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Slide of the Seminar

Coupled Oscillations in Biology: Arnold Tongues and Mode Hopping

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ERC Advanced Grant (N. 339032) "NewTURB"
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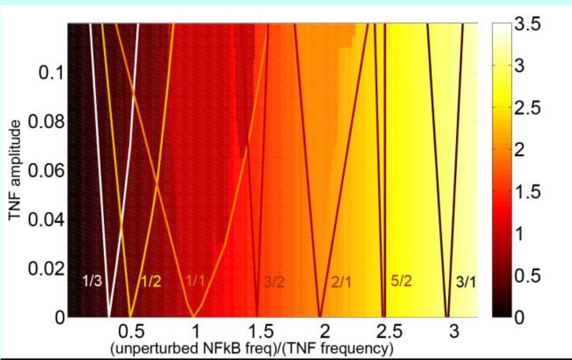
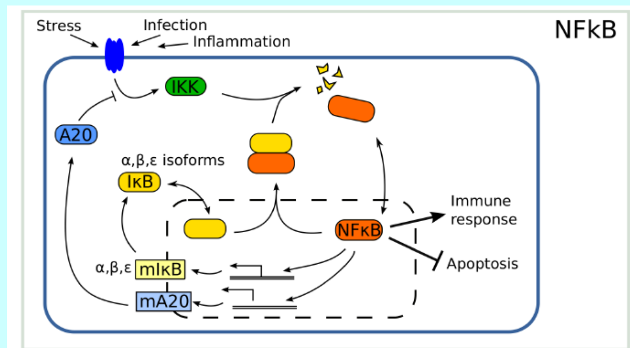
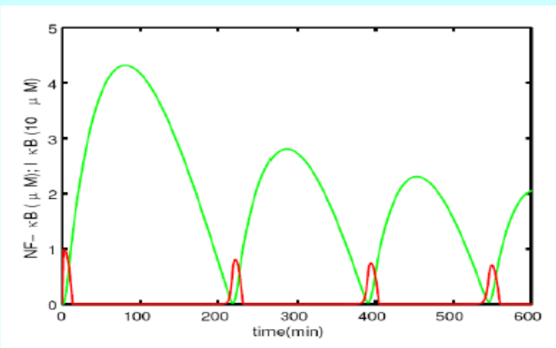
Coupled Oscillations in Biology: Arnold Tongues and Mode Hopping.

Rome II, 3 July 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: Oscillations synchronize (entrain)

Arnold tongues → Overlap → Mode hopping

5. Pulsatile extracellular signaling in experiments (Chicago):

Observe mode hopping. A way to control cell dynamics ?

A way to 'jump' between different genes 'multiplexing'→

Gives different protein production, gene control !

6. Mode hopping between several states:

Results in chaotic motion ! Strong time correlations

7. Is deterministic chaos relevant for gene productions ? Yes!

Collaborators:

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

M. Heltberg, R. Kellogg, S. Krishna, S. Tay and M.H. Jensen, "Noise-induced NF-kB Mode Hopping Enables Temporal Gene Multiplexing", 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).

R. Rasmussen, M.H. Jensen and M.L. Heltberg, "Chaotic Dynamics Mediate Brain State Transitions Driven by Changes in Extracellular Ion Concentrations", Cell Systems 5, 591-603 (2017).

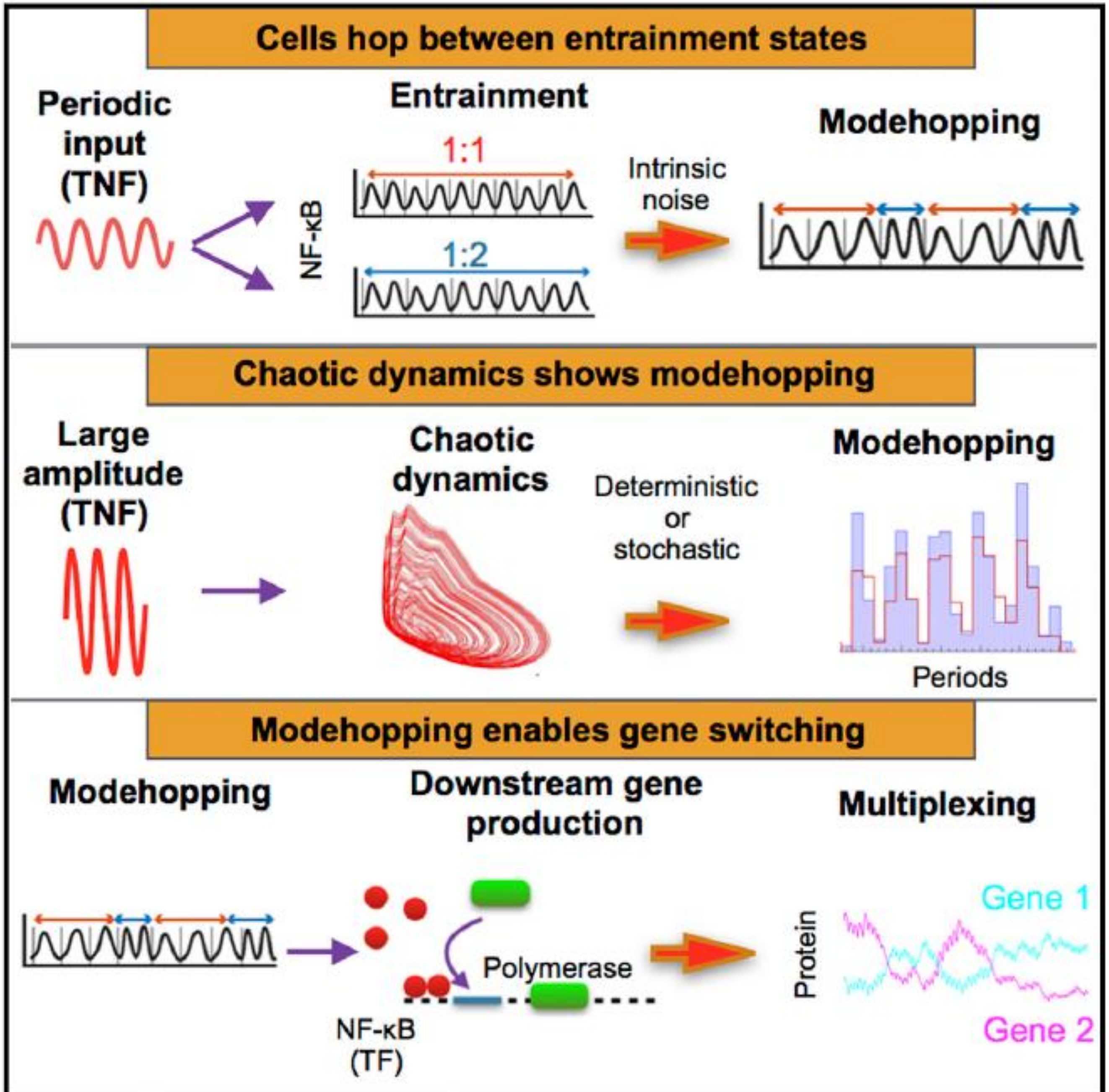
N. Mitarai, U. Alon and M.H. Jensen, "Entrainment of linear and non-linear system under noise", Chaos, 23, 023125 (2013).

Leo Kadanoff, S. Krishna and M.H. Jensen, "Chaos and Universality in Coupled Oscillators: Lessons for Biology", Review (2014)

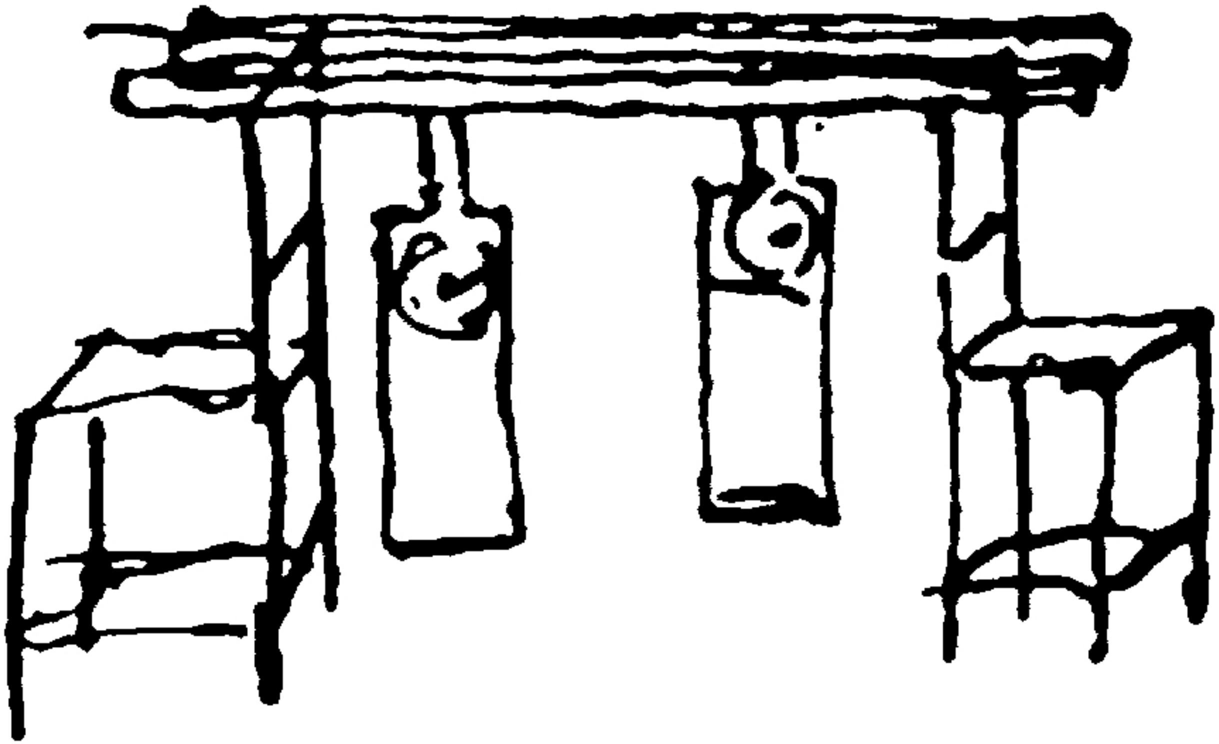
M. Heltberg, S. Krishna and M.H. Jensen, "Chaotic Dynamics in Transcription Factors: Enhancement of Low Affinity Genes, Efficient Protein Complex Formation and Generation of Population Heterogeneity, Nature Communication (2018) .

