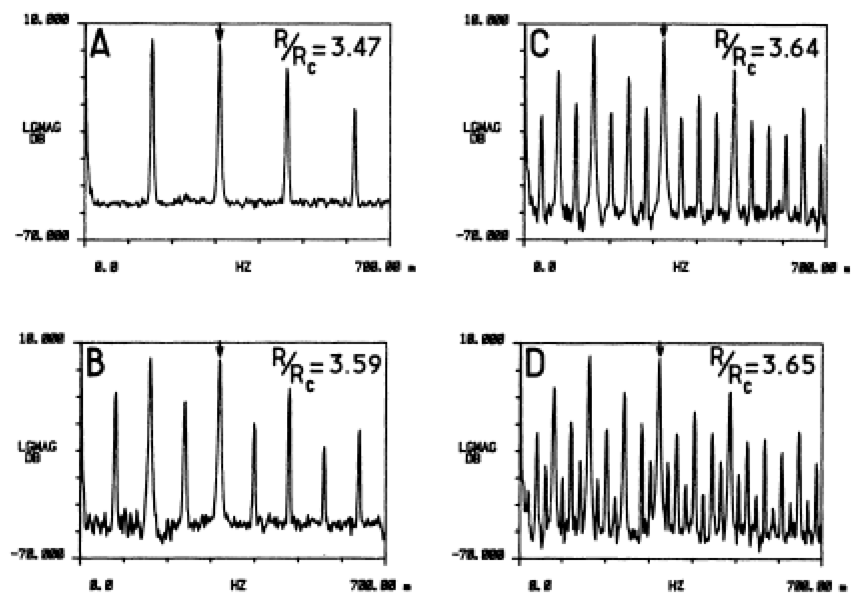
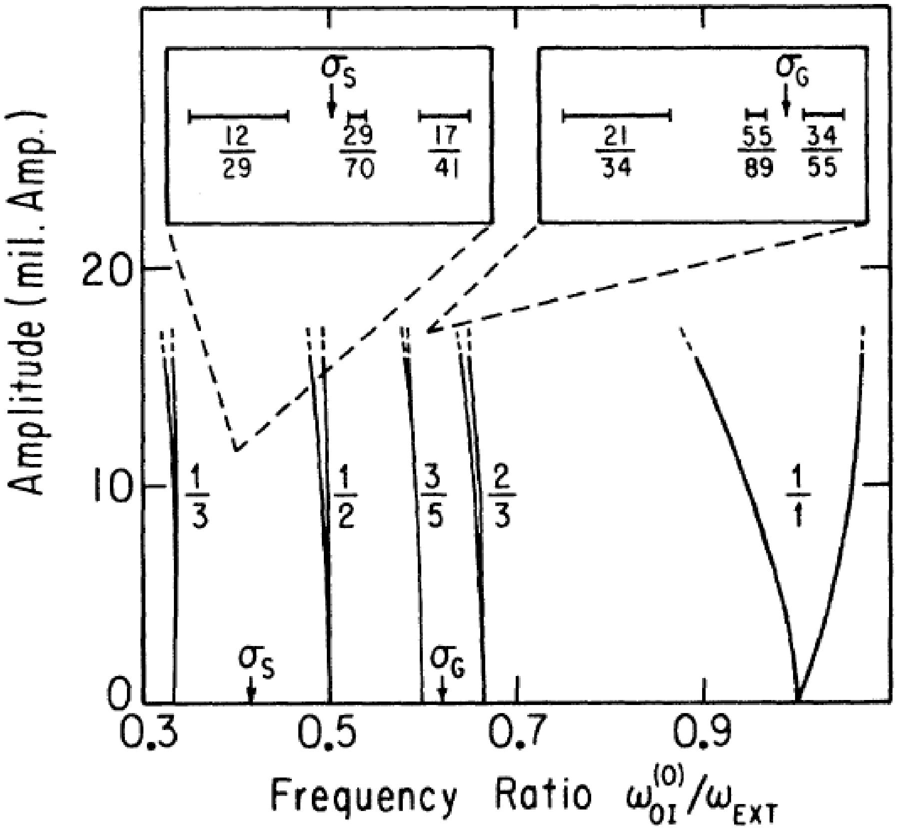
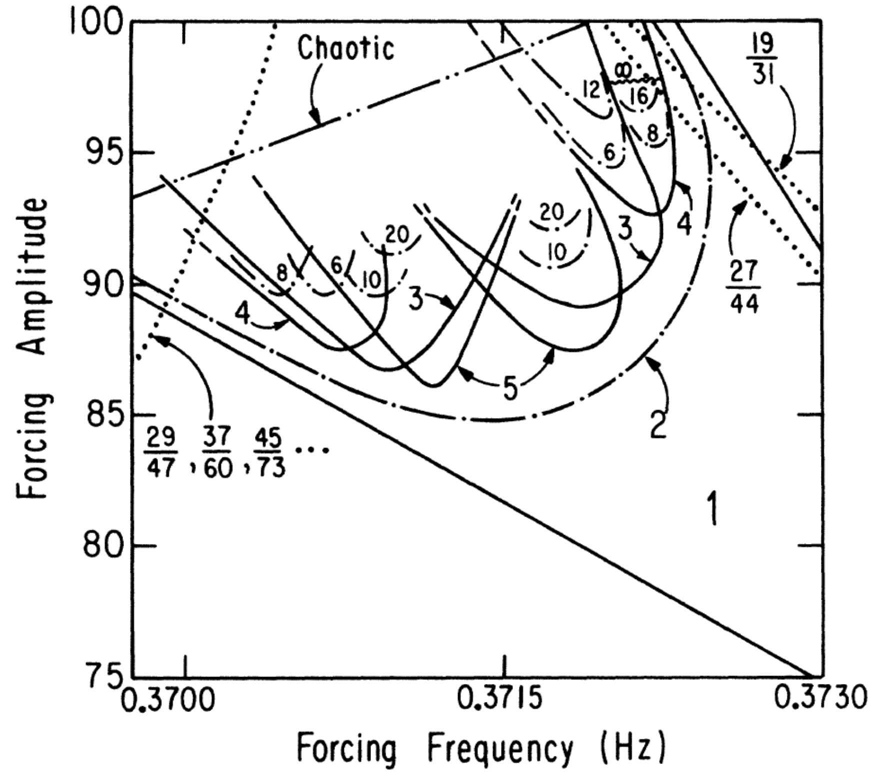


Fig. 3. — The Fourier spectrum. Arrows indicate the peak at the frequency f_1.

Chicago basement convection !

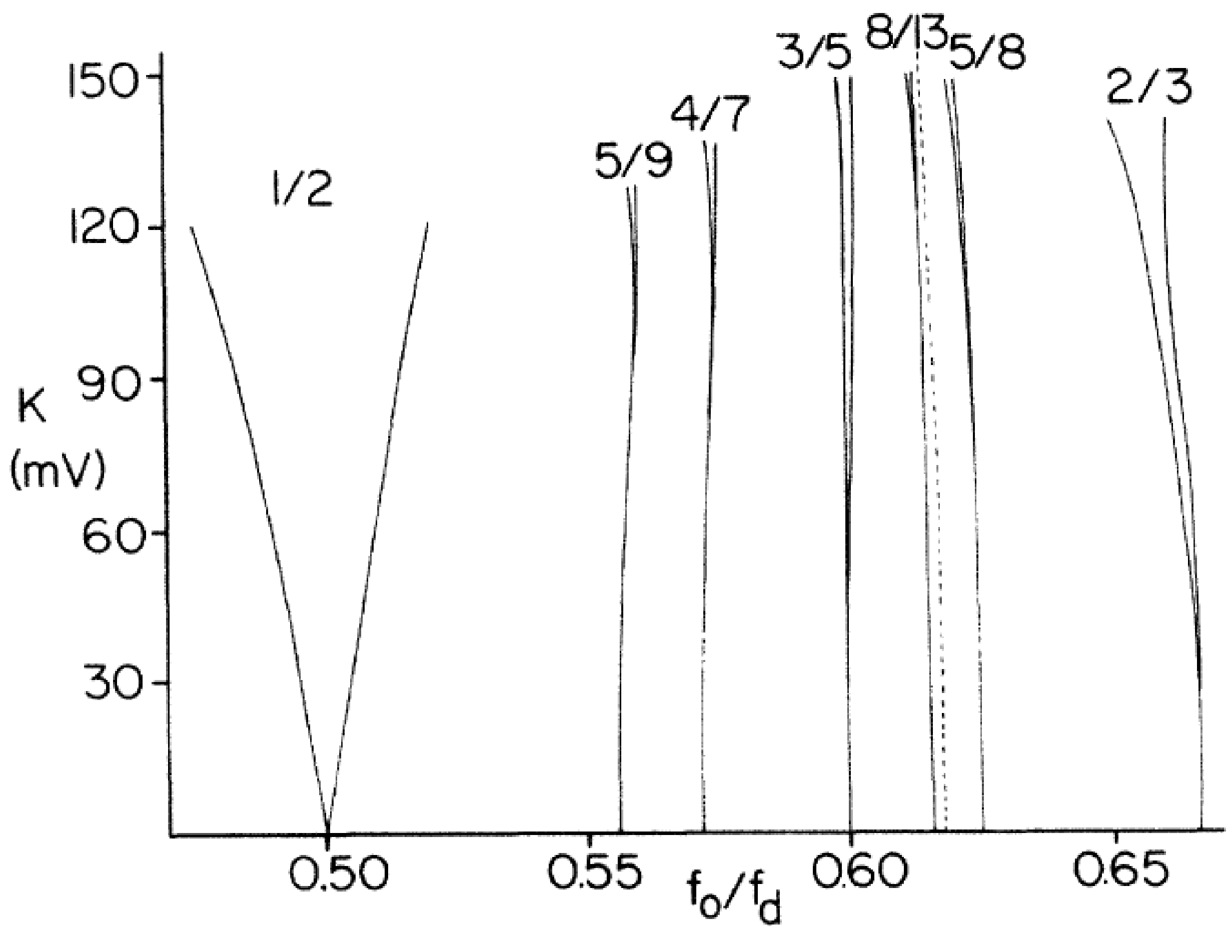


Stavans, Heslot, Libchaber

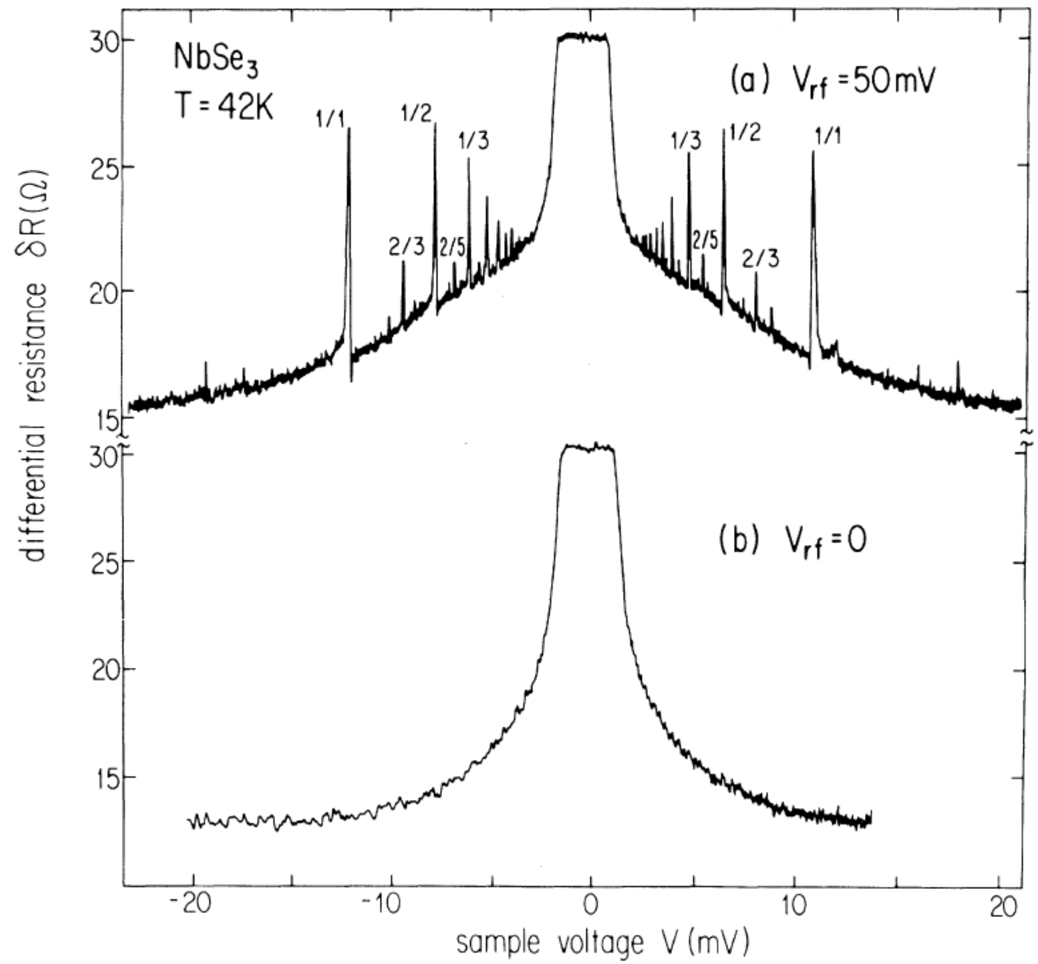


Glazier, Jensen, Libchaber, Stavans

Semiconductors: Gwinn, Westervelt, Harvard



Sliding CDW's at UCLA

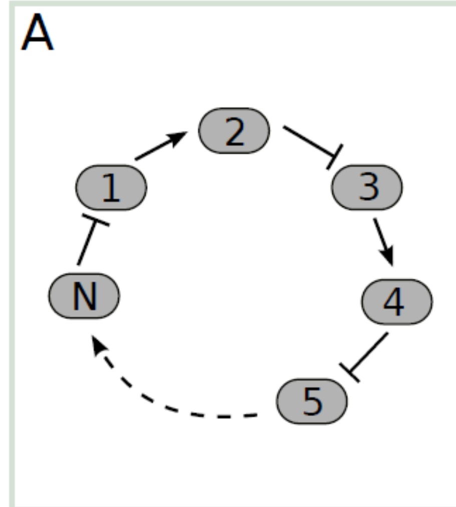


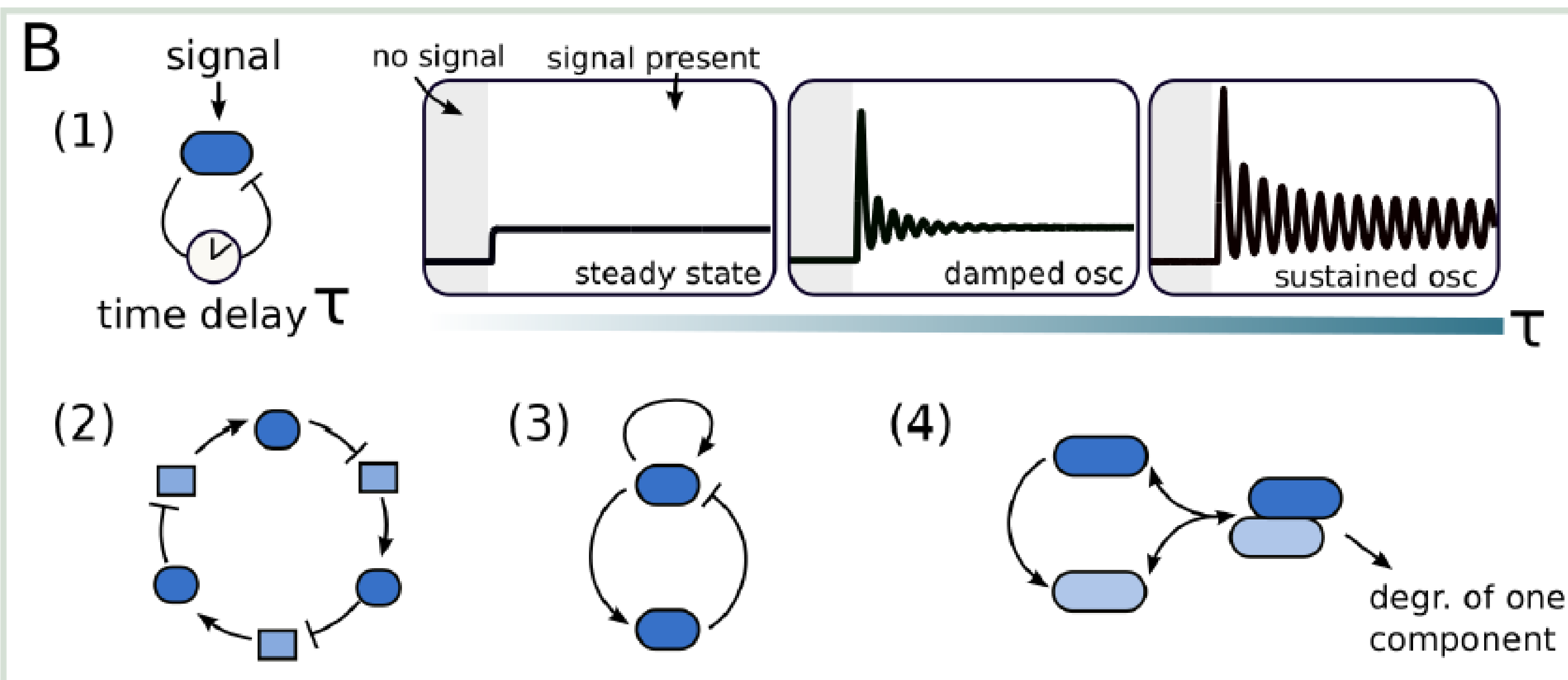
Brown, Mozurkewich, Gruner

What about biology – many oscillators !