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

Graphical Abstract

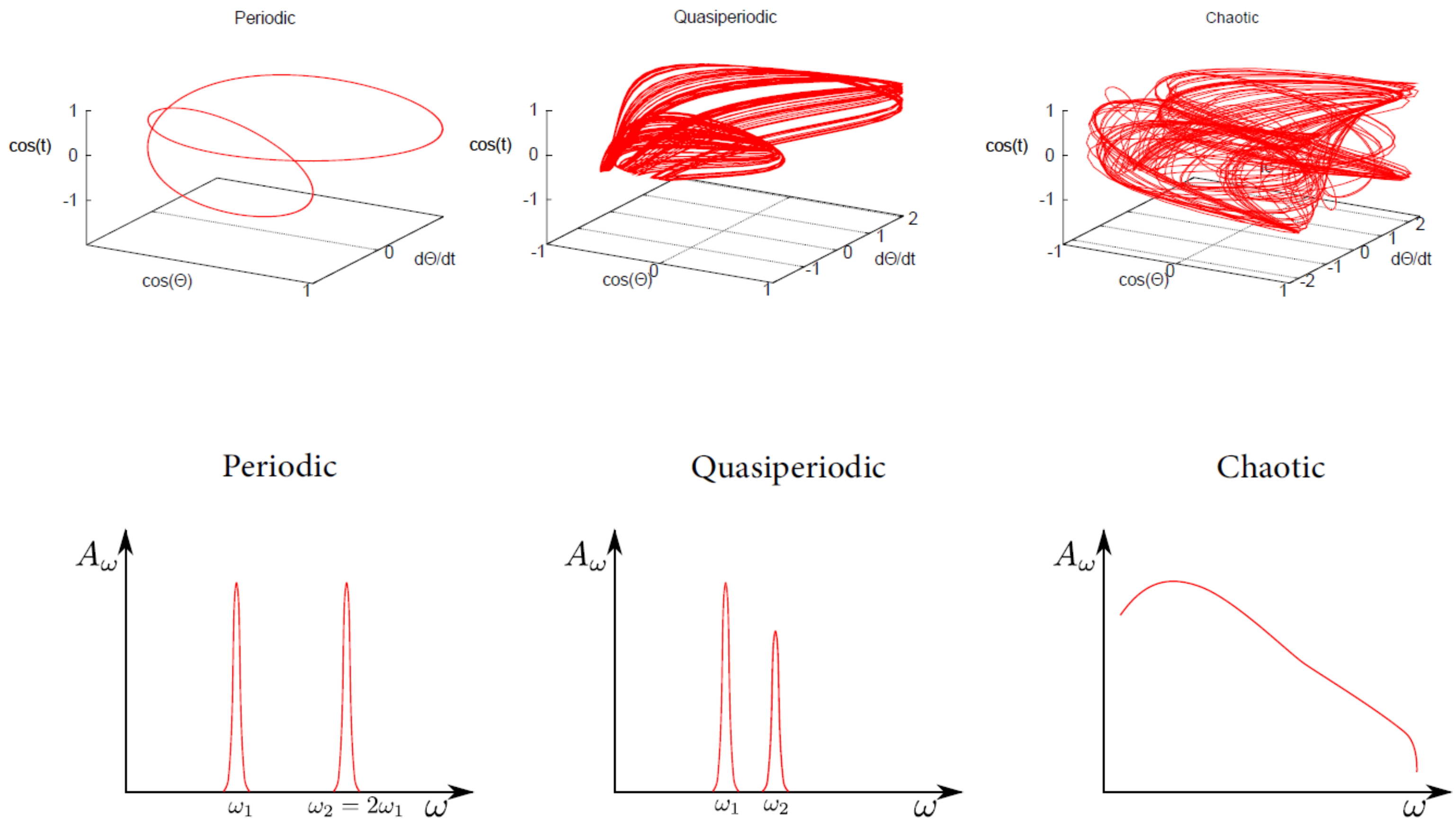


Synchronization of two oscillators



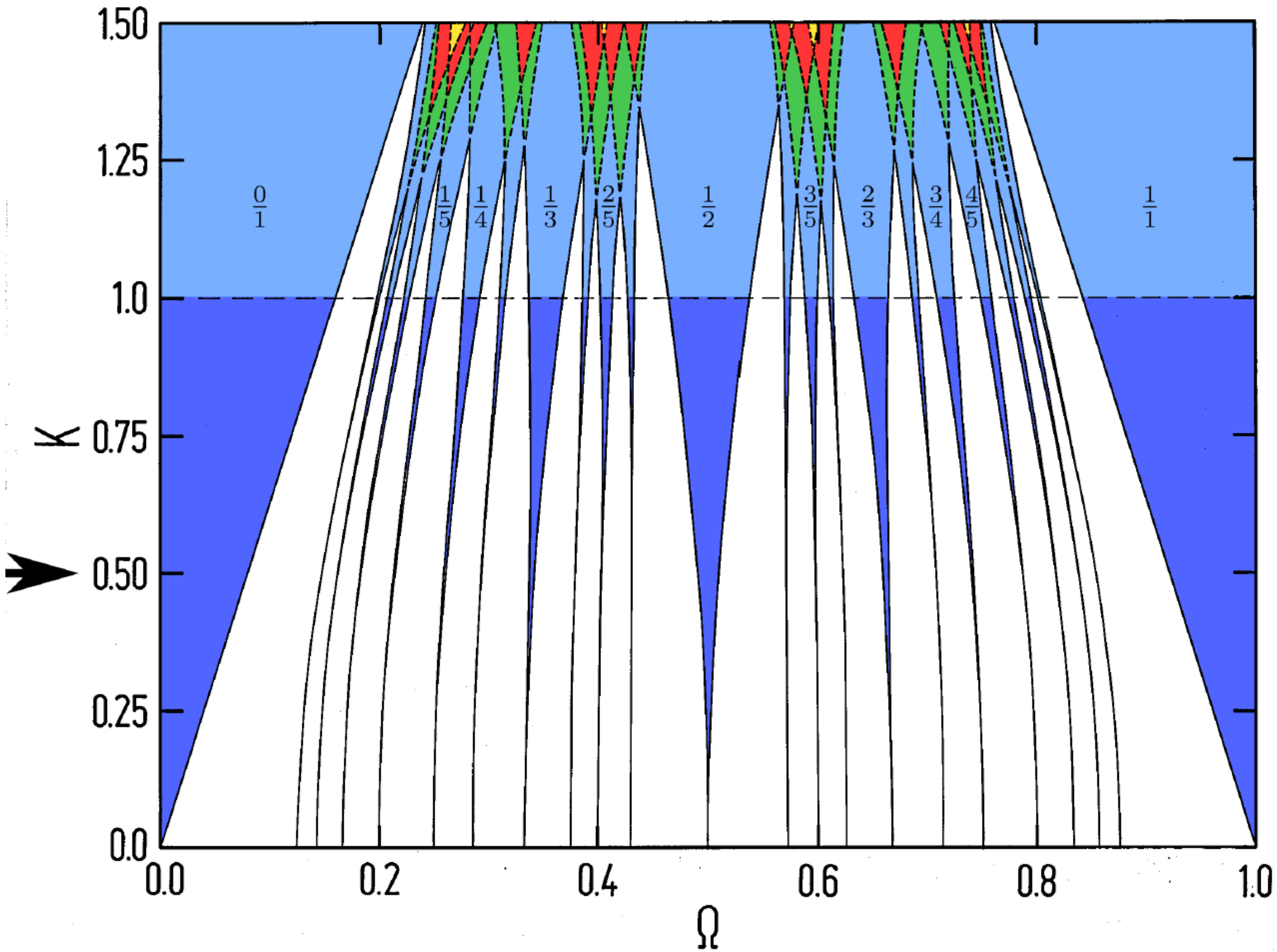
Huygens' clocks 1665

Three different non-linear dynamics

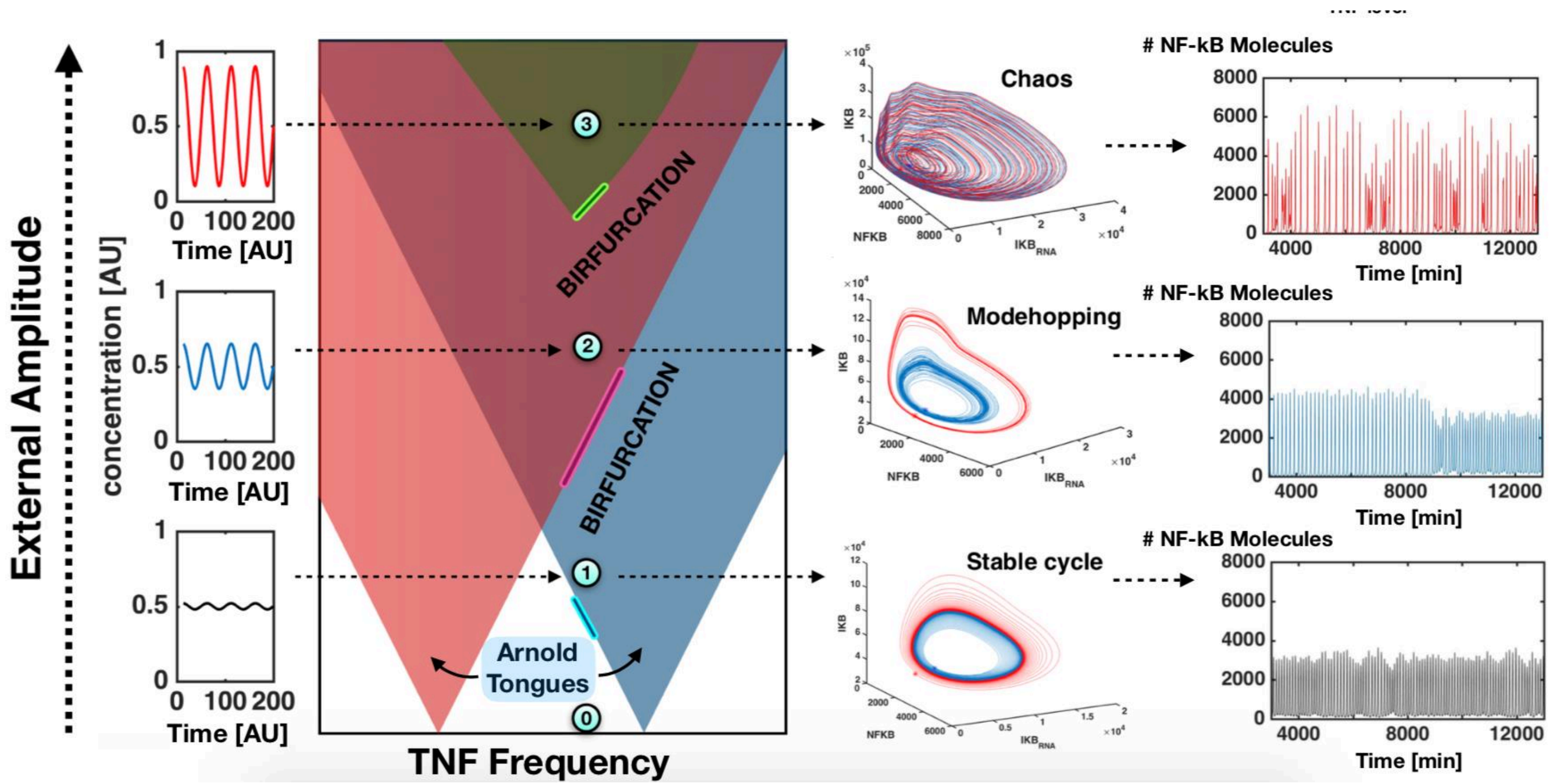