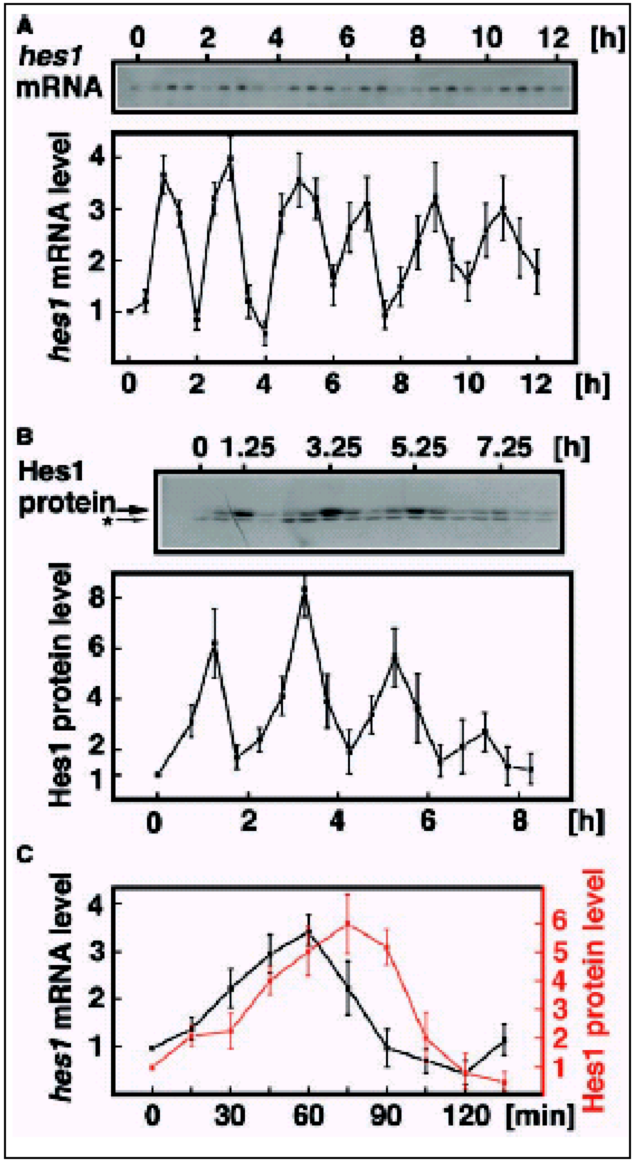
- Cell cycles
- Circadian clocks
- Calcium oscillators
- Embryos
- Pace maker cells
- Protein oscillations (DNA damage)
- Population dynamics

Basic oscillator: Negative Feed-Back loops:



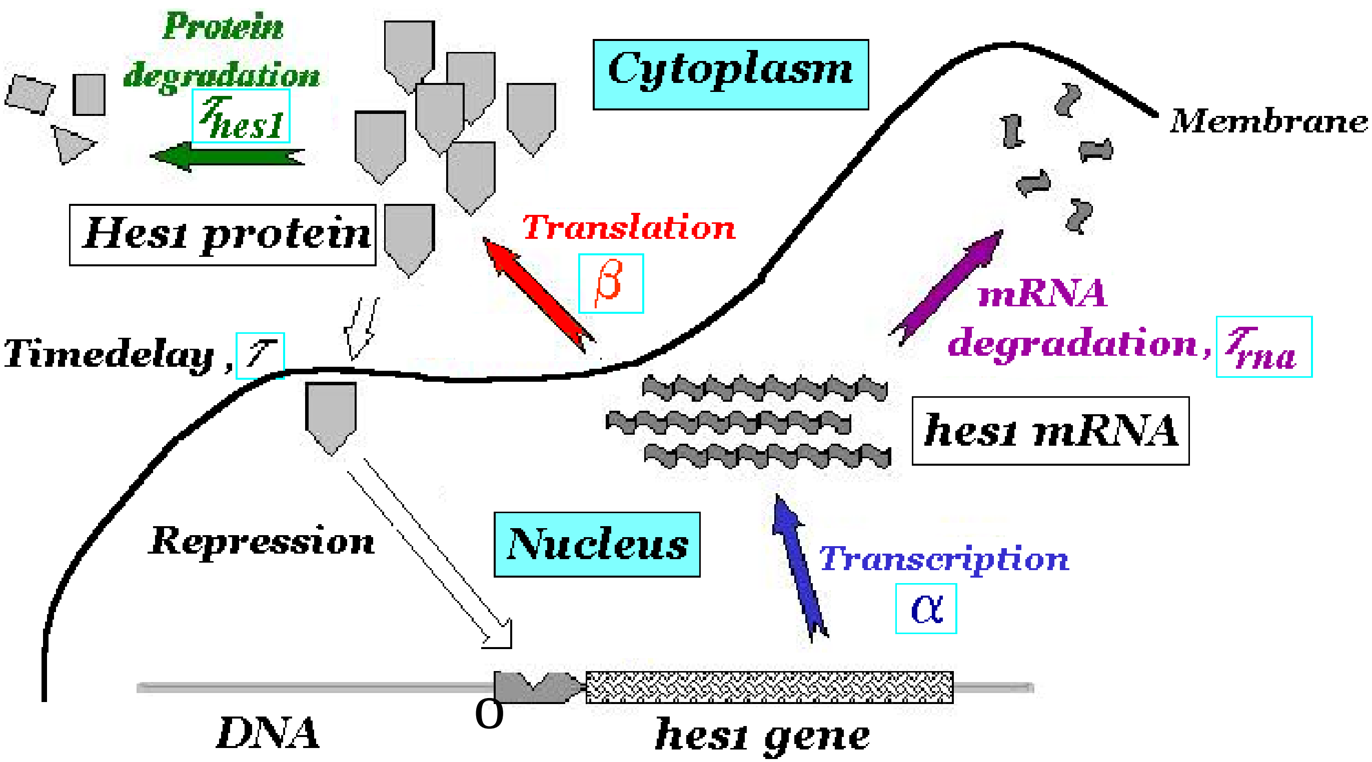


‘Typical’ Oscillating data: Hes1 - segmentation



(Hirata et al, 2002)

Simplest negative feed-back loop: Hes1



$$\frac{d[mRNA]}{dt} = \alpha \cdot [o_{free}] - \frac{[mRNA(t)]}{\tau_{rna}}$$

$$\frac{d[Hes1]}{dt} = \beta \cdot [mRNA(t)] - \frac{[Hes1(t)]}{\tau_{hes1}}$$

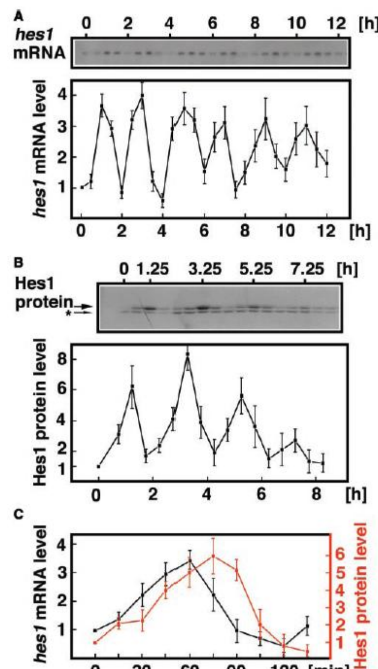
Jensen et al 2003

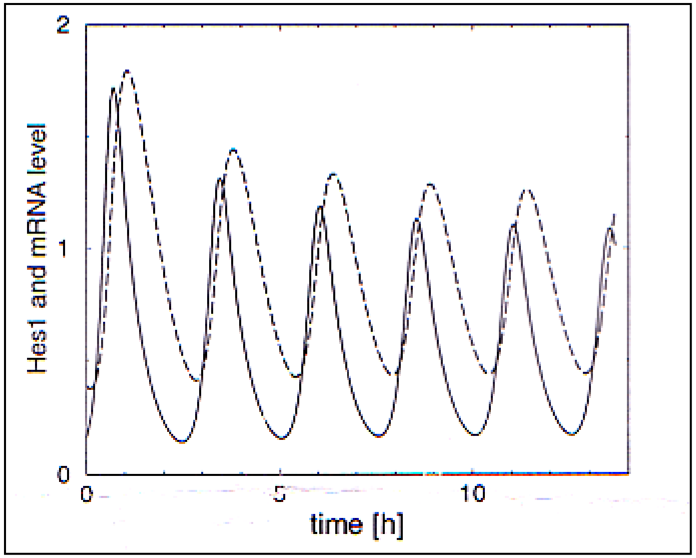
$$\frac{d[mRNA]}{dt} = \alpha \cdot \frac{K_M}{K_M + [Hes1(t-\tau)]^n} - \frac{[mRNA(t)]}{\tau_{rna}}$$

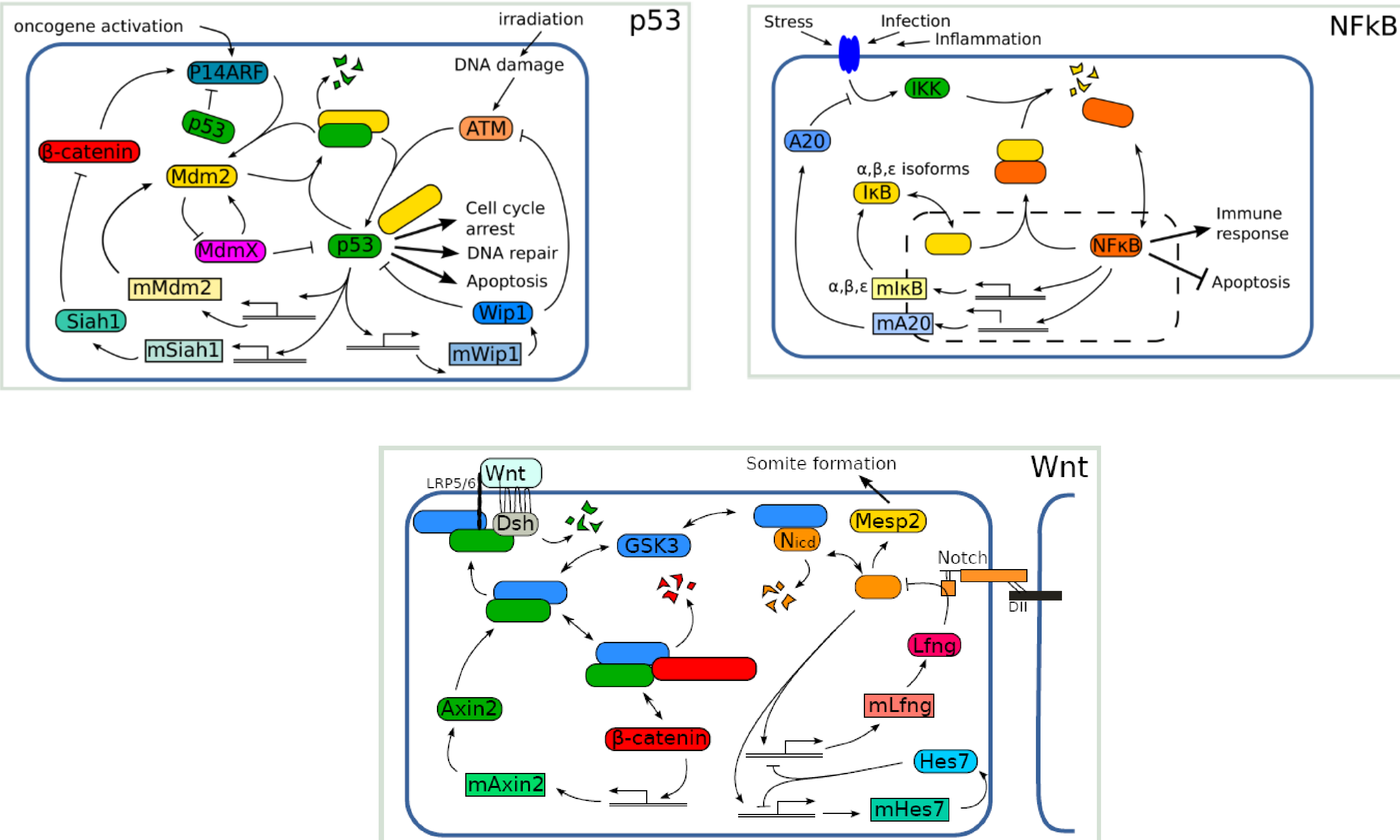
$$\frac{d[Hes1]}{dt} = \beta \cdot [mRNA(t)] - \frac{[Hes1(t)]}{\tau_{hes1}}$$

- Dashed curve [Hes1]
- Solid curve [mRNA]

- τ_{rna} = 24.1 min
- τ_{hes1} = 22.3 min
- τ = 24 min
- $\alpha = 20\ [R]_0\ \text{min}^{-1}$
- $\beta = 1/20\ \text{min}^{-1}$
- $K_M = (0.1[R]_0)^n$
- n = 4

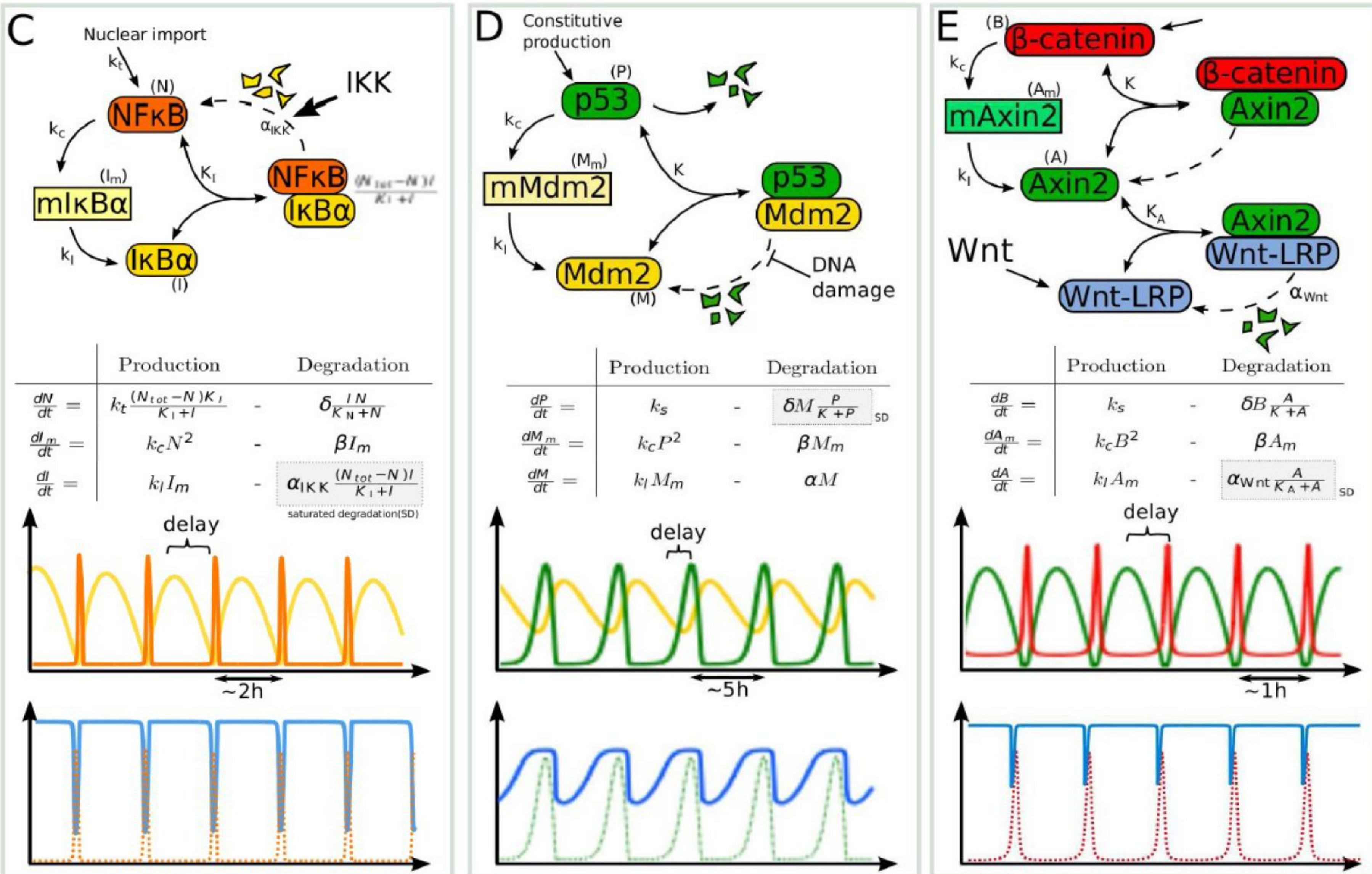





p53
oncogene activation
irradiation
DNA damage
P14ARF
p53
β-catenin
Mdm2
ATM
Cell cycle arrest
DNA repair
Apoptosis
MdmX
p53
mMdm2
Siah1
Wip1
mSiah1
mWip1
NFkB
Stress
Infection
Inflammation
IKK
A20
α,β,ε isoforms
IκB
NFκB
Immune response
Apoptosis
α,β,ε mIκB
mA20
Wnt
Somite formation
LRP5/6
Wnt
Dsh
GSK3
Mesp2
Nicd
Notch
Dll
Lfng
mLfng
Axin2
β-catenin
Hes7
mAxin2
mHes7

Simple models of ultradian oscillations

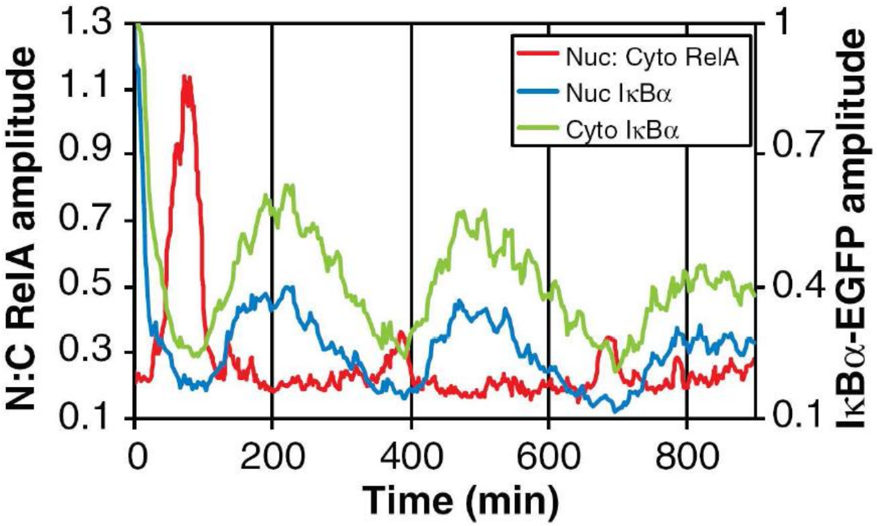
Krishna, Jensen, Sneppen (2006); Hunziker, Jensen, Krishna (2010); Pedersen, Jensen, Krishna (2011);
Mengel, Hunziker, Pedersen, Trusina, Jensen, Krishna (2010)



The NF-κB System in Mammalian Cells

- NF-κB family: dimeric transcription factors
- Regulates immune response, inflammation, apoptosis
- Over 150 triggering signals, over 150 targets
- Each NF-κB has a partner inhibitor IκB
- Flourescence imaging of NF-κB and IκB in human S-type neuroblastoma cells.

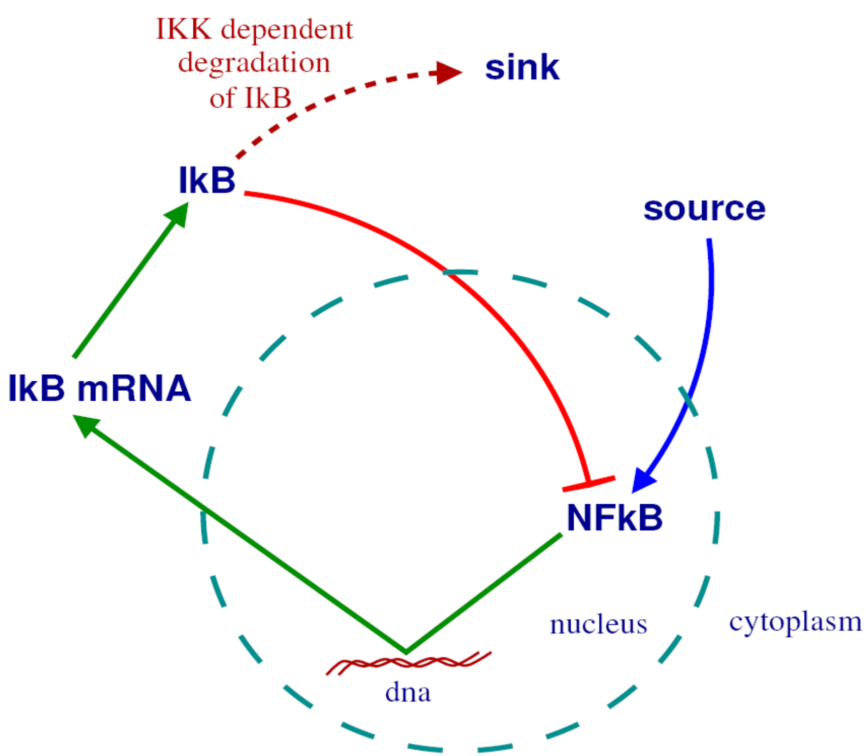
Nelson et al. (2004) Science 306, 704.



How does the network produce oscillations?

Why does the cell need the oscillations?

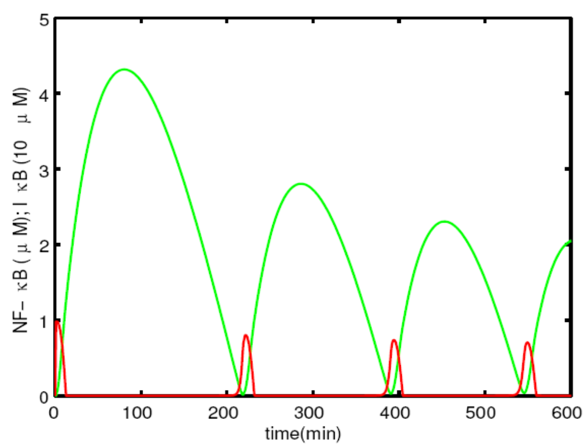
Simple Model for Protein Oscillations



$$\frac{dN_n}{dt} = A\frac{(1-N_n)}{\epsilon + I} - B\frac{I N_n}{\delta + N_n},$$

$$\frac{dI_m}{dt} = N_n^2 - I_m,$$

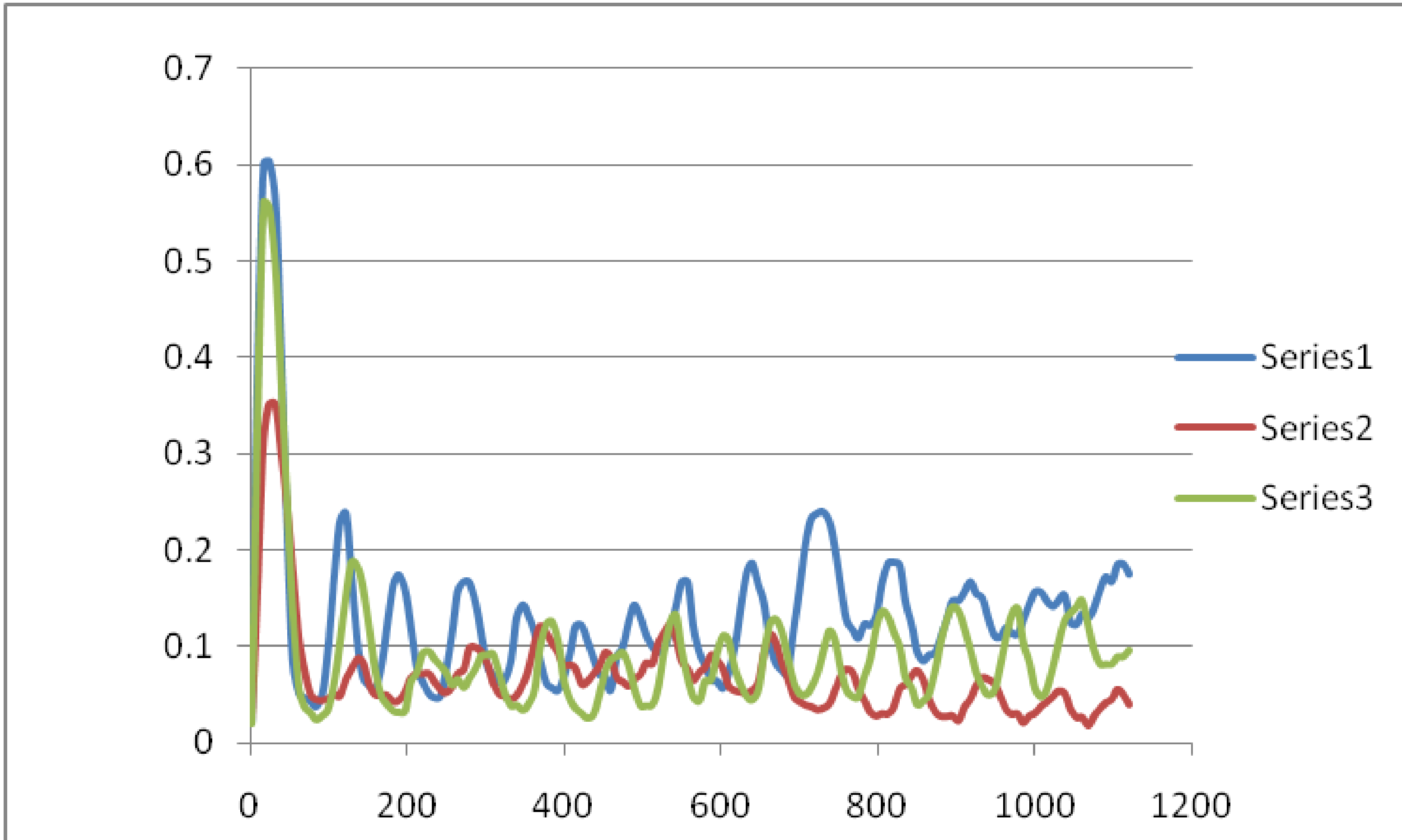
$$\frac{dI}{dt} = I_m - C\frac{(1-N_n)I}{\epsilon + I}.$$



$$A = 0.007,\ B = 954.5,\ C = 0.035,$$

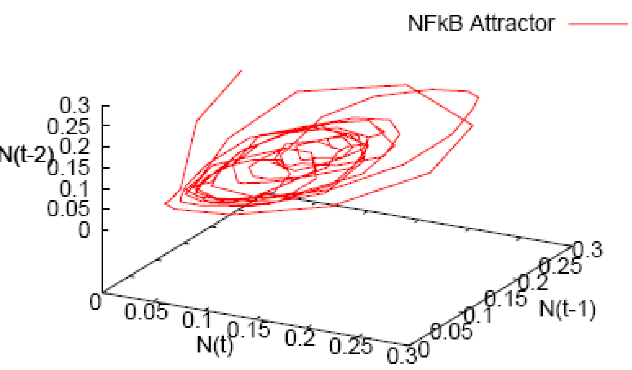
$$\delta = 0.029,\ \epsilon = 2 \times 10^{-5}$$

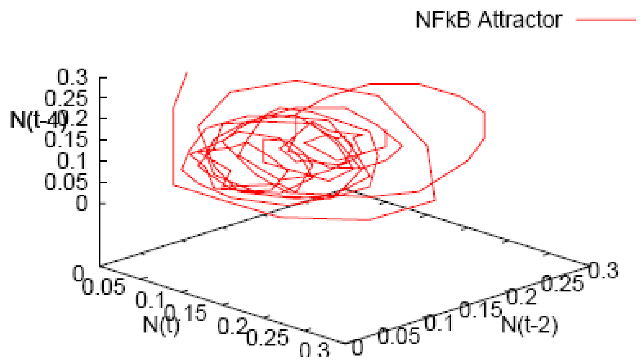
Oscillations of protein densities in a single cell

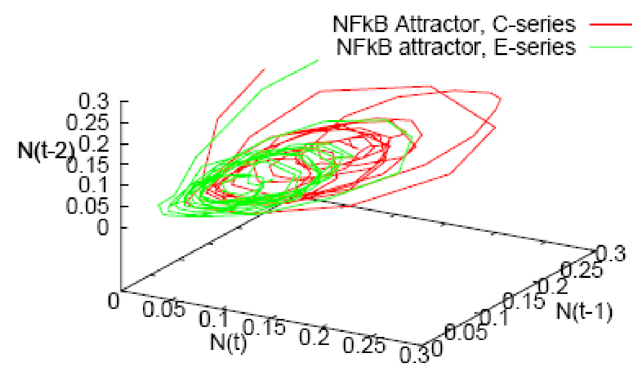


(M. Covert, Stanford, unpublished)
(Savas Tay, Chicago)

Embedded attractors:
Chaos ??







Externally ‘forced’ NF-κB system

External modulation of TNF cytokine signal

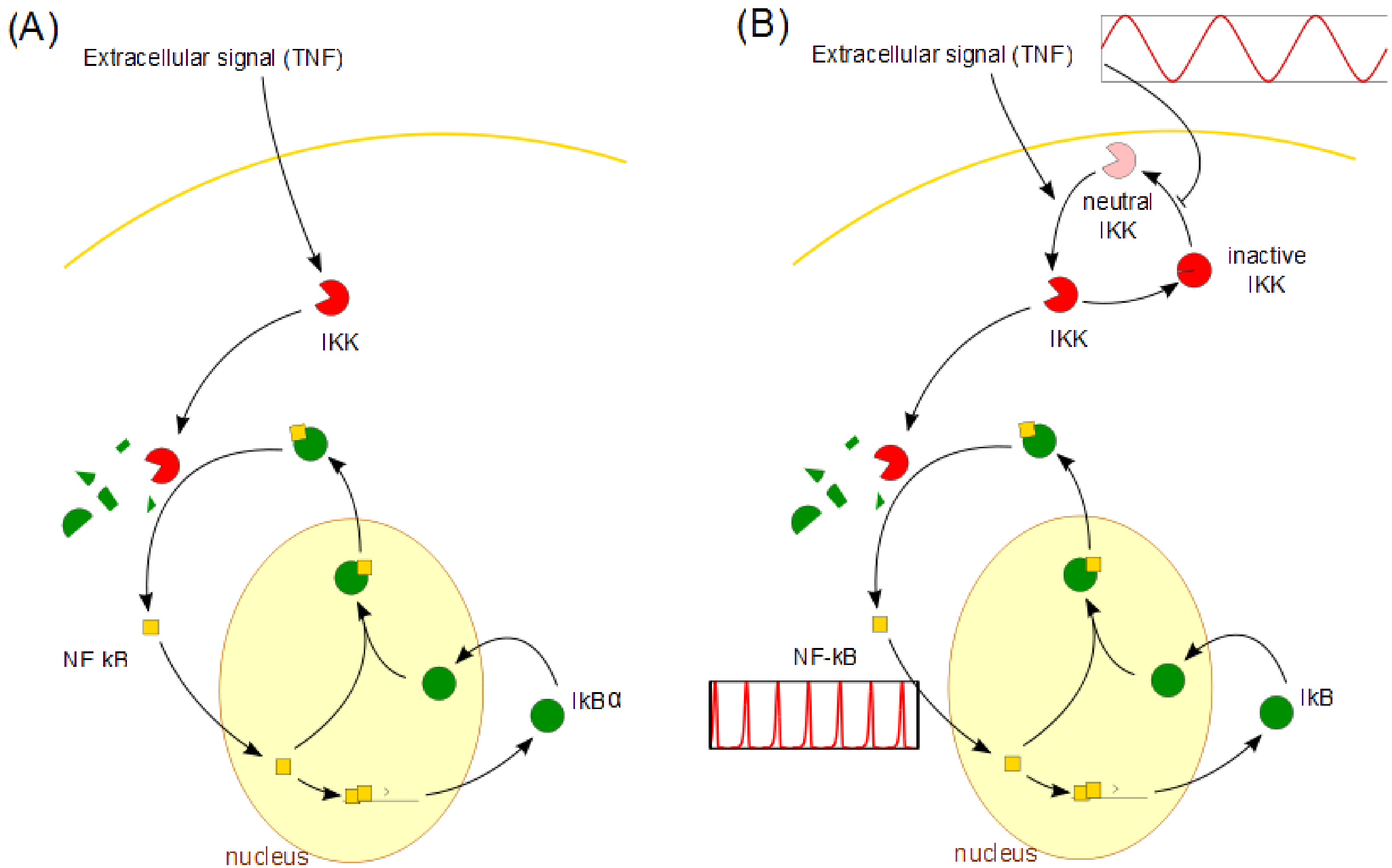
Cells can ‘learn’ (memorize after transient) and synchronize their dynamics →

Arnold tongues:

Maybe a way to control DNA damage/DNA repair

(S. Krishna, L. Kadanoff, MHJ)

Externally 'forced' NF-κB system



(S. Krishna, MHJ)

NFκB model, driven by TNF:

NFκB

$$\frac{dN_n}{dt} = k_{Nin}(N_{tot} - N_n)\frac{K_I}{K_I + I} - k_{Iin}I\frac{N_n}{K_N + N_n}$$

$$\frac{dI_m}{dt} = k_t N_n^2 - \gamma_m I_m$$

IκBα

$$\frac{dI}{dt} = k_{tl}I_m - \alpha[IKK]_a(N_{tot} - N_n)\frac{I}{K_I + I}$$

IKK

$$\frac{d[IKK]_a}{dt} = k_a[TNF]([IKK]_{tot} - [IKK]_a - [IKK]_i) - k_i[IKK]_a$$

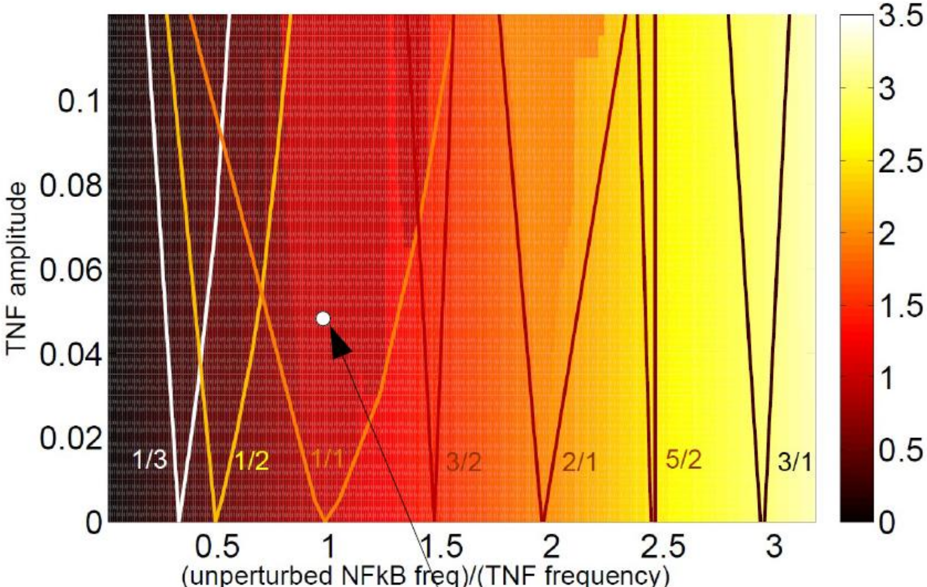
TNF

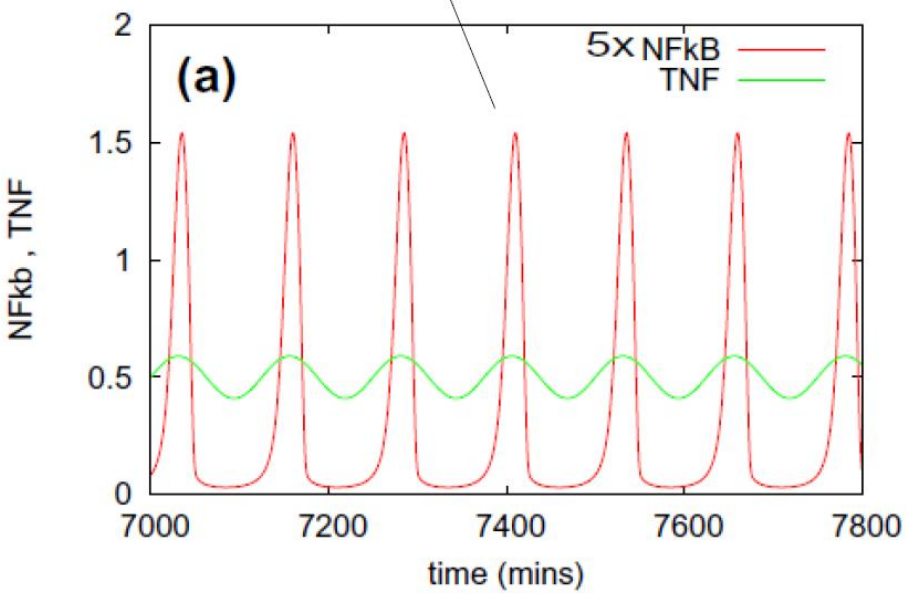
$$\frac{d[IKK]_i}{dt} = k_i[IKK]_a - k_p[IKK]_i\frac{k_{A20}}{k_{A20} + [A20][TNF]}$$