Two coupled oscillators: Arnold tongues

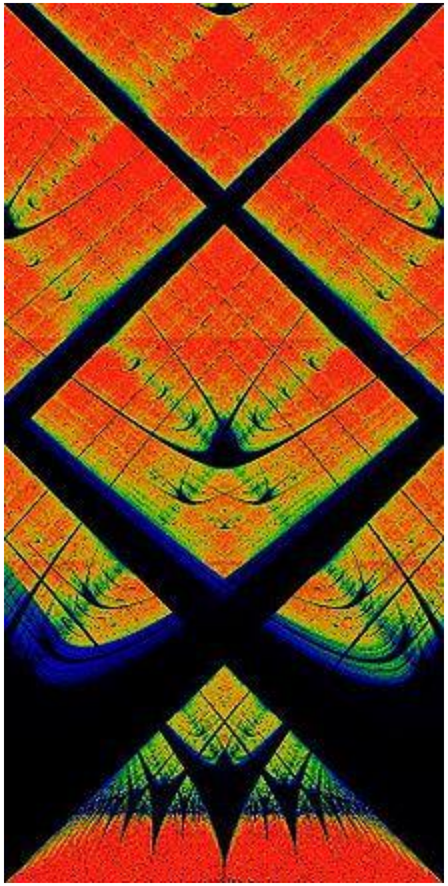
$$\omega/\Omega = P/Q$$

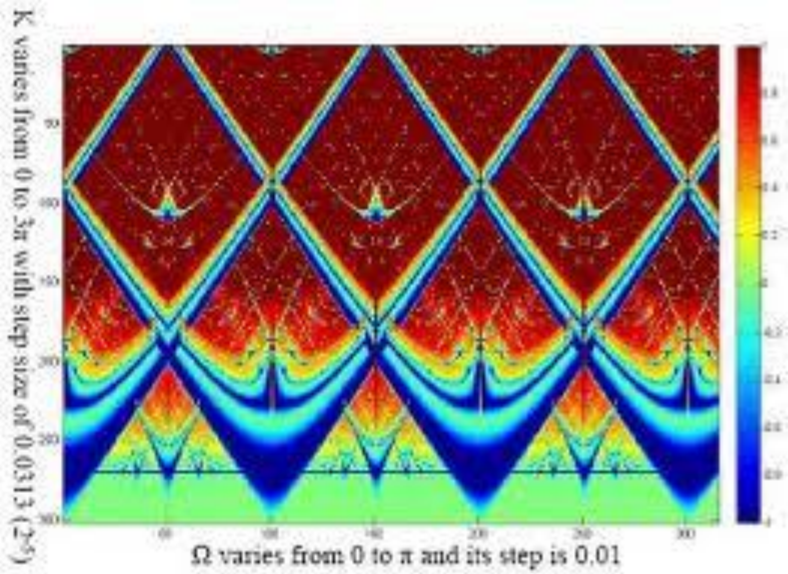


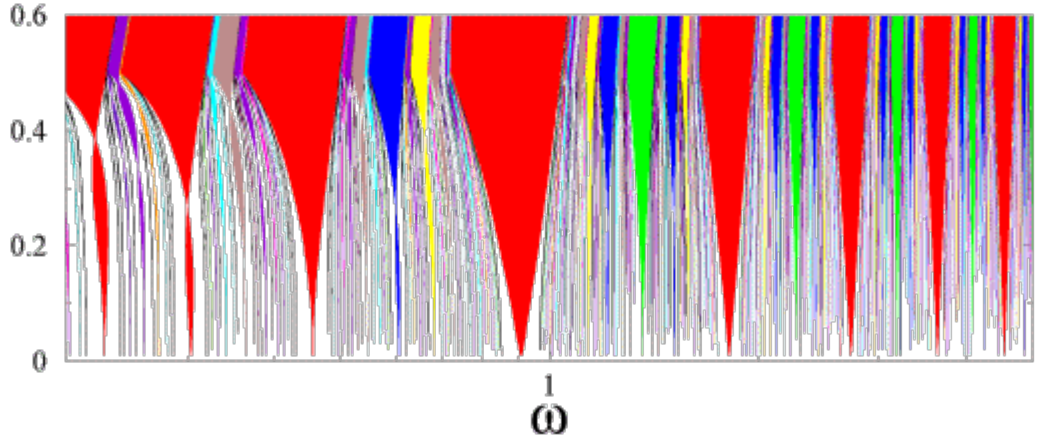
Strongly coupled oscillations: Overlap of tongues !
Transitions to chaos !



Examples of Arnold tongues !