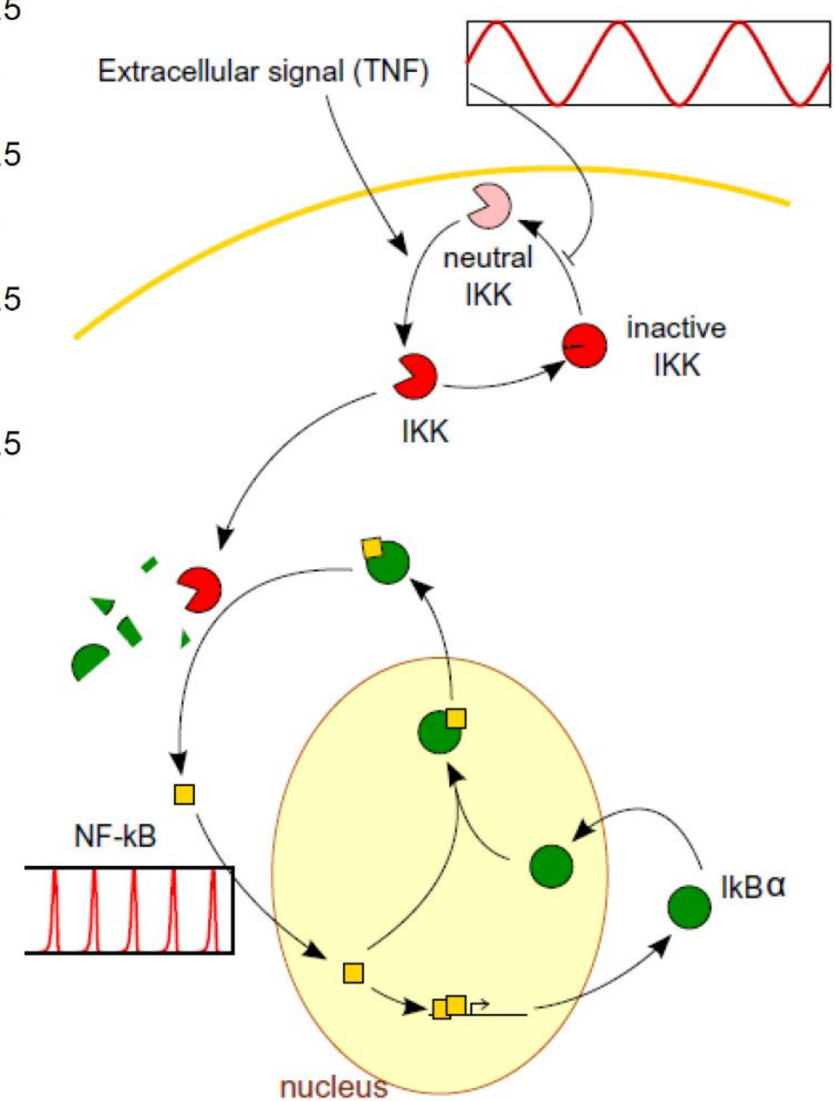
A20

IKK, TNF, A20:Ashall, Rand, White, et al…. Science (2009)

Sinusoidally driven NF-kB oscillations

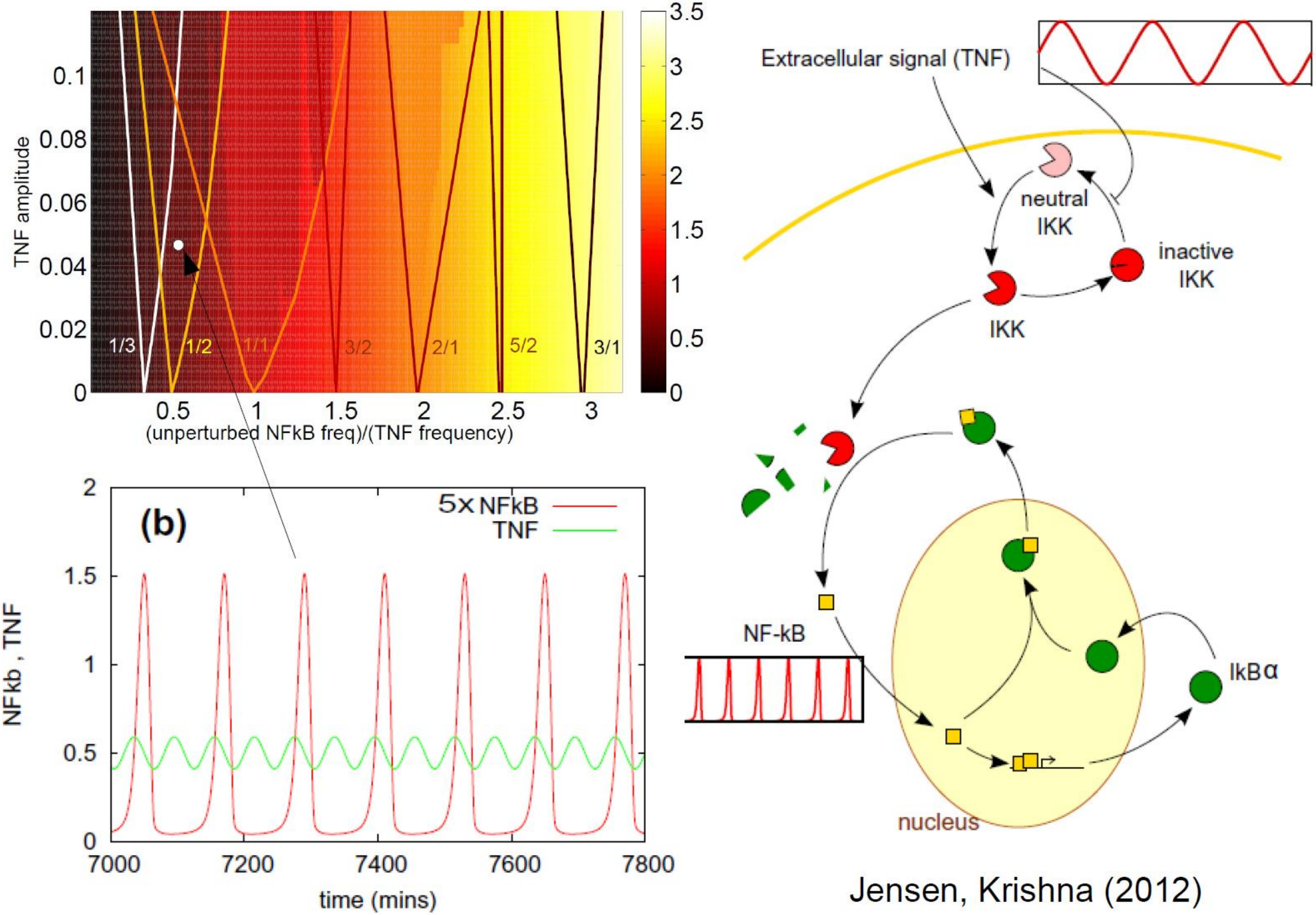






Jensen, Krishna (2012)

Sinusoidally driven NF-kB oscillations



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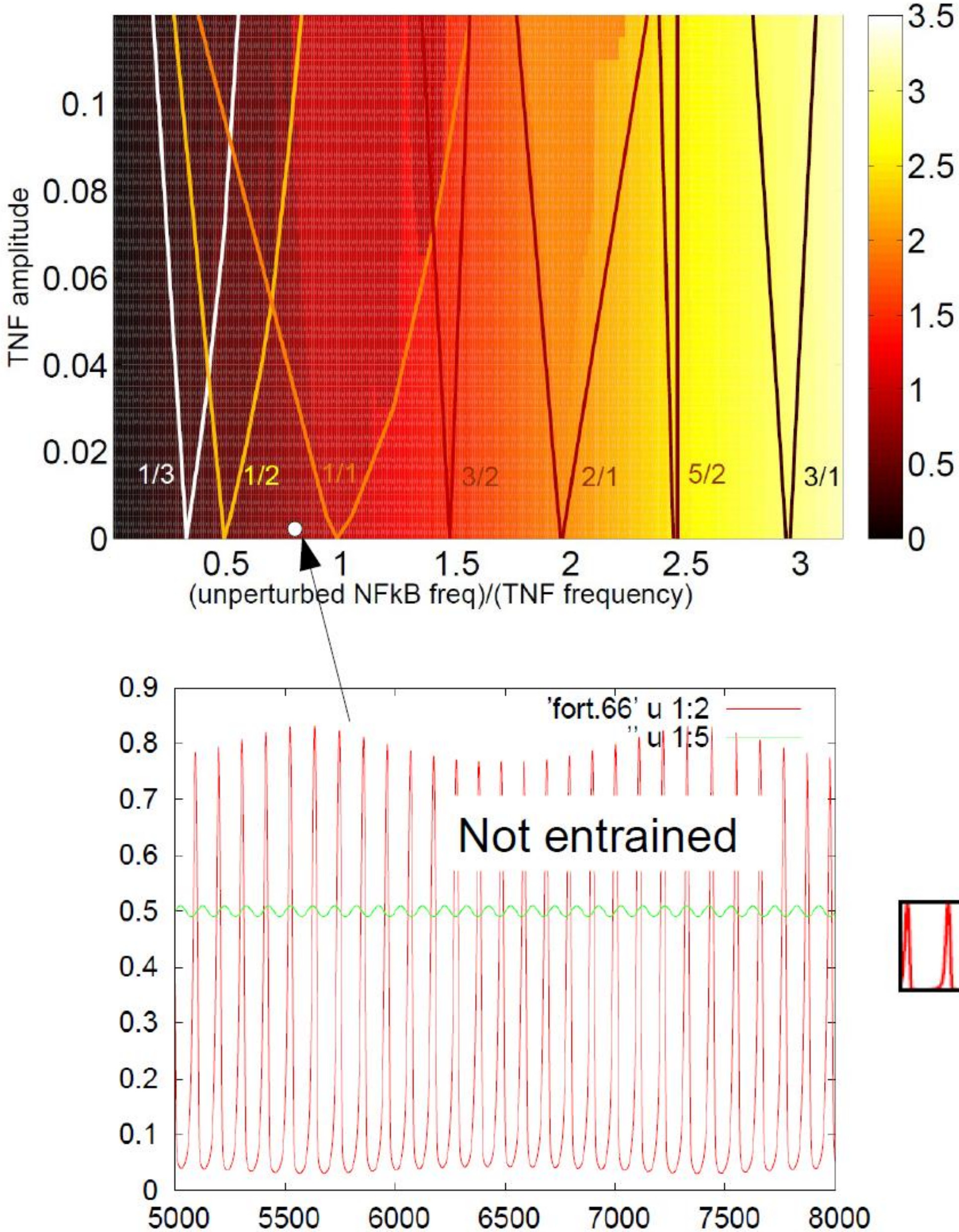

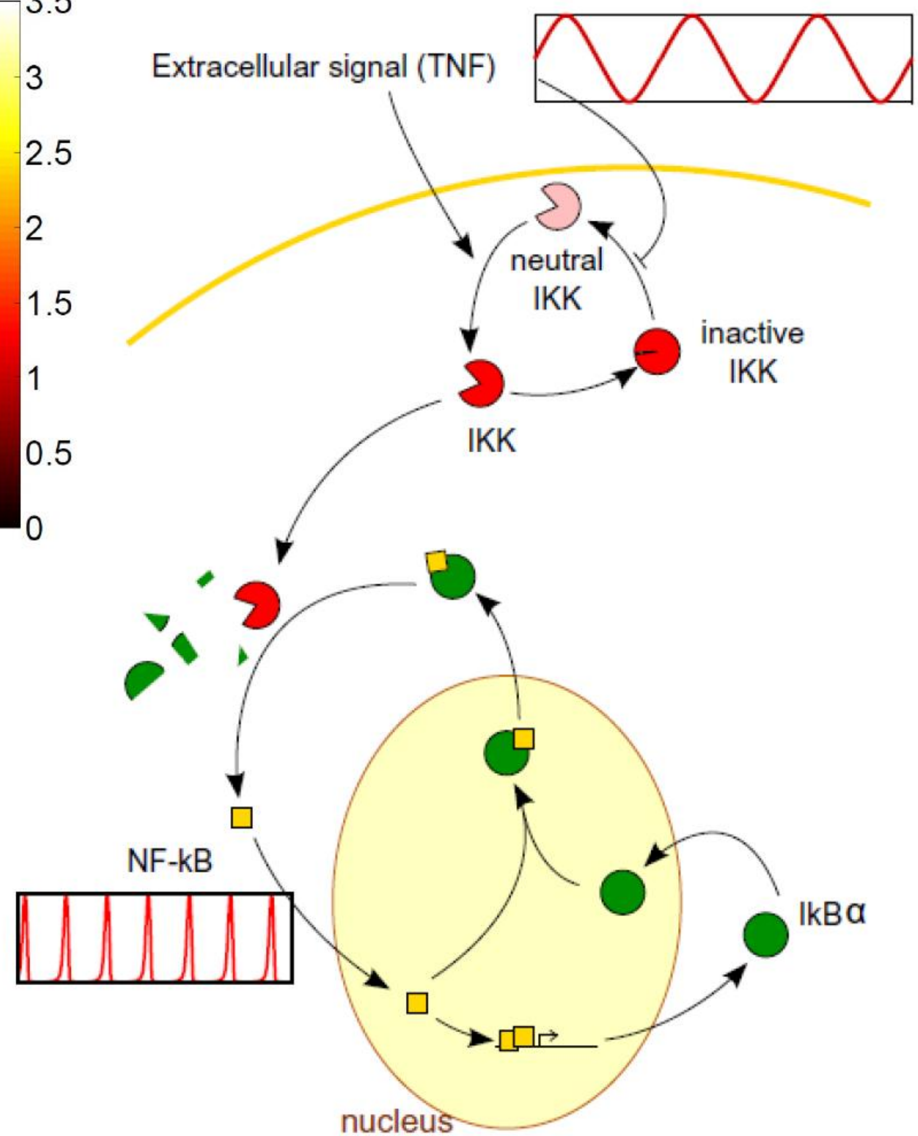

Jensen, Krishna (2012)

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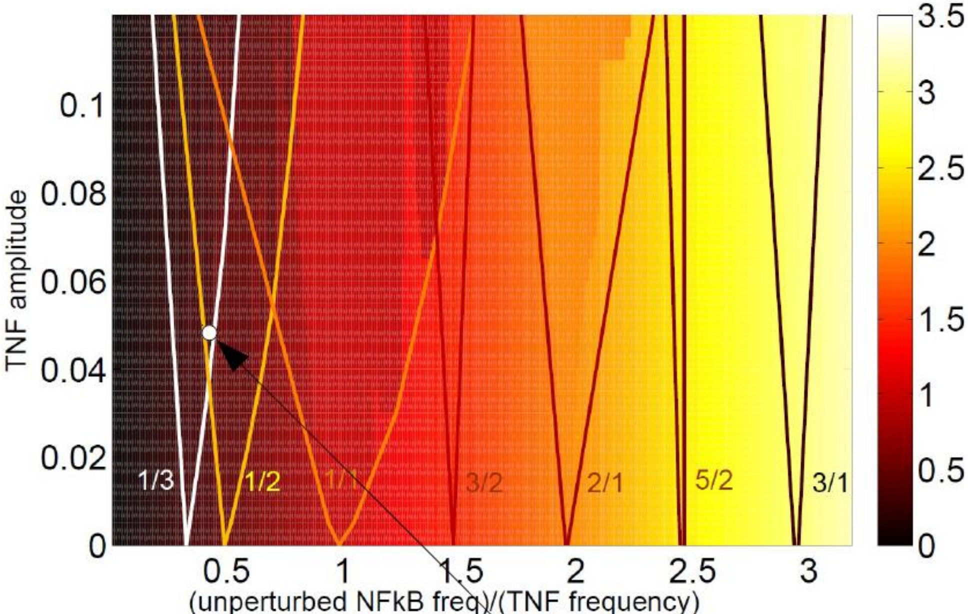
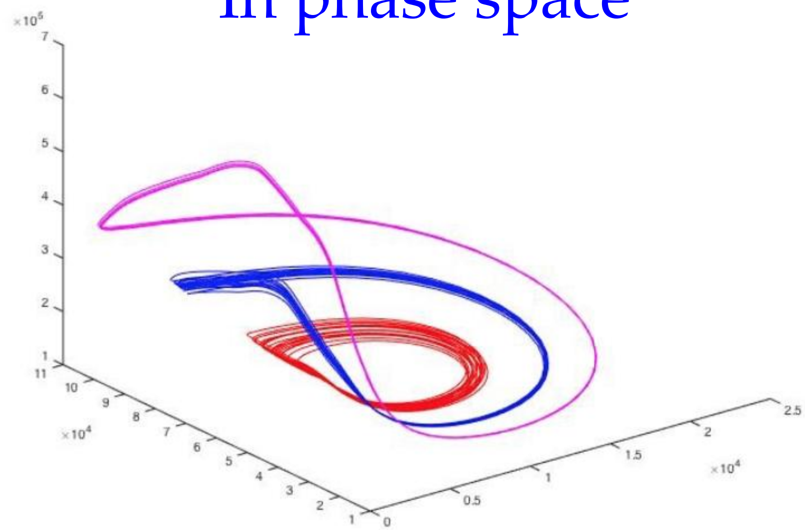
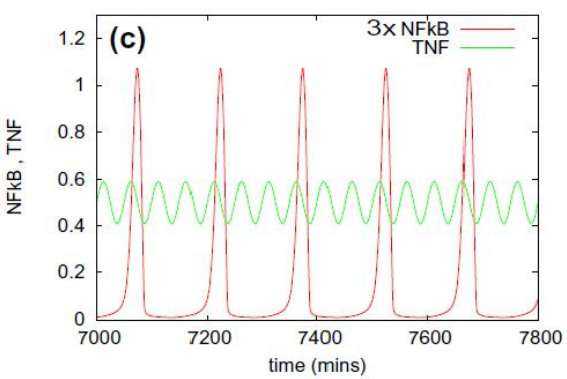
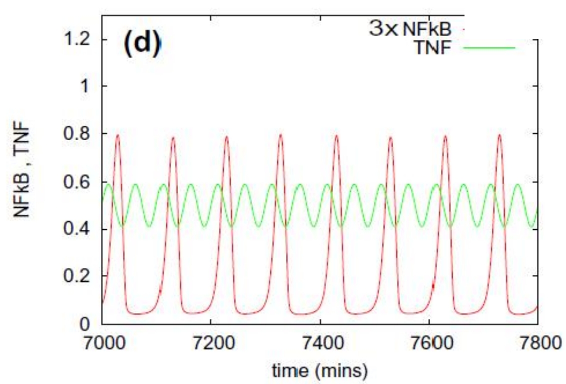


Tongues overlap !

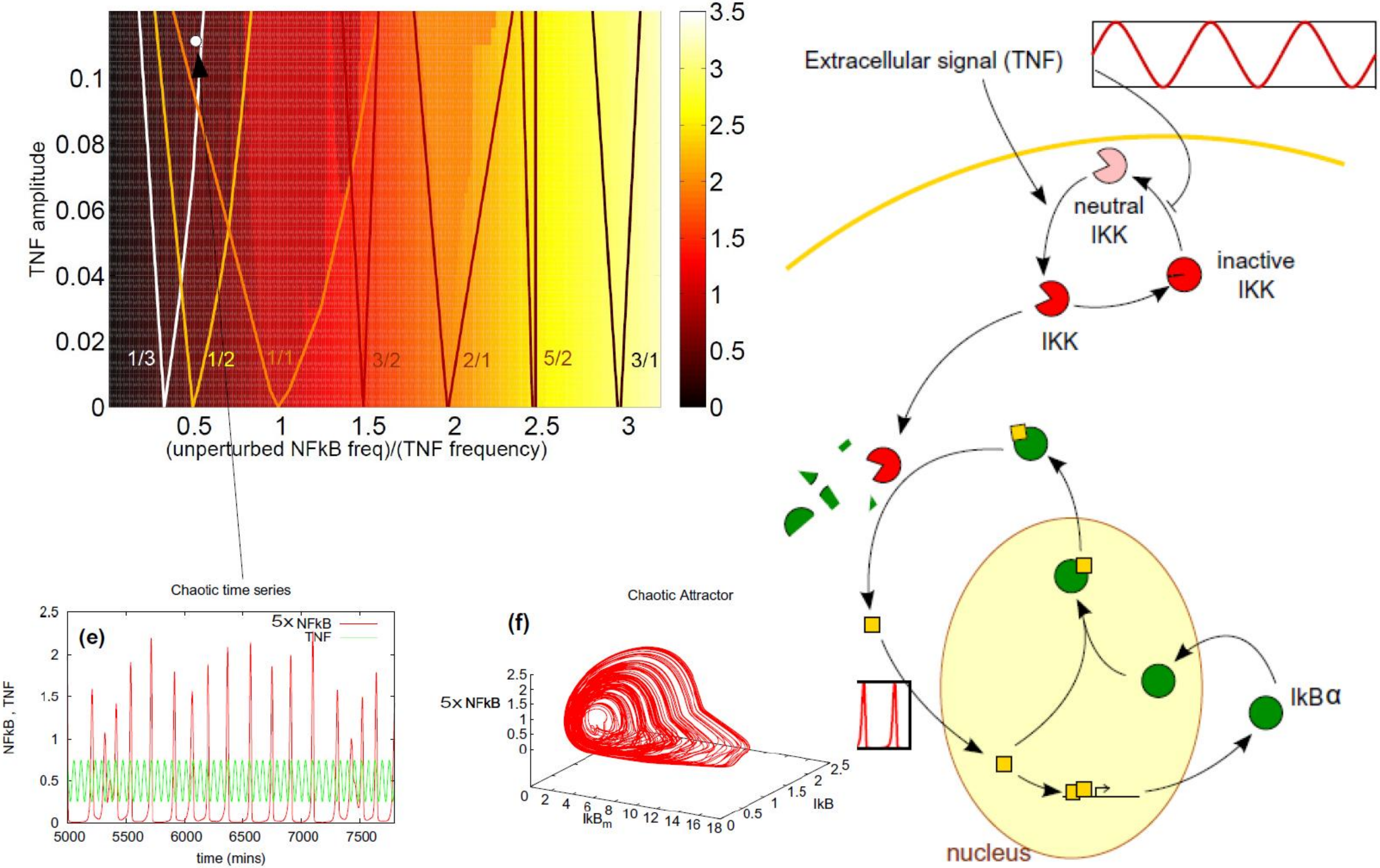
In phase space





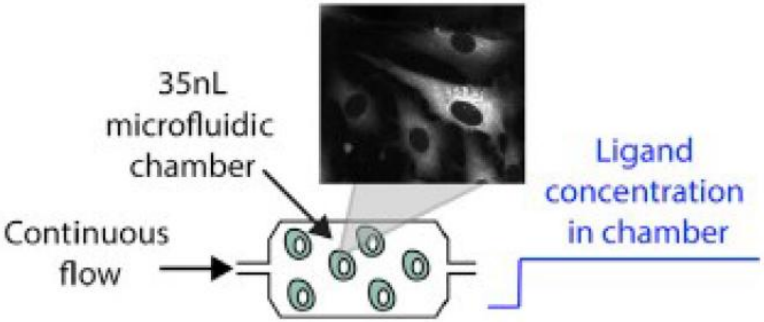


Sinusoidally driven NF-kB oscillations



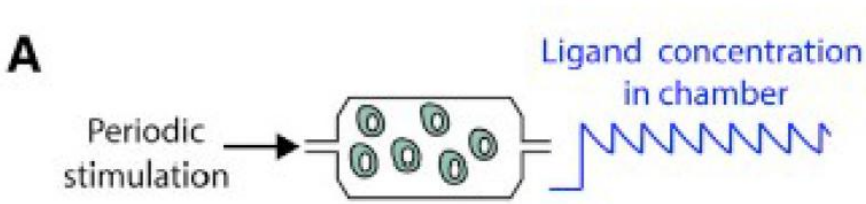
Jensen, Krishna (2012)

Sinusoidally driven NF-kB oscillations

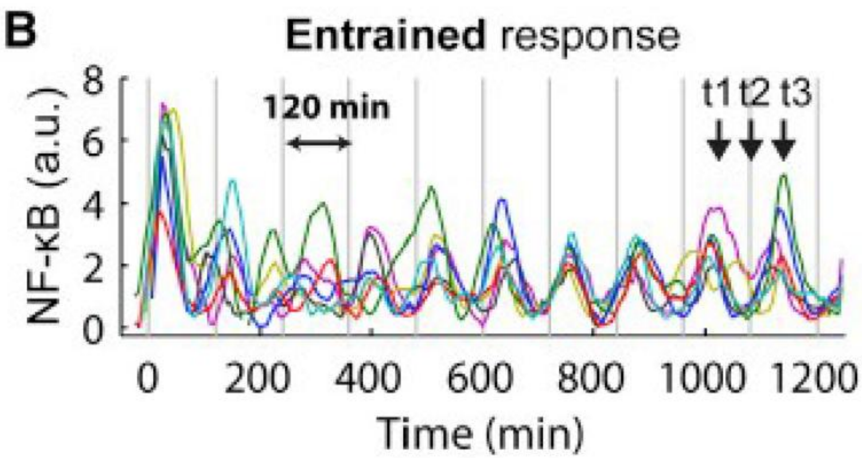


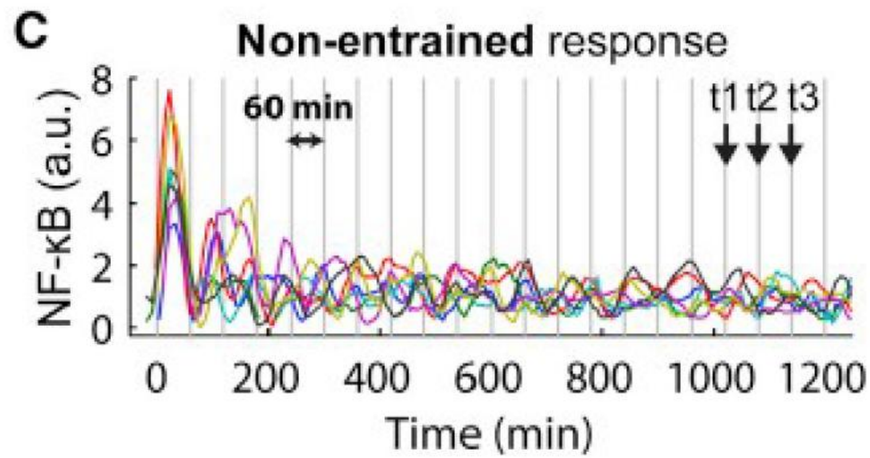
Ryan Kellog, Savas Tay (2015)

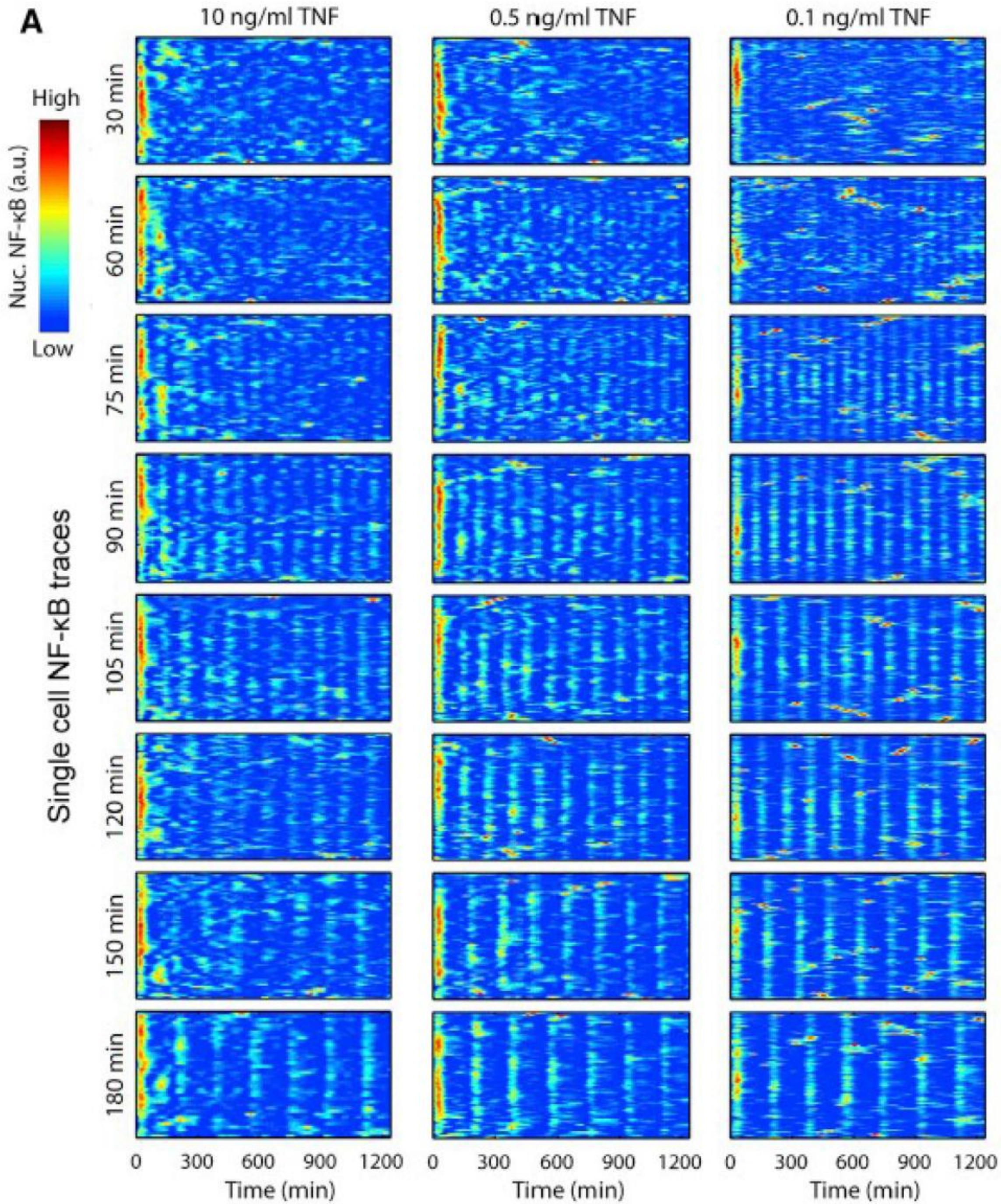
Microfluidic chamber with mouse fibroblast cells