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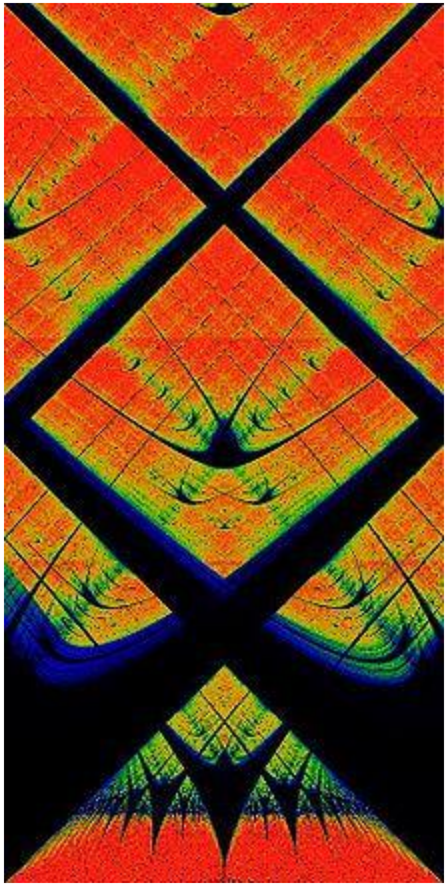
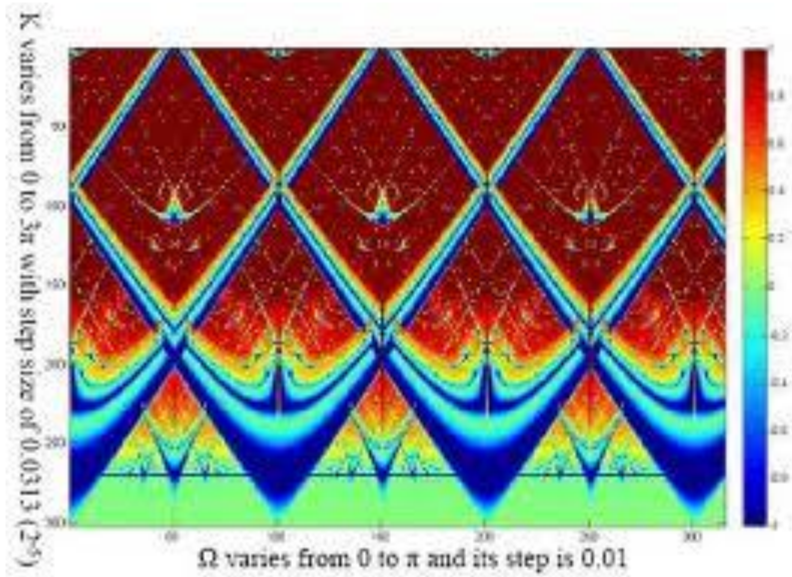
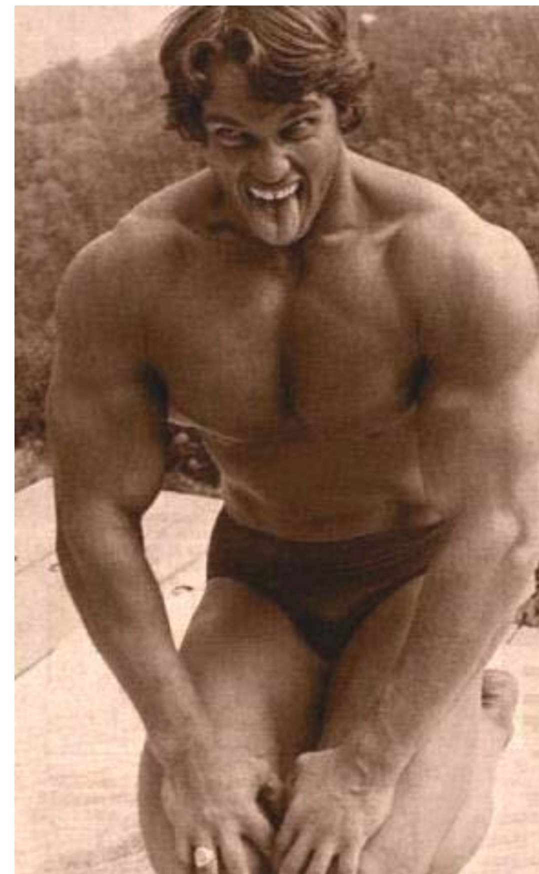
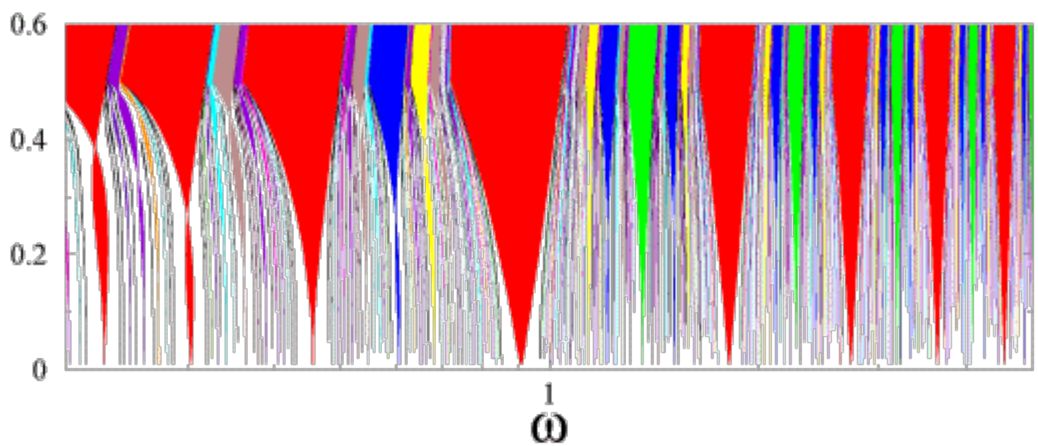
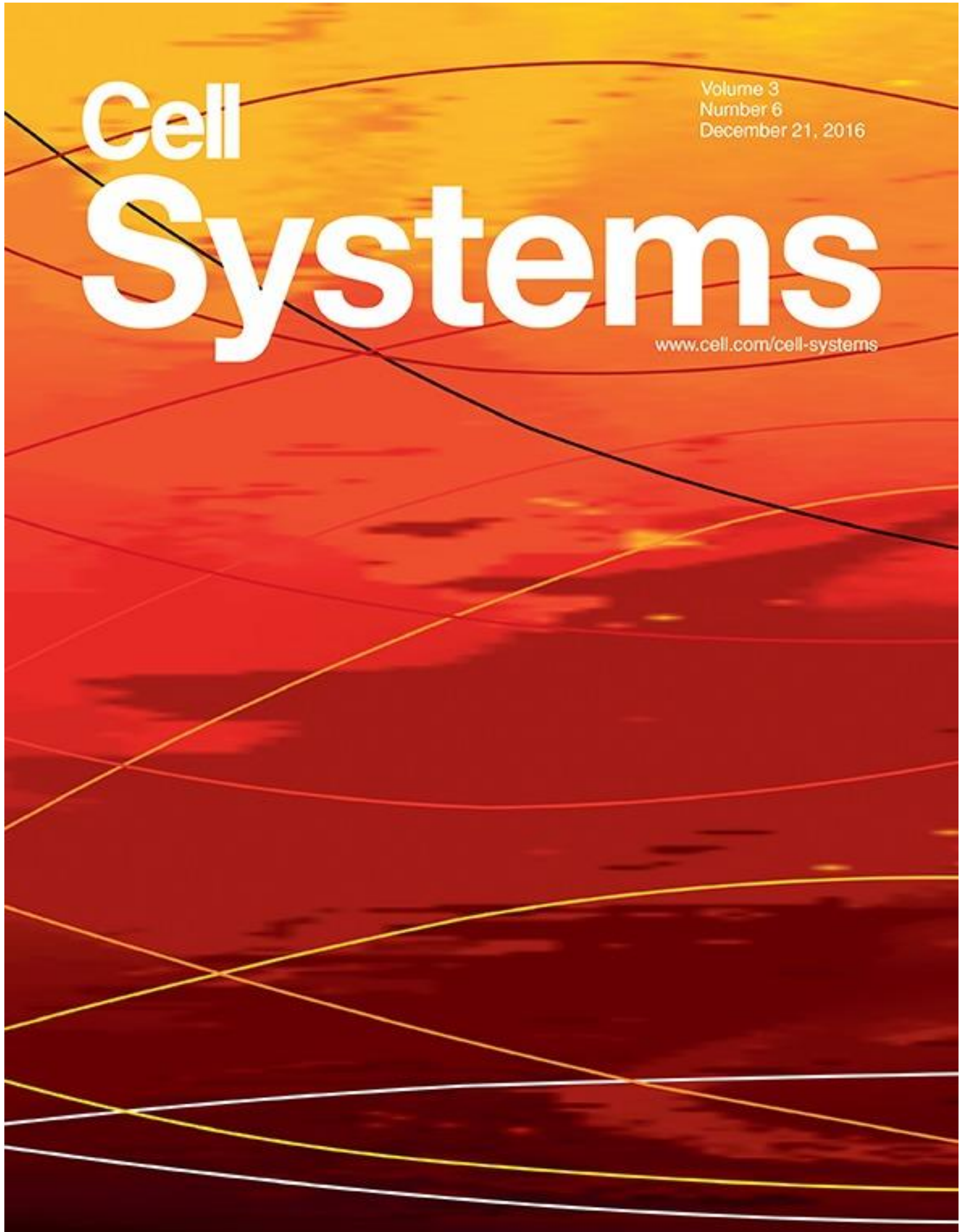


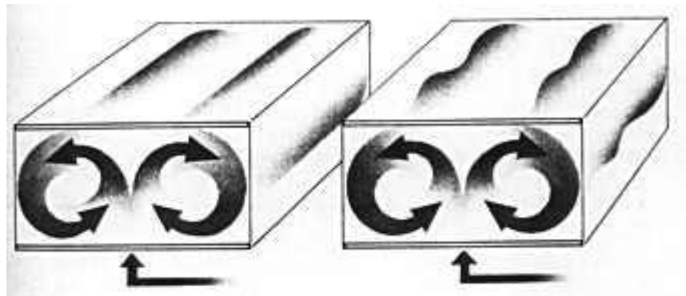







Cell
Systems
Volume 3
Number 6
December 21, 2016
www.cell.com/cell-systems

Chicago basement convection !



Libchaber, Stavans, Glazier:

External oscillating current !

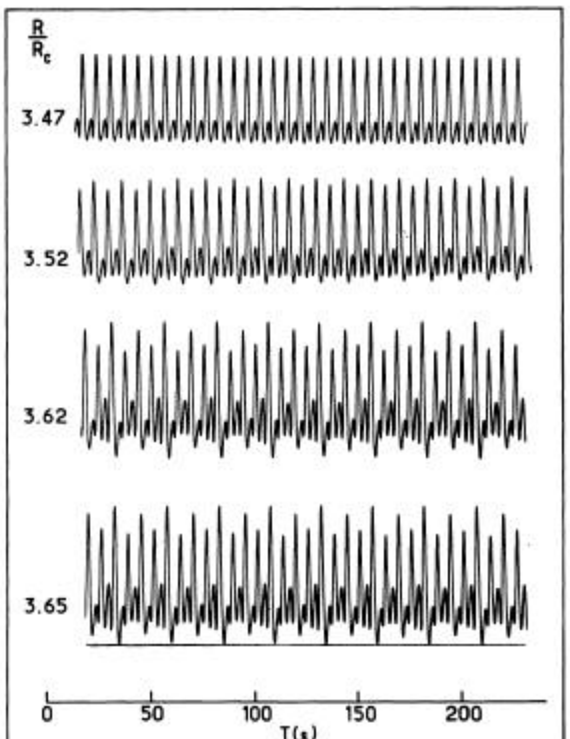


Fig. 2. — Direct time recordings of temperature for various stages of the period doubling cascade showing the onset of $f/4$ ($R/R_c = 3.52$), $f/8$ ($R/R_c = 3.62$), $f/16$ ($R/R_c = 3.65$).

L-214 JOURNAL DE PHYSIQUE — LETTRES

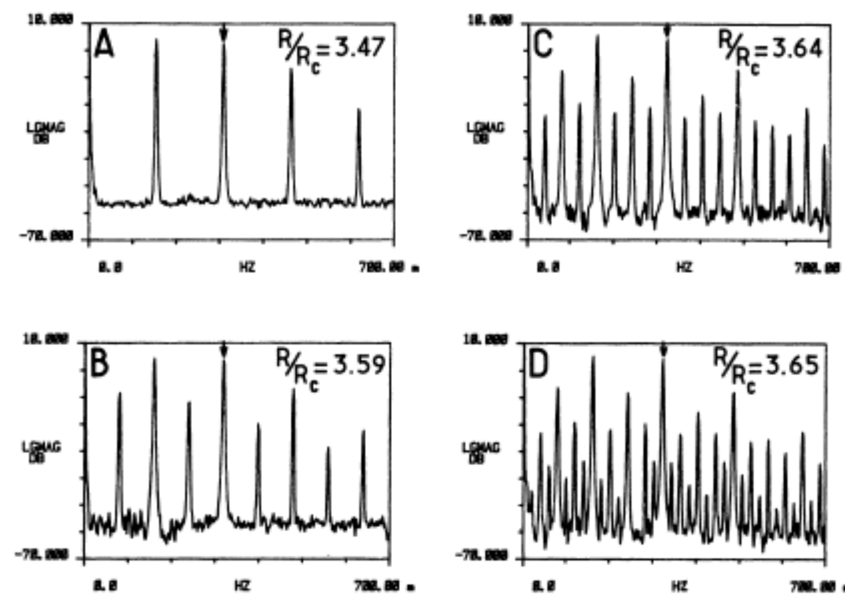
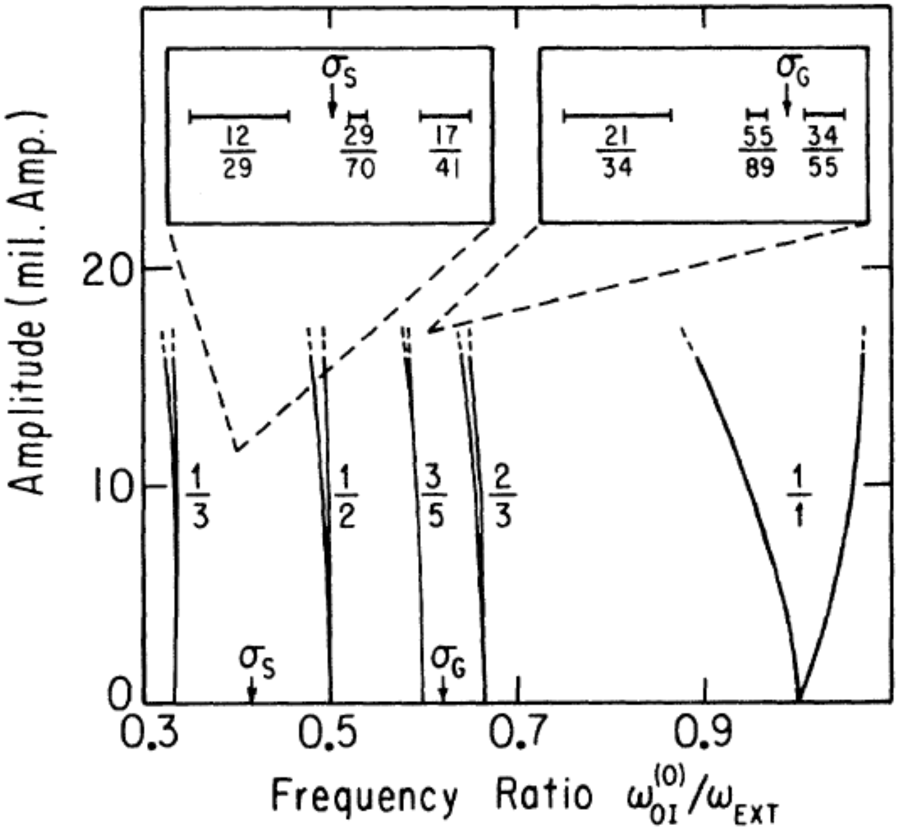
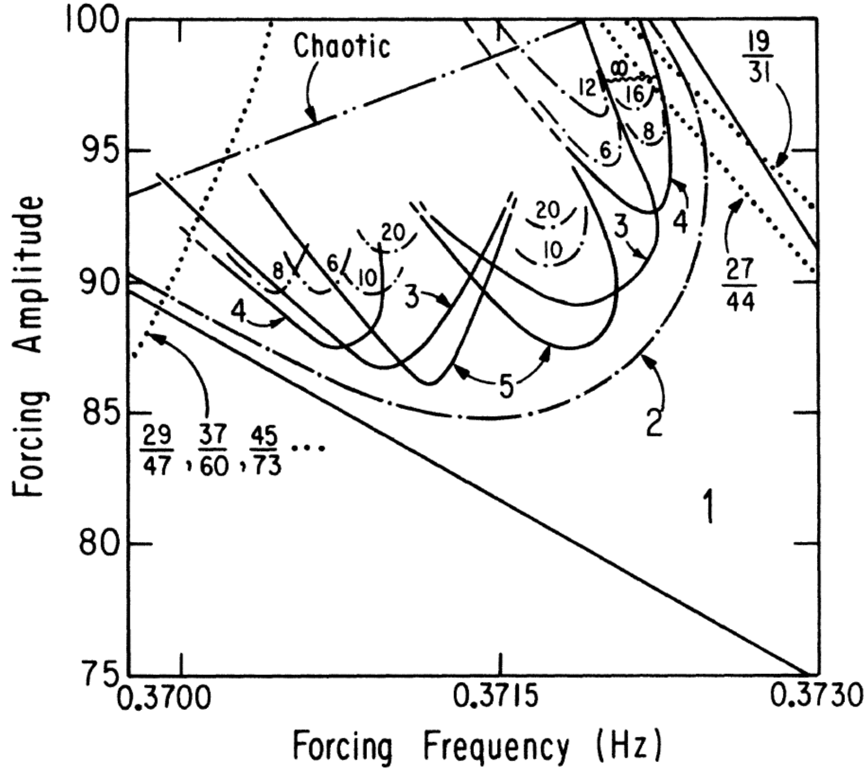


Fig. 3. — The Fourier spectrum. Arrows indicate the peak at the frequency f_1.

Chicago basement convection !