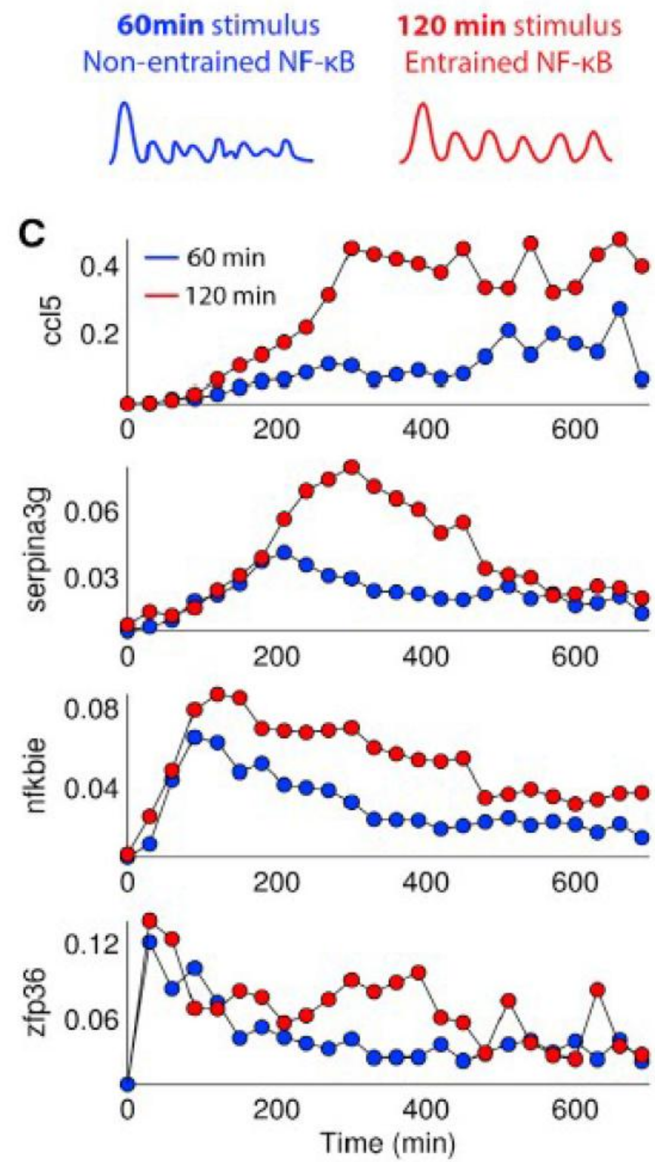


Can be driven by a periodic sawtooth shaped stimulation



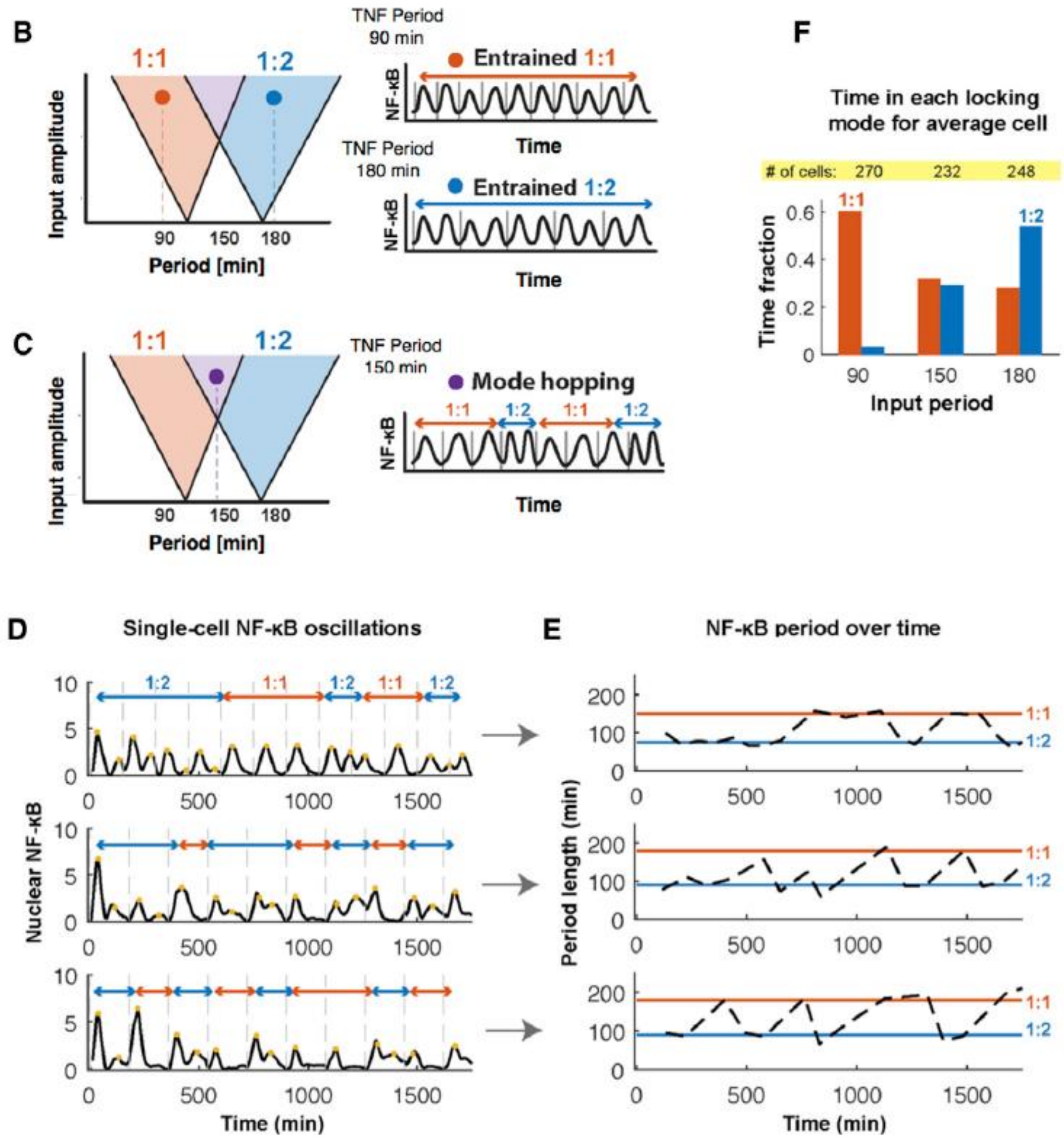




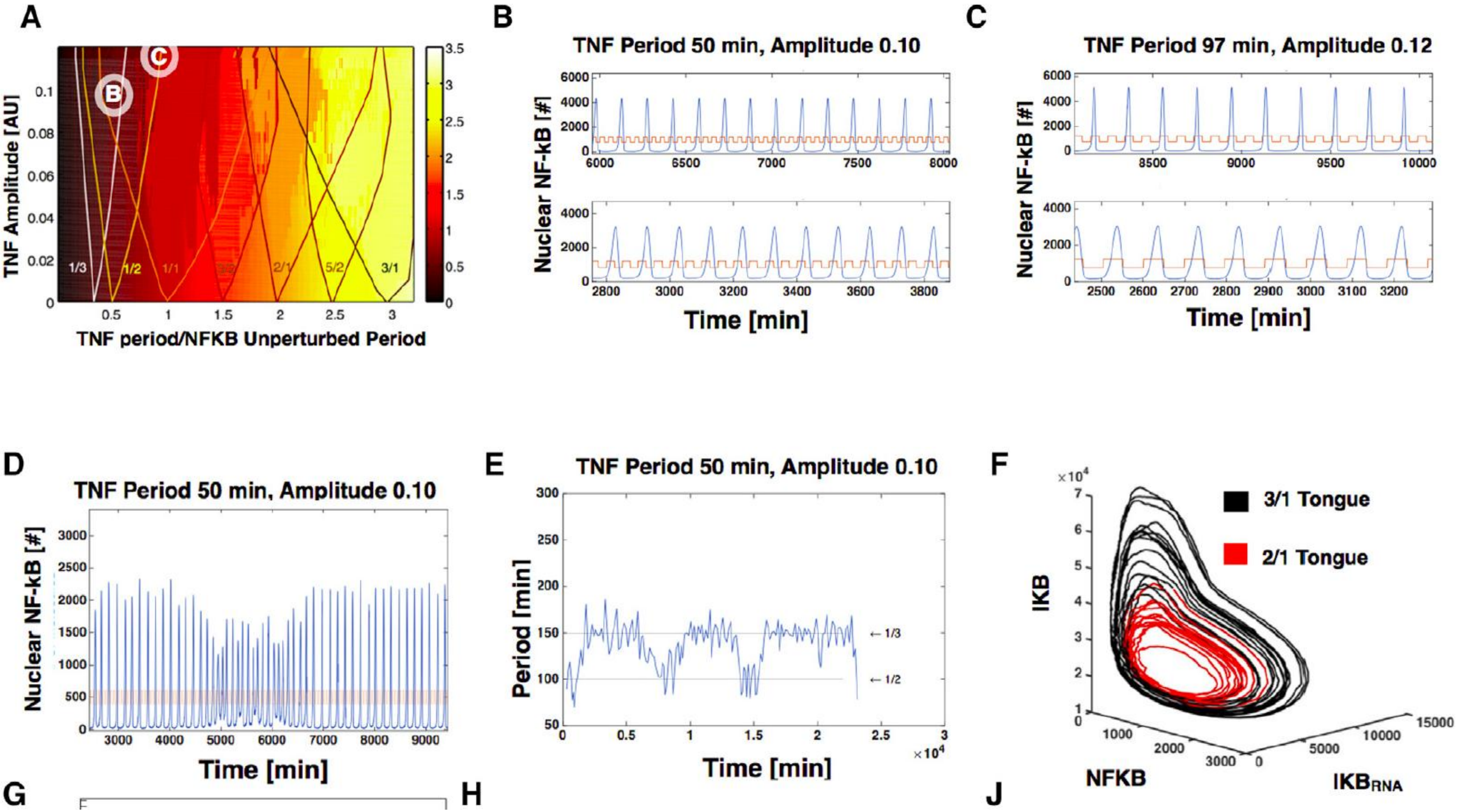


Entrained NF-kB seems to aid expression of certain genes

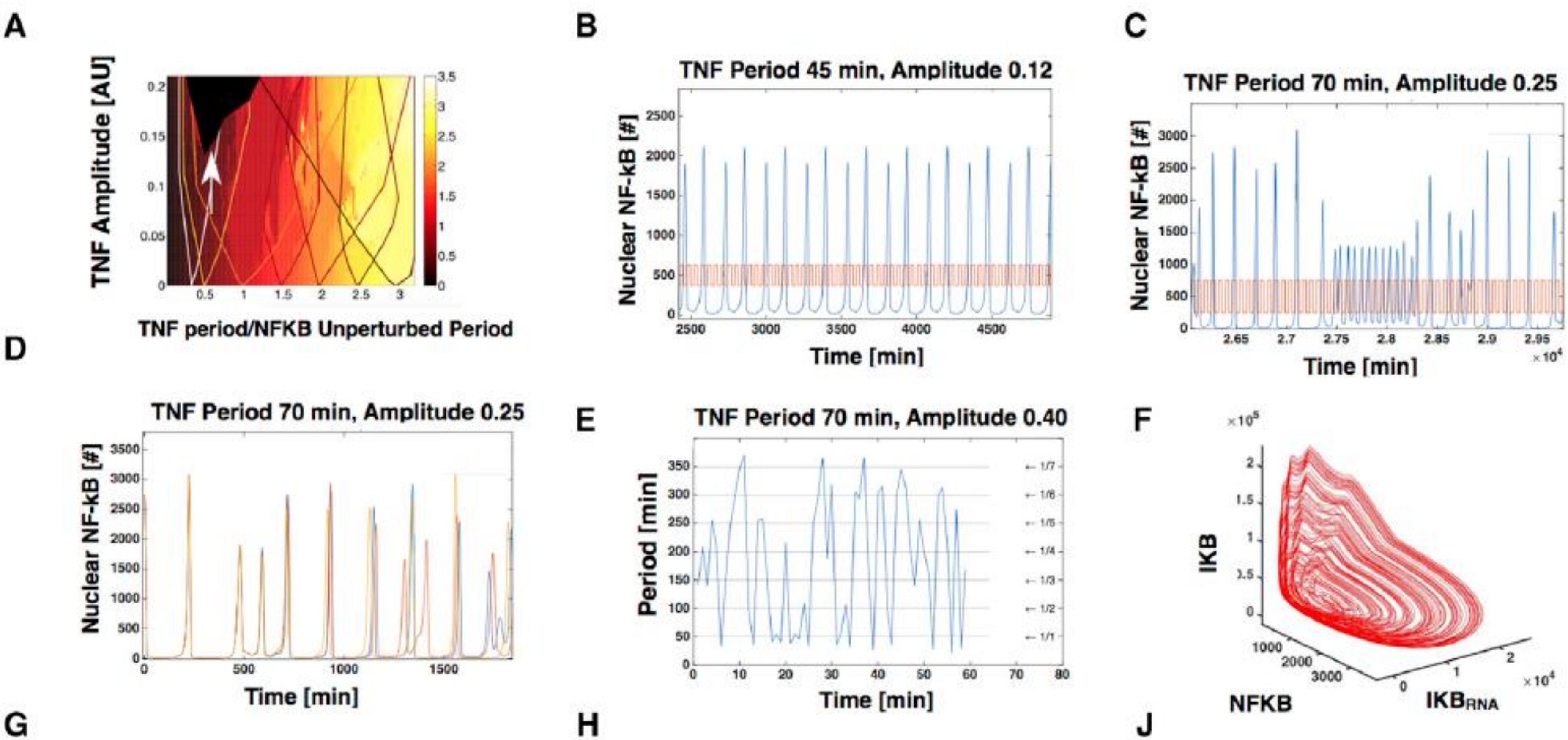
When tongues overlap:
Experimentally observed mode hopping between entrained states



Stochastic Gillespie simulations: manifest as modehopping between entrained states

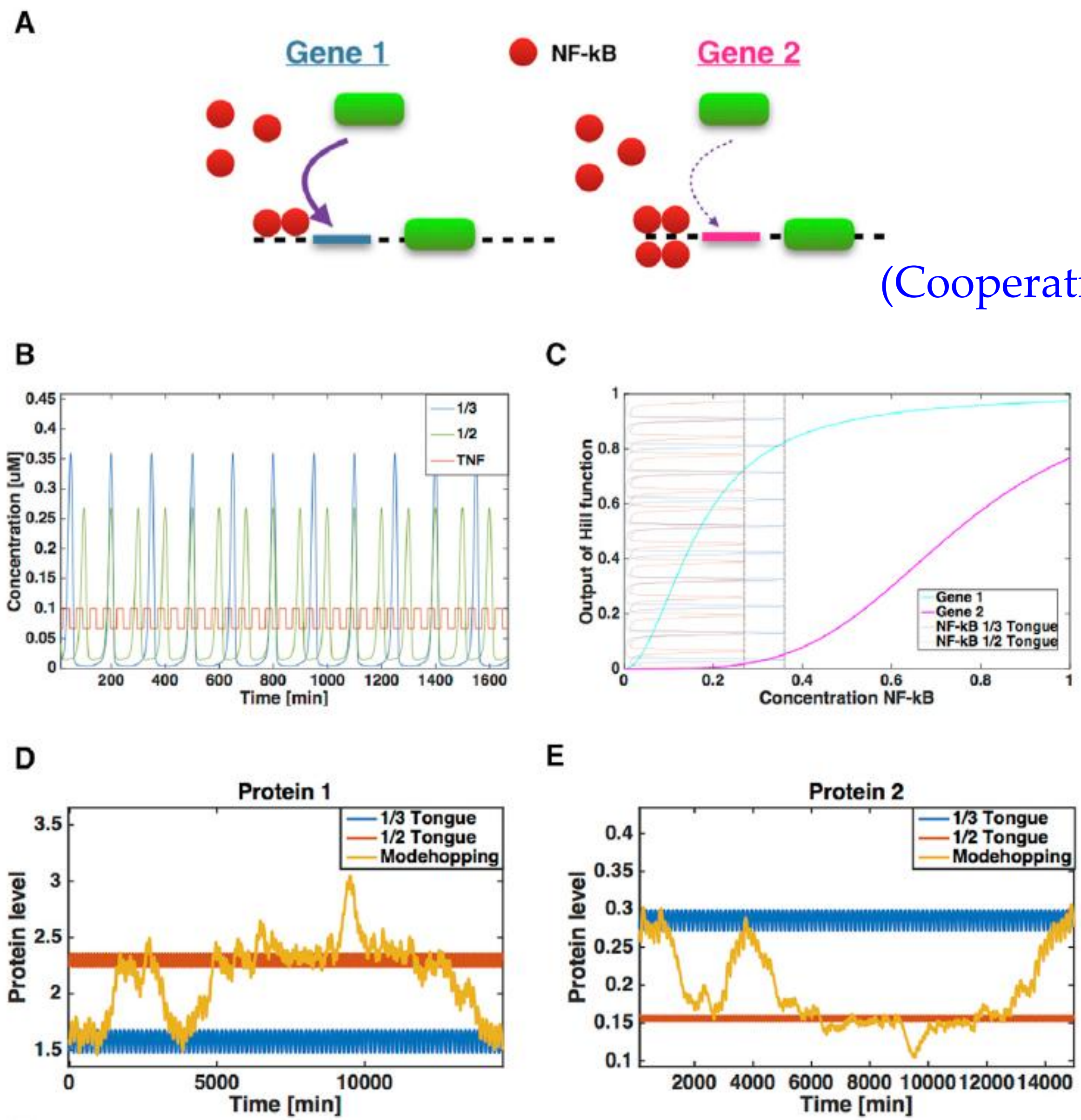


Deterministic chaos:
Mode hopping between several entrained states



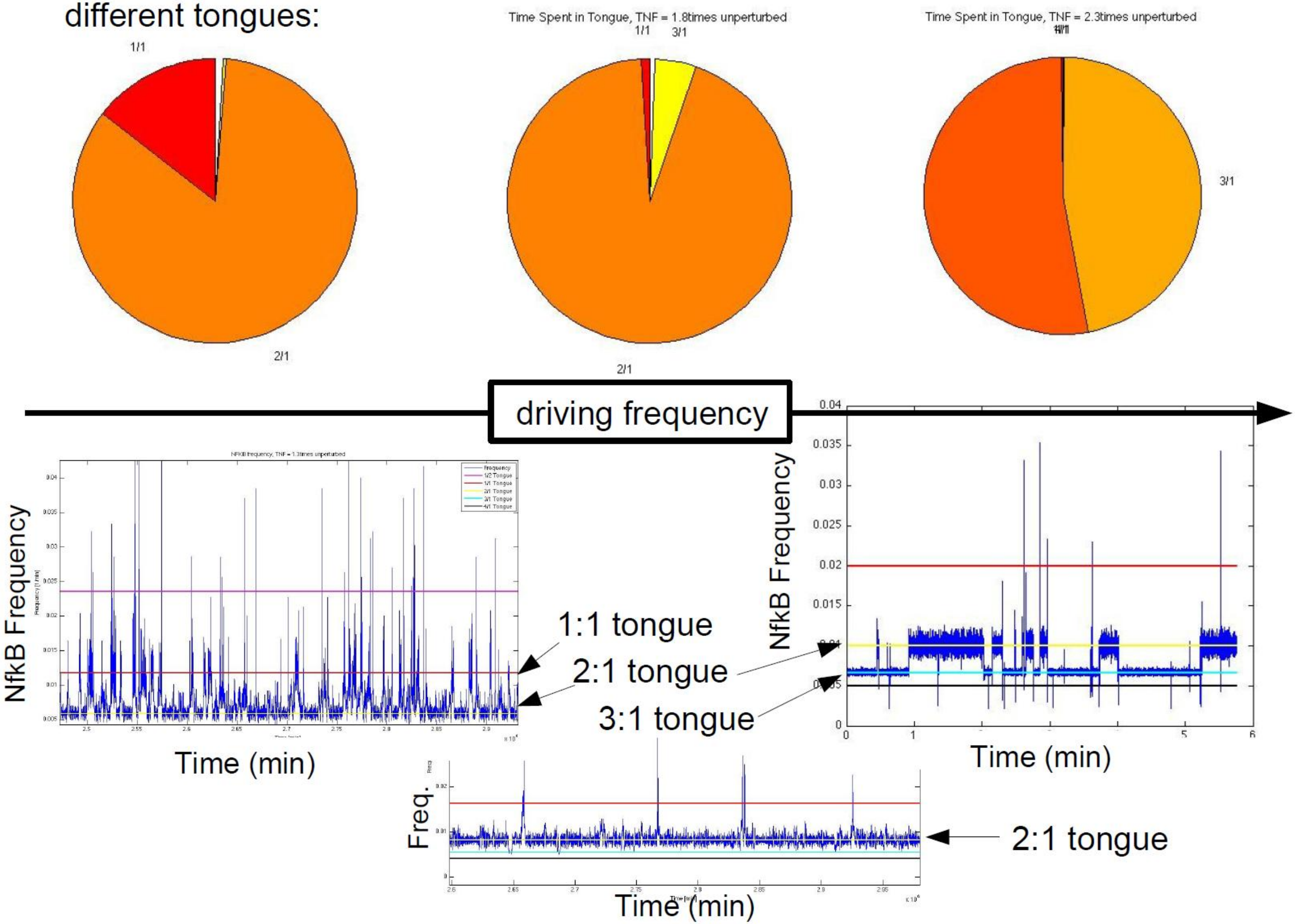
Modehopping a way to switch between genes?: Multiplexing