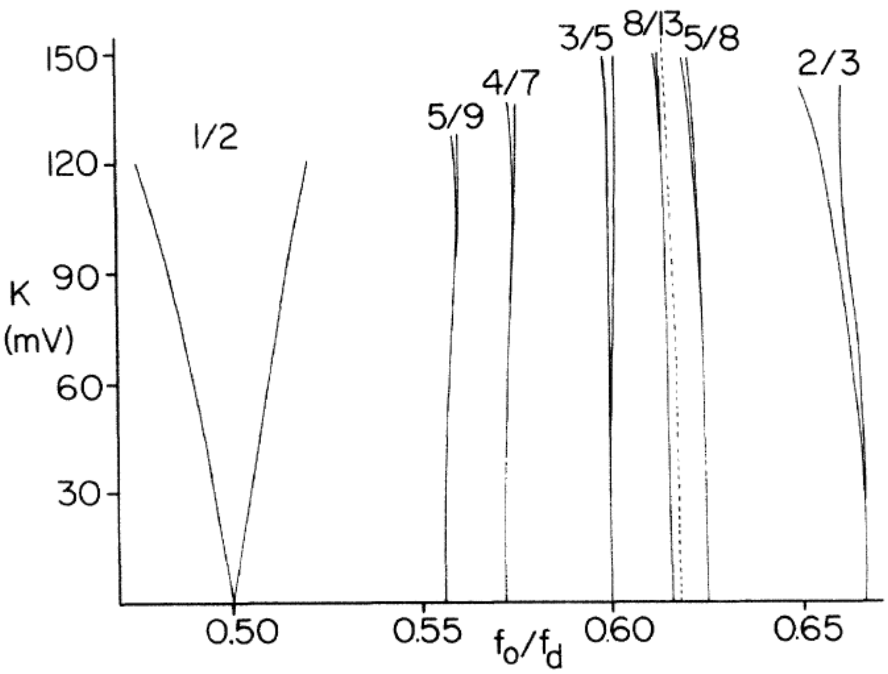


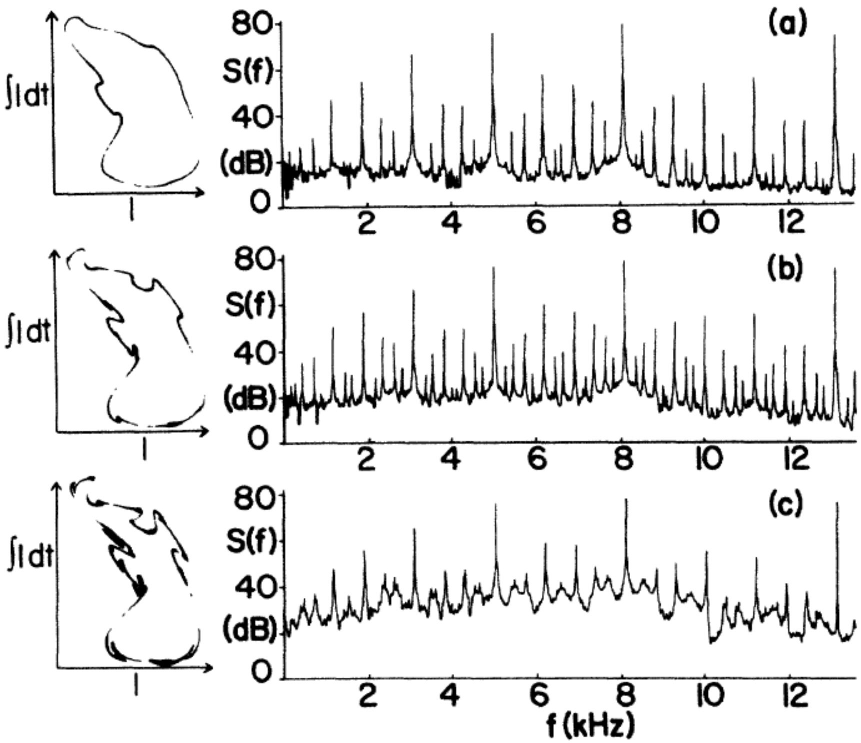
Stavans, Heslot, Libchaber



Glazier, Jensen, Libchaber, Stavans

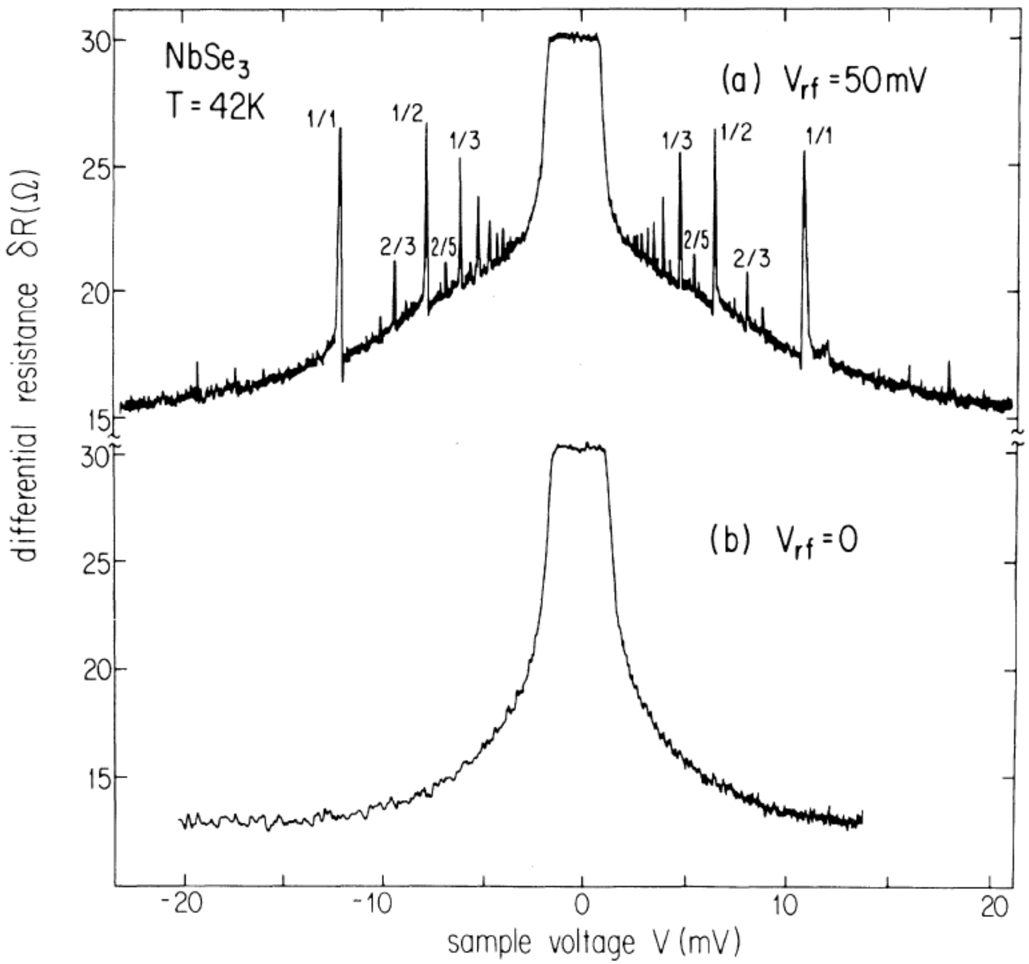
Semiconductors at Harvard : Gwinn, Westervelt





(p-type Ge: Phys Rev Lett. 57)

Sliding CDW's at UCLA: Brown, Mozurkewich, Gruner

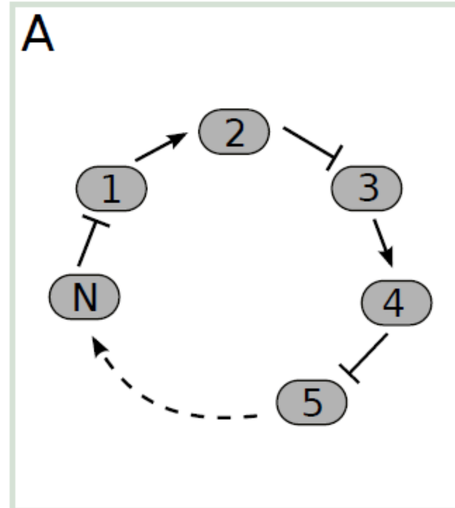


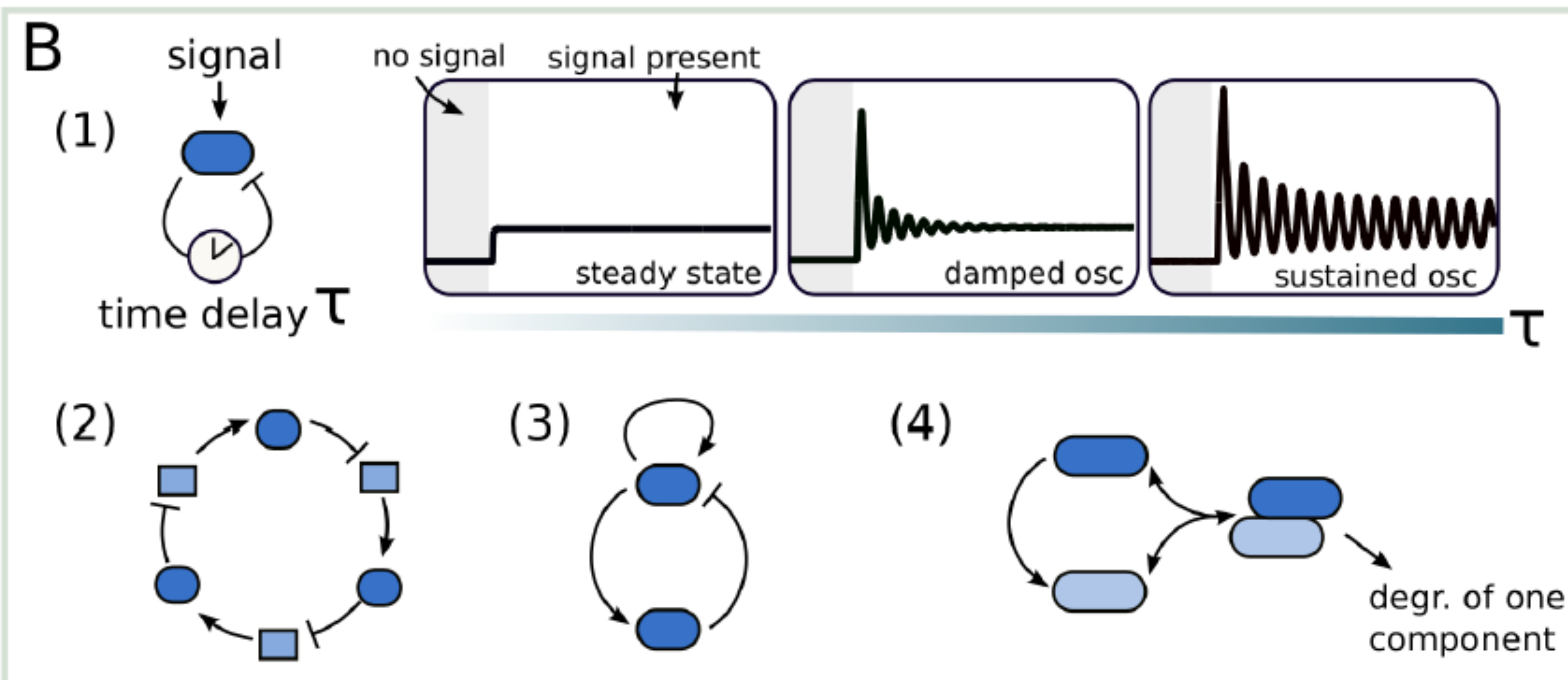
(Phys Rev Lett. 52)

What about biology – many oscillators !

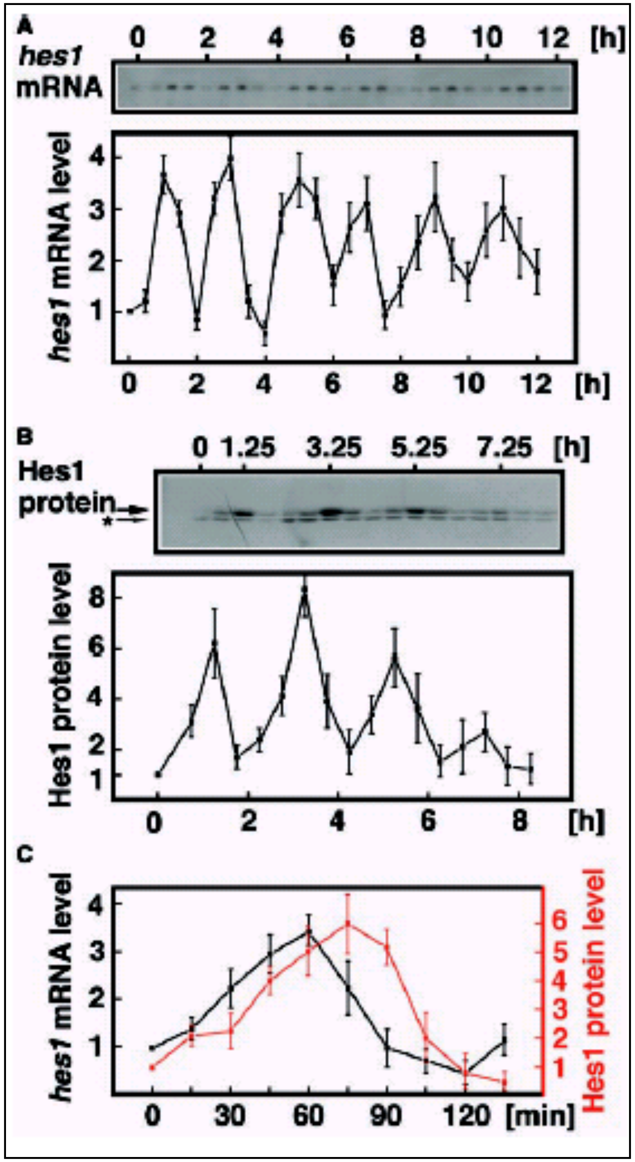
- Cell cycles
- Circadian clocks
- Calcium oscillators
- Embryos
- Pace maker cells
- Protein oscillations (DNA damage)
- Population dynamics

Basic oscillator: Negative Feed-Back loops:



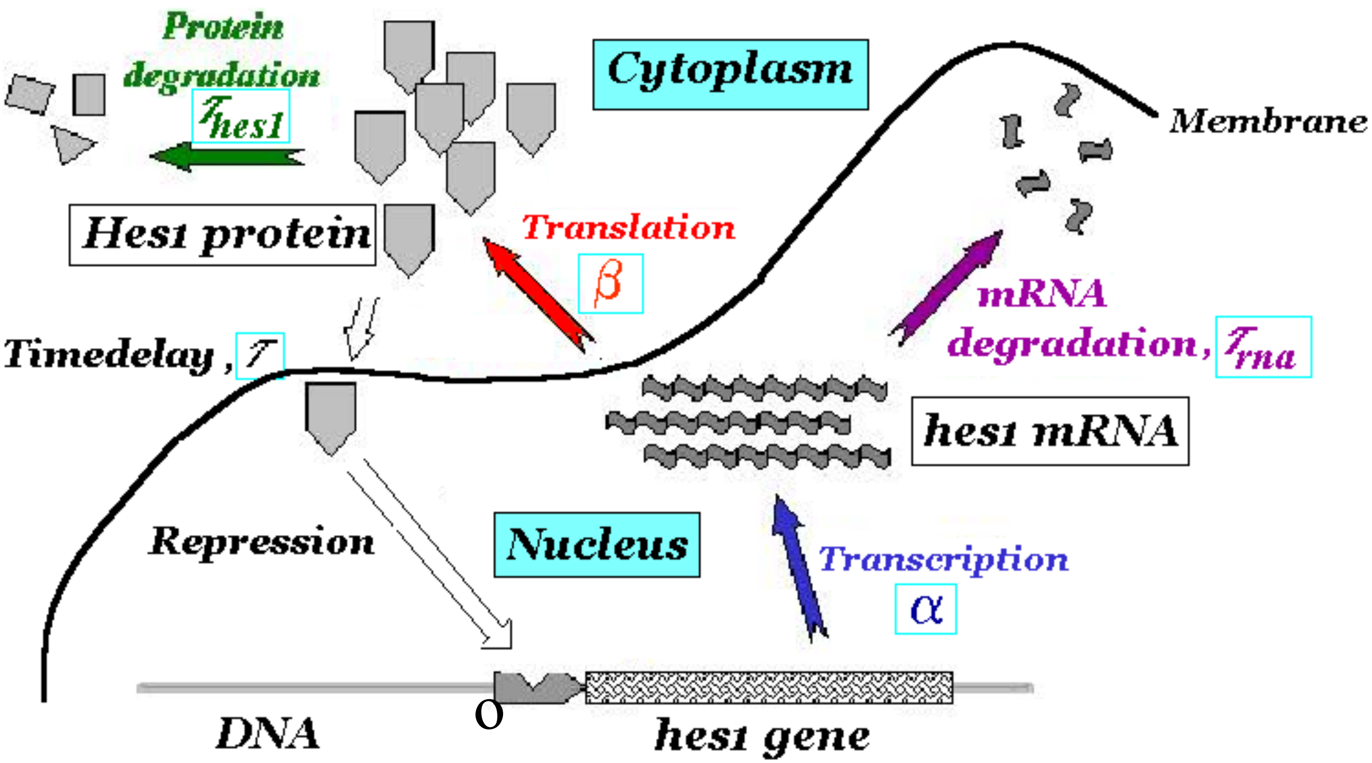


‘Typical’ Oscillating data: Hes1 - segmentation



(Hirata et al, 2002)

Simplest negative feed-back loop: Hes1



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

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

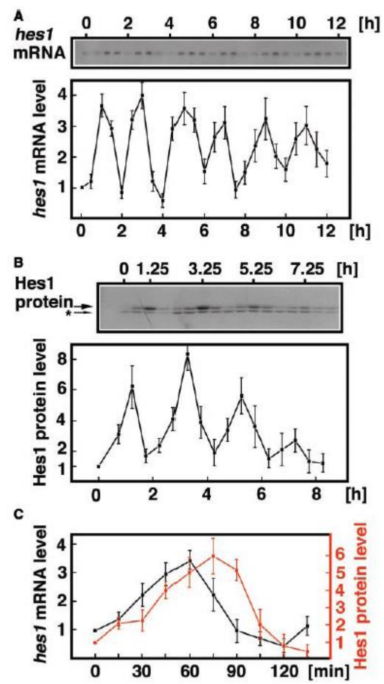
Jensen et al 2003

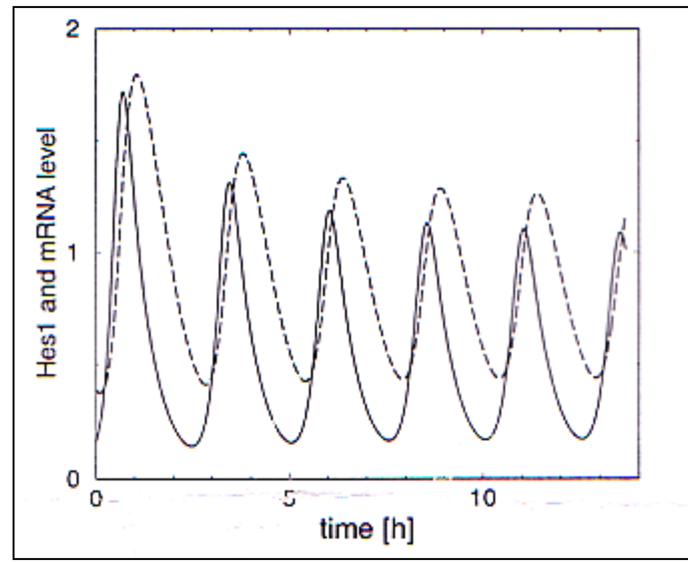
$$\frac{d[mRNA]}{dt} = \alpha \cdot \frac{K_M}{K_M + [Hes1(t-\tau)]^n} - \frac{[mRNA(t)]}{\tau_{rna}}$$

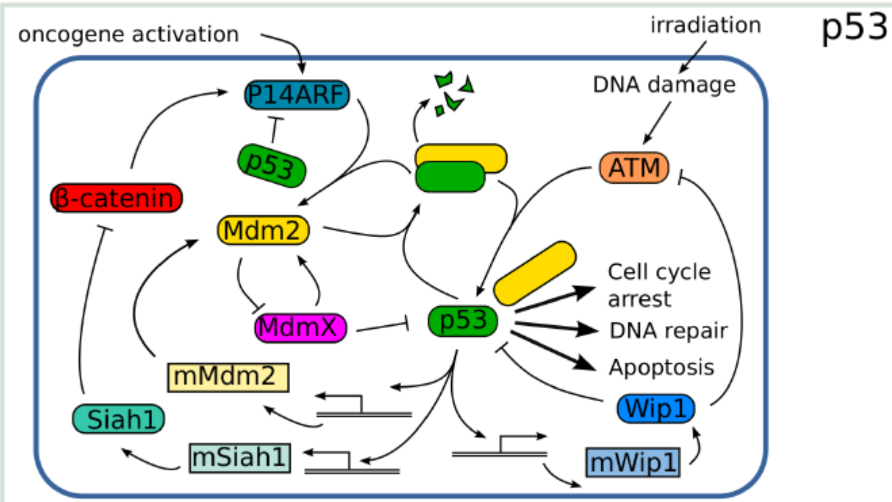
$$\frac{d[Hes1]}{dt} = \beta \cdot [mRNA(t)] - \frac{[Hes1(t)]}{\tau_{hes1}}$$

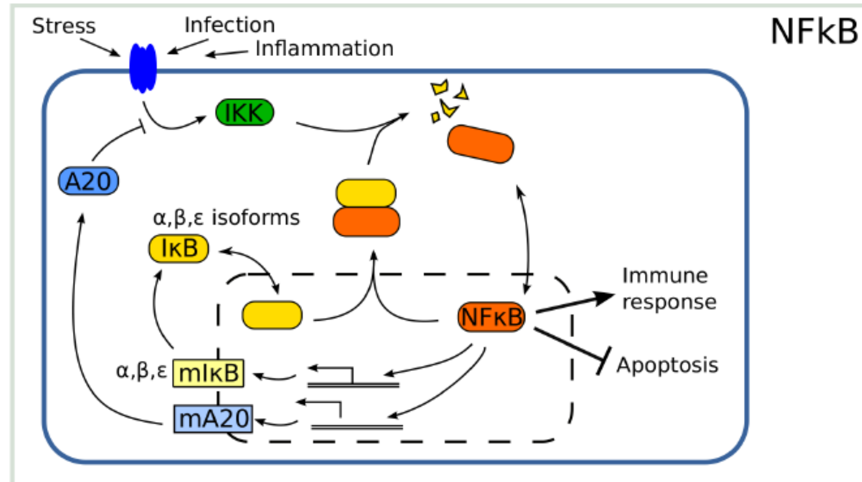
- Dashed curve [Hes1]
- Solid curve [mRNA]

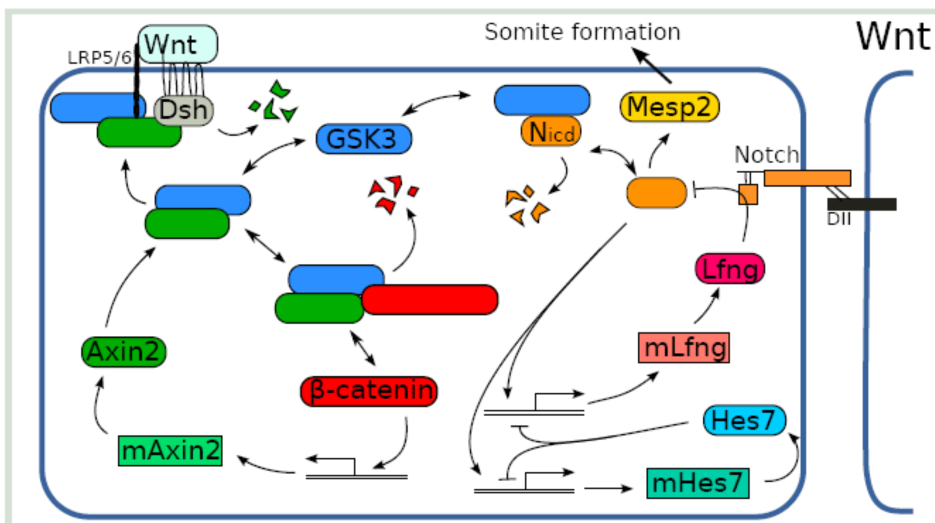
- τ_{rna} = 24.1 min
- τ_{hes1} = 22.3 min
- τ = 24 min
- $\alpha = 20\ [R]_0\ \text{min}^{-1}$
- $\beta = 1/20\ \text{min}^{-1}$
- $K_M = (0.1[R]_0)^n$
- n = 4