(Cooperativity vs affinity)



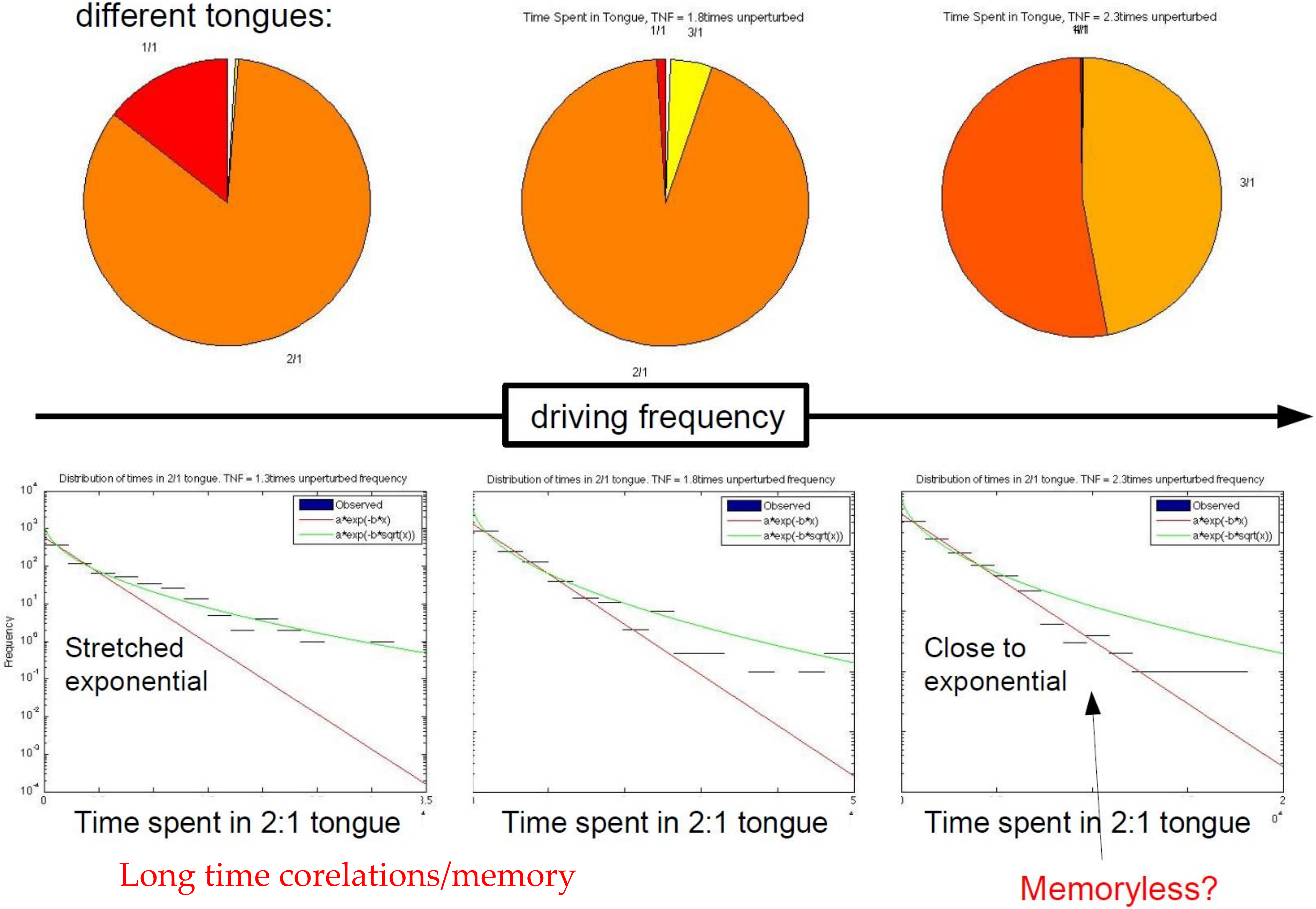
Gillespie simulations of NF-kB network by Mathias Heltberg

Probability to be in different tongues:

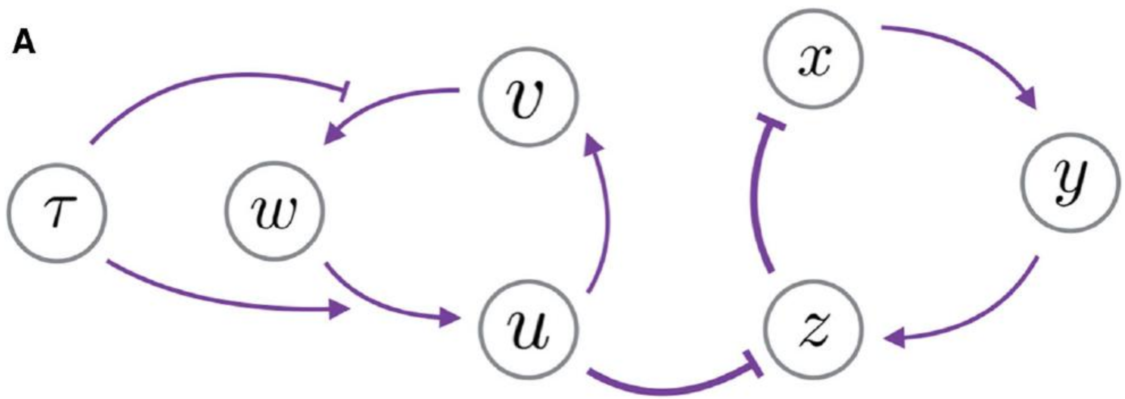


Gillespie simulations of NF-kB network by Mathias Heltberg

Probability to be in different tongues:



To understand memory:
Simplify the NF-kB model: Overlap of two tongues



$$\dot{N}_n = k_{Nin}(N_{tot} - N_n)\frac{K_I}{K_I + I} - k_{Iin} I \frac{N_n}{K_N + N_n}$$

$$\dot{I_{RNA}} = k_t N_n^2 - \gamma_m I_{RNA}$$

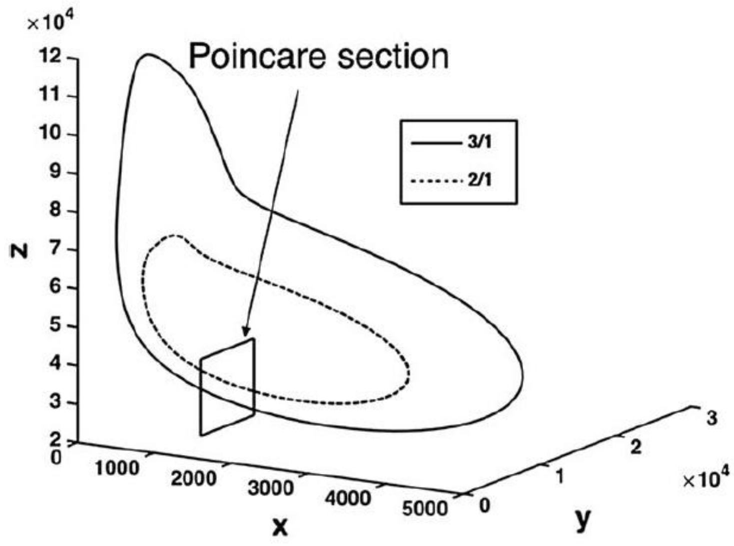
$$\dot{I} = k_{tl} I_{RNA} - \alpha IKK_a (N_{tot} - N_n)\frac{I}{K_I + I}$$

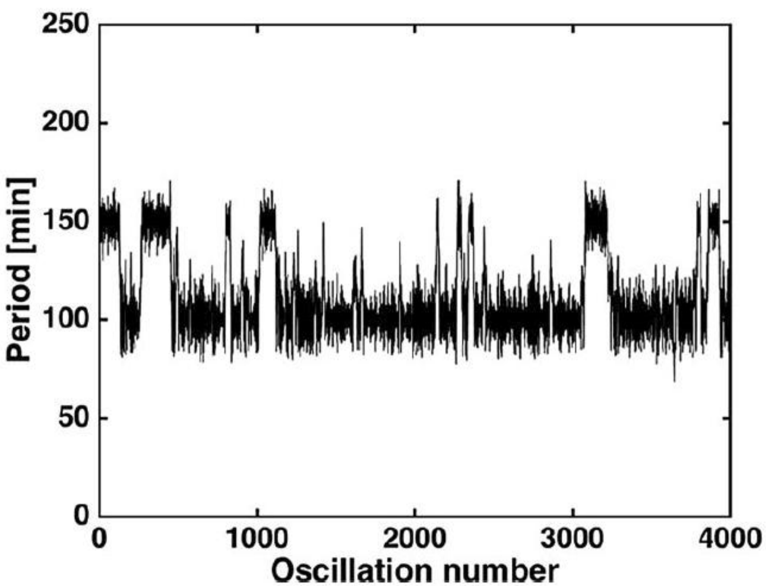
$$\dot{IKK_a} = k_a f(t)([IKK]_{tot} - IKK_a - IKK_i) - k_i IKK_a$$

$$\dot{IKK_i} = k_i IKK_a - k_p IKK_i \frac{k_{A20}}{k_{A20} + [A20] f(t)}$$

$$f(t) = 0.5 + A\sin\left(\frac{2\pi}{T} t\right)$$

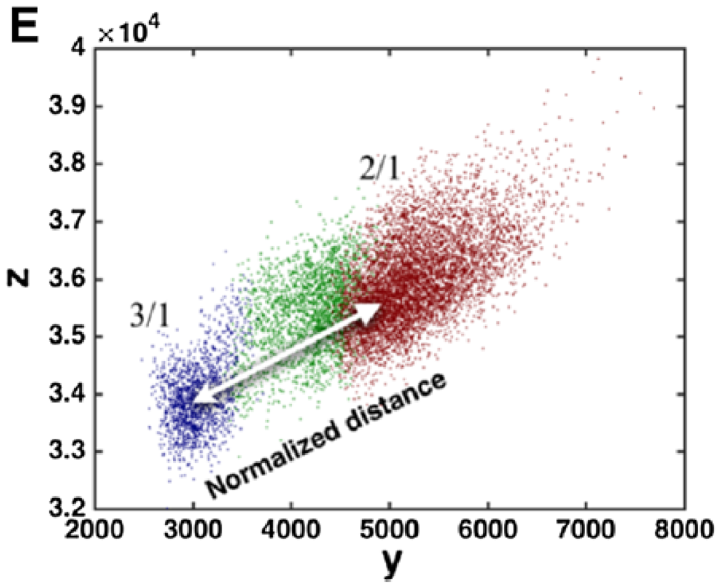
To simplify: Make a Poincare cut

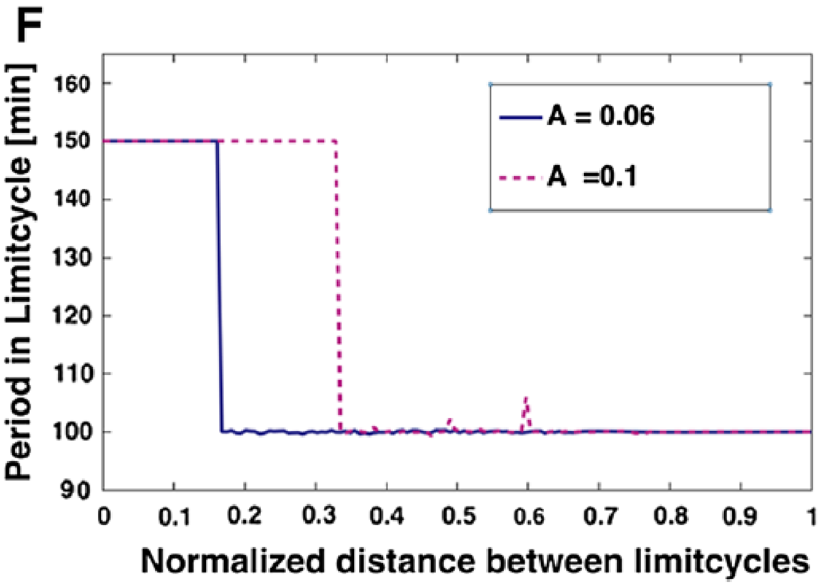




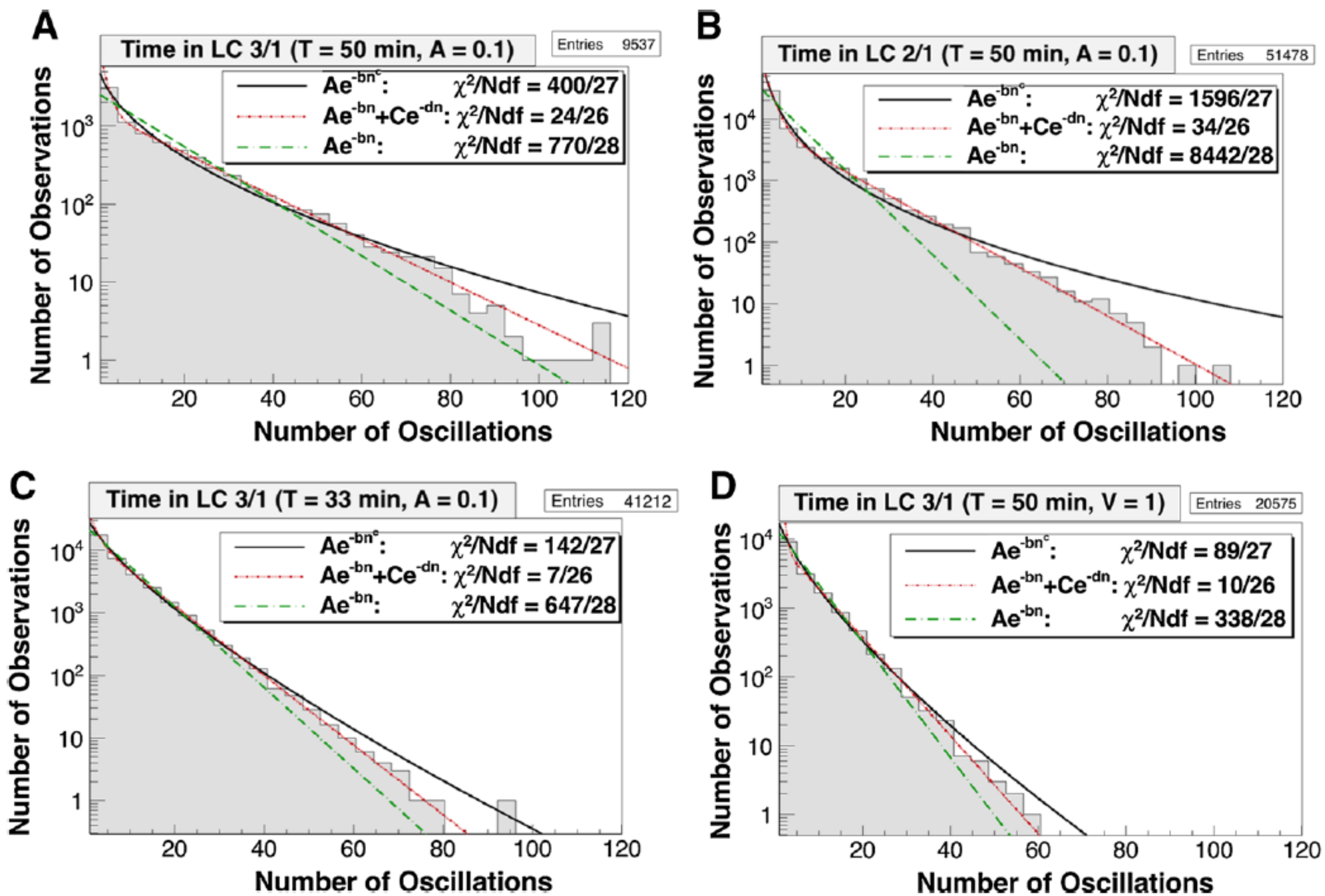
Stochastic simulation: Jumps between the tongues !

Basin of attraction for the two tongues





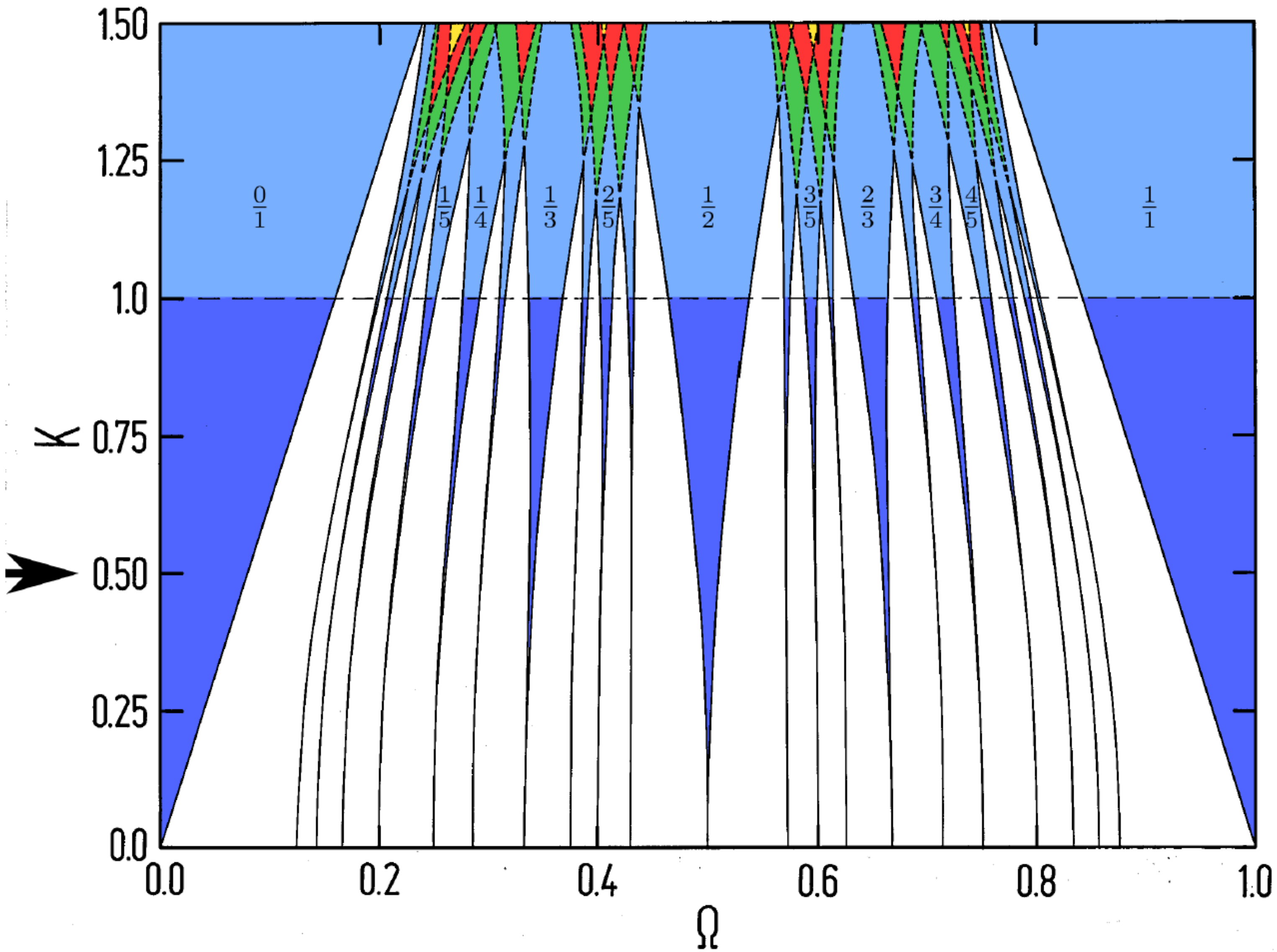
Number of oscillations before leaving a tongue



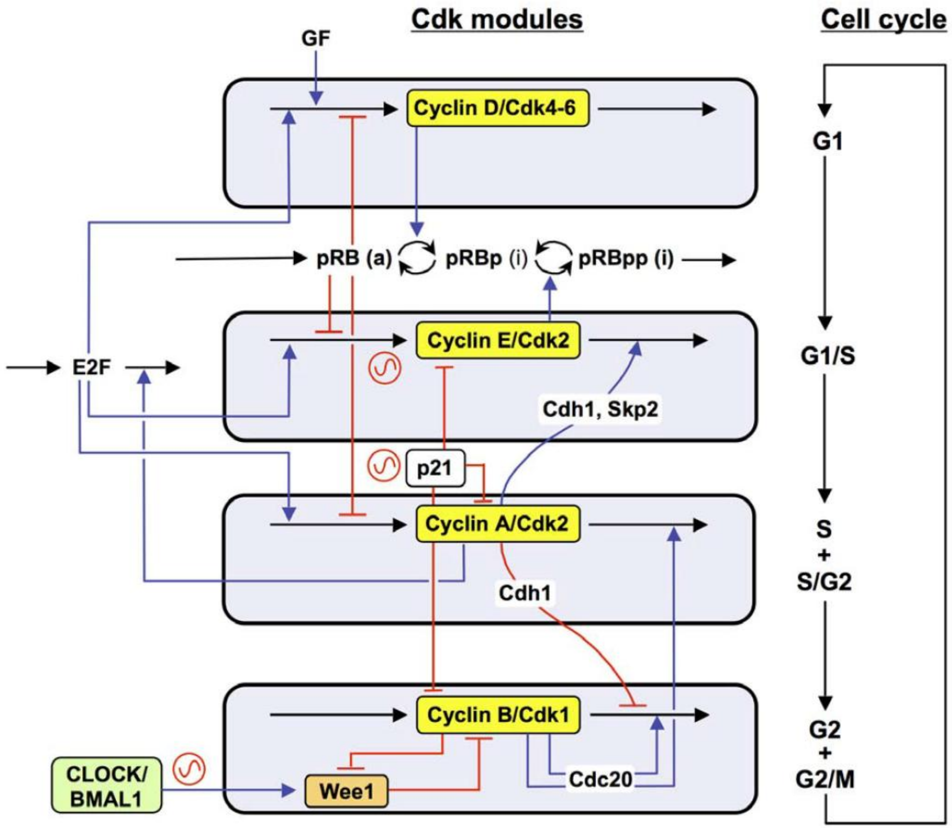
Strongly time correlated (memory):
Stretched exponential – or sum of two exponentials

Two coupled oscillators: Arnold tongues

$$\omega/\Omega = P/Q$$



Only few examples Arnold tongues in other biological systems: Cell cycle and circadian clock



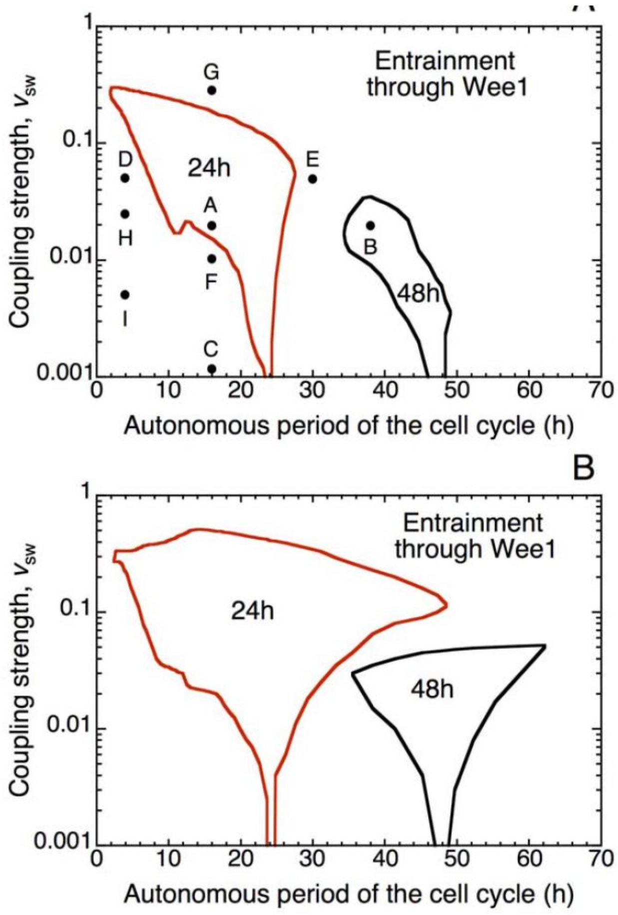
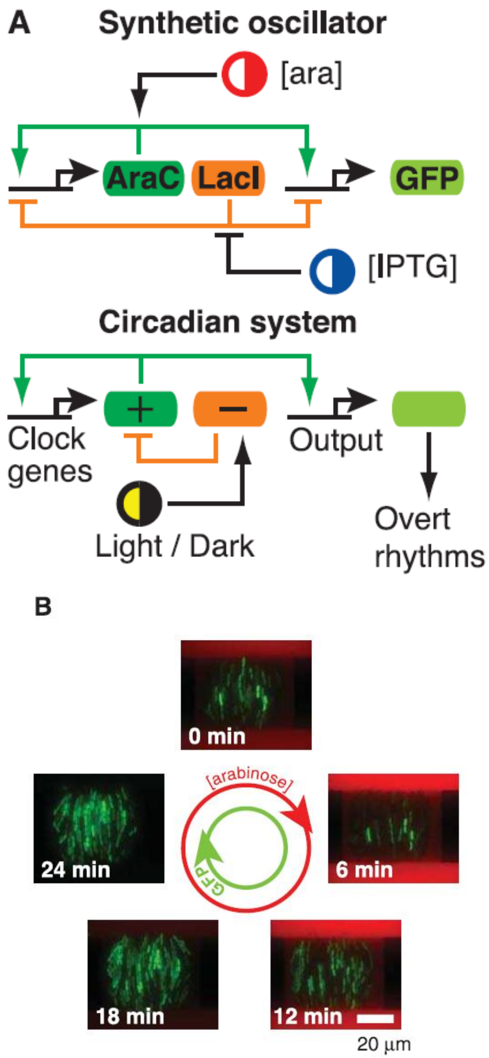
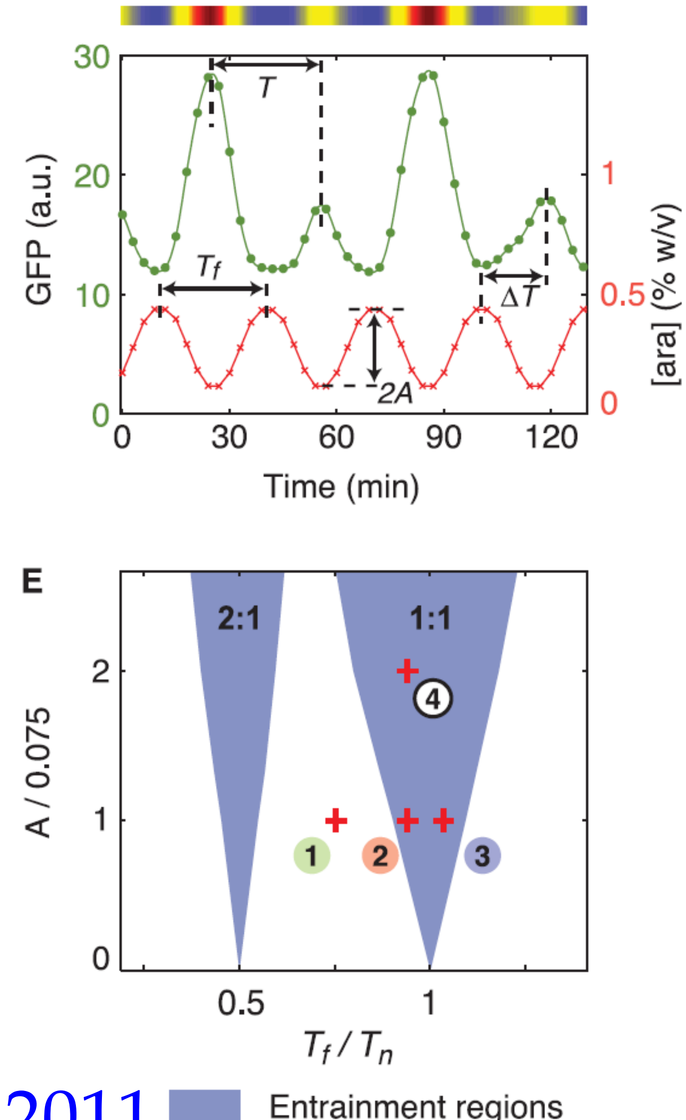


Figure 4. Domains of entrainment of the cell cycle by the circadian clock via circadian control of the kinase Wee1. The

Gerard and Goldbeter, May, 2012

Populations of genetic oscillators





Jeff Hasty et al, Science 2011

Cross, Charvin, Siggia: Budding yeast cell cycle:

Experiments and Model
(PNAS 2009)

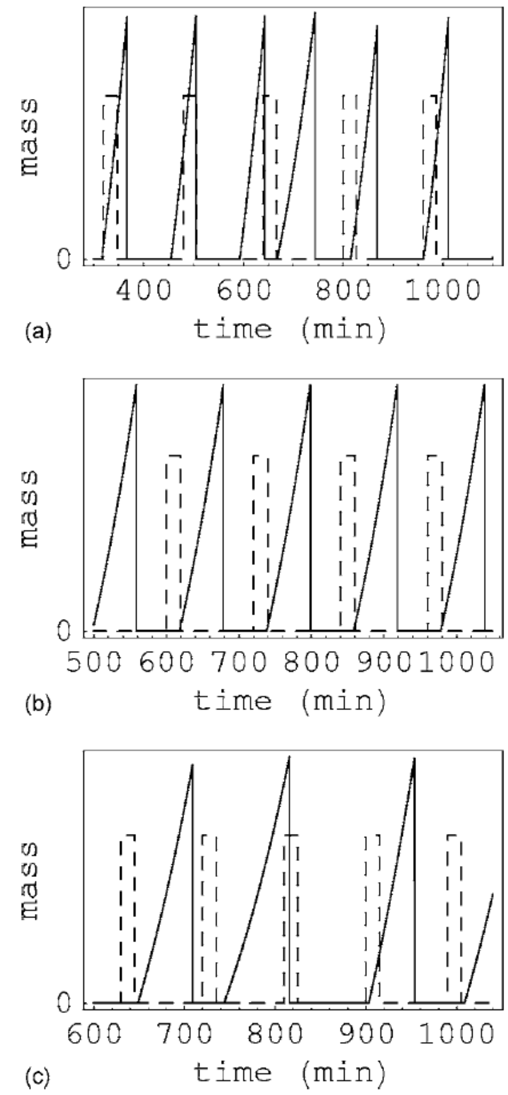
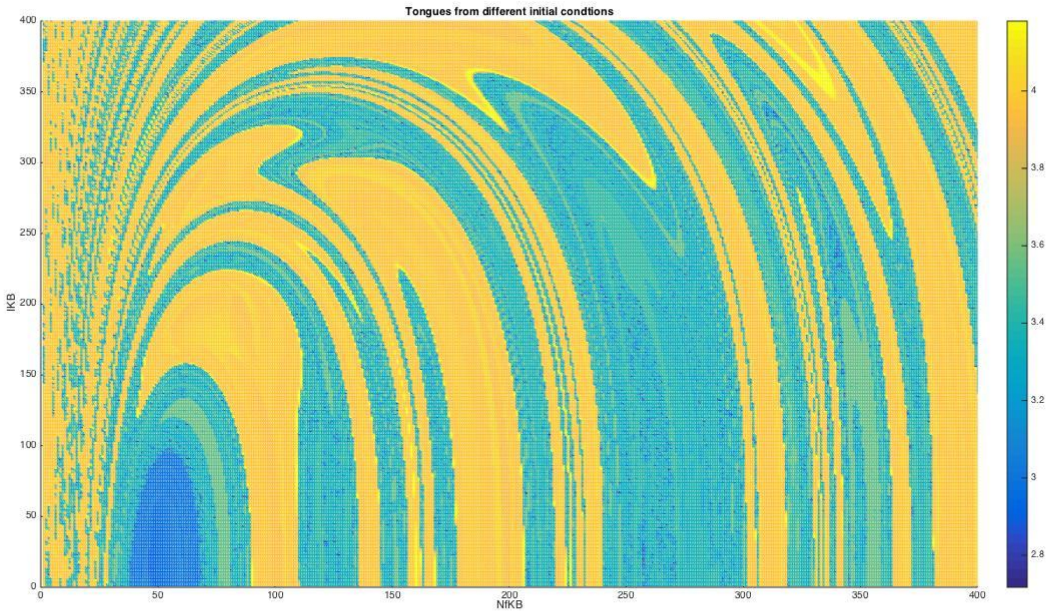
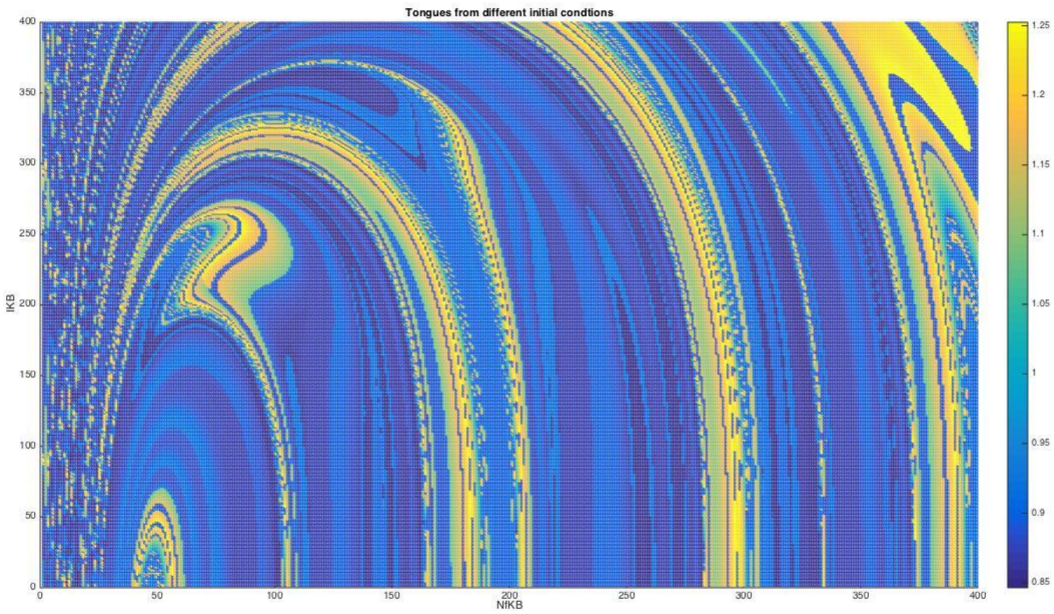


FIG. 3. The daughter mass (solid line, arbitrary units) as a function of time for impulses of Cln3 (dashed) with periods T, longer than the locking interval [T=160 min, (a)], within the mode-locked interval [T=120 min, (b)], and shorter than the mode-locked interval [T=90 min, (c)]. The amplitude of the perturbation is given by the first entry in Table I. Note that there is an extra cell cycle in (a) and an extra pulse in (c). The natural period of the cell is 138 min, which is the average period in (c).

Initial conditions in "phase space" to different tongues





Mathias Heltberg