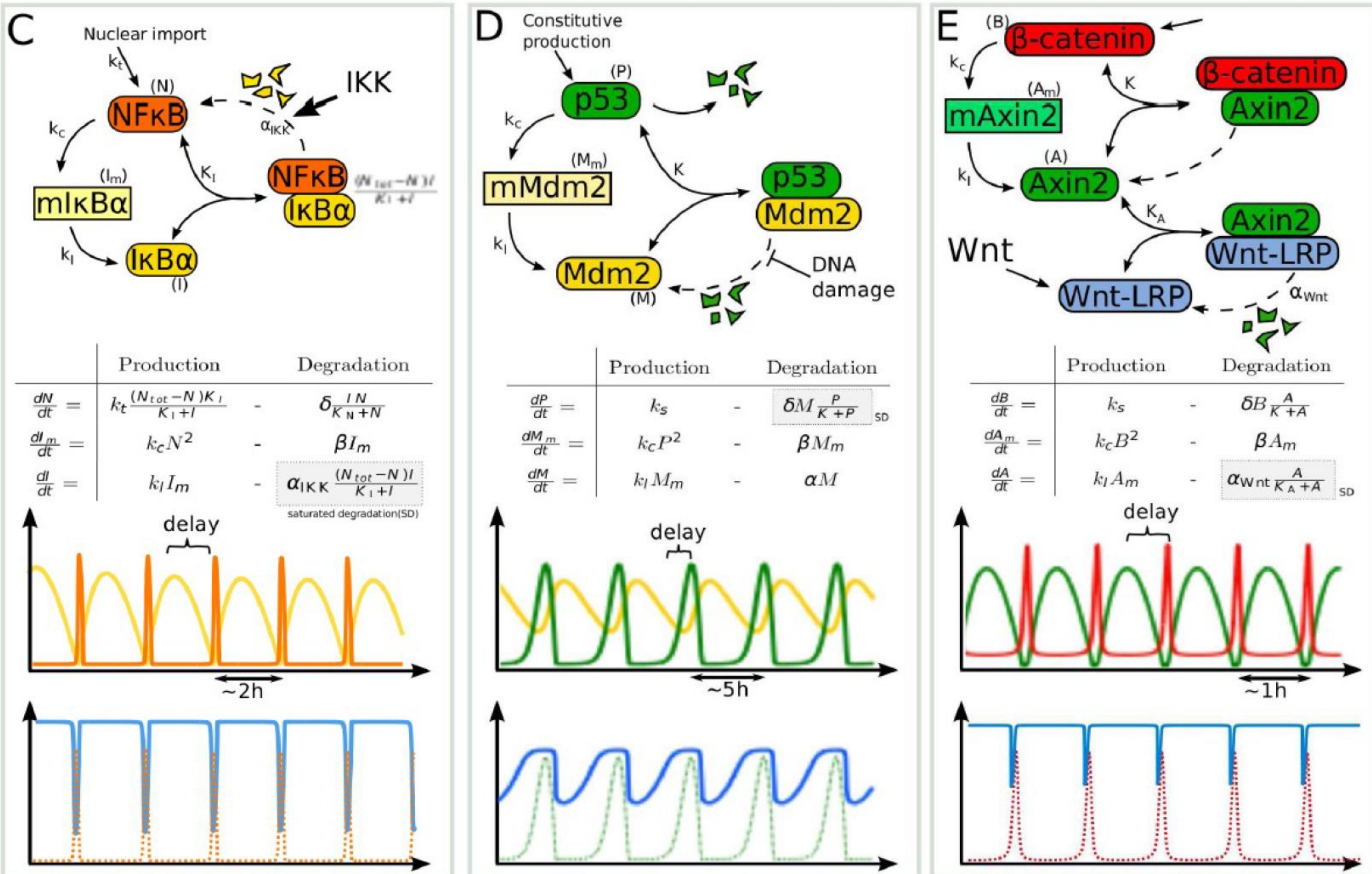

p53
oncogene activation
irradiation
DNA damage
P14ARF
p53
ATM
β-catenin
Mdm2
MdmX
p53
Cell cycle
arrest
DNA repair
Apoptosis
mMdm2
Wip1
Siah1
mSiah1
mWip1


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
Nicd
Mesp2
Notch
Dll
Lfng
mLfng
Axin2
β-catenin
Hes7
mAxin2
mHes7

Simple models of ultradian oscillations

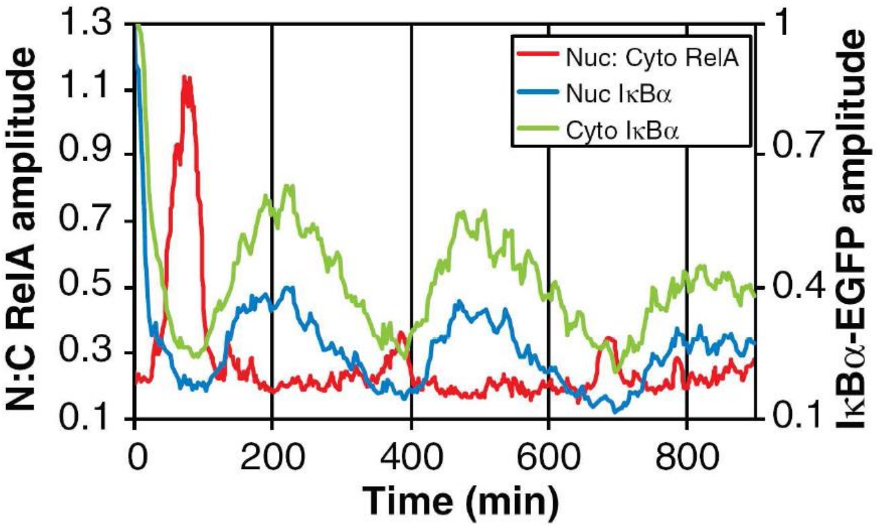
Krishna, Jensen, Sneppen (2006); Hunziker, Jensen, Krishna (2010); Pedersen, Jensen, Krishna (2011); Mengel, Hunziker, Pedersen, Trusina, Jensen, Krishna (2010)



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?

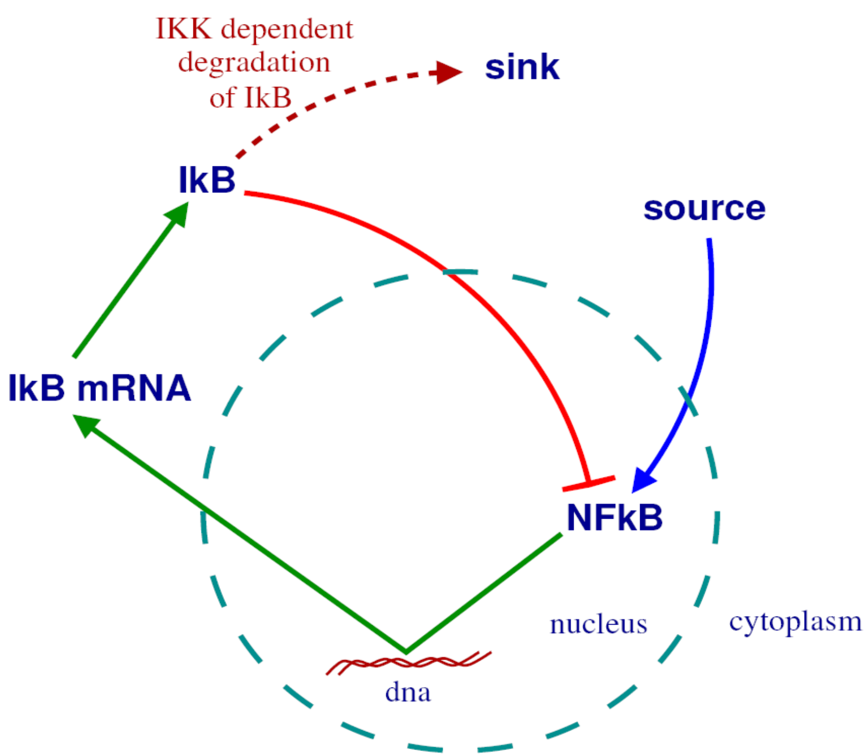
Why does the cell need the oscillations?

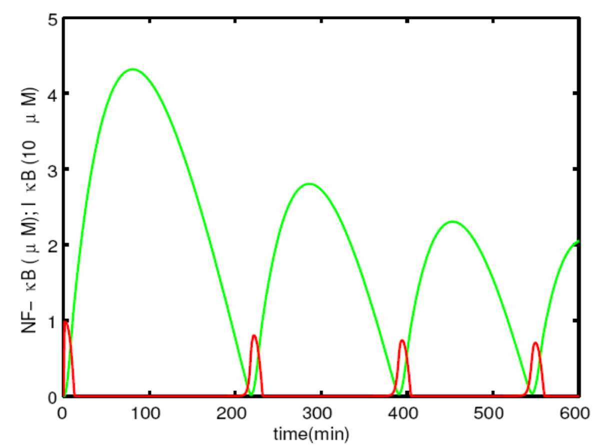
Simple Model for Protein Oscillations

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

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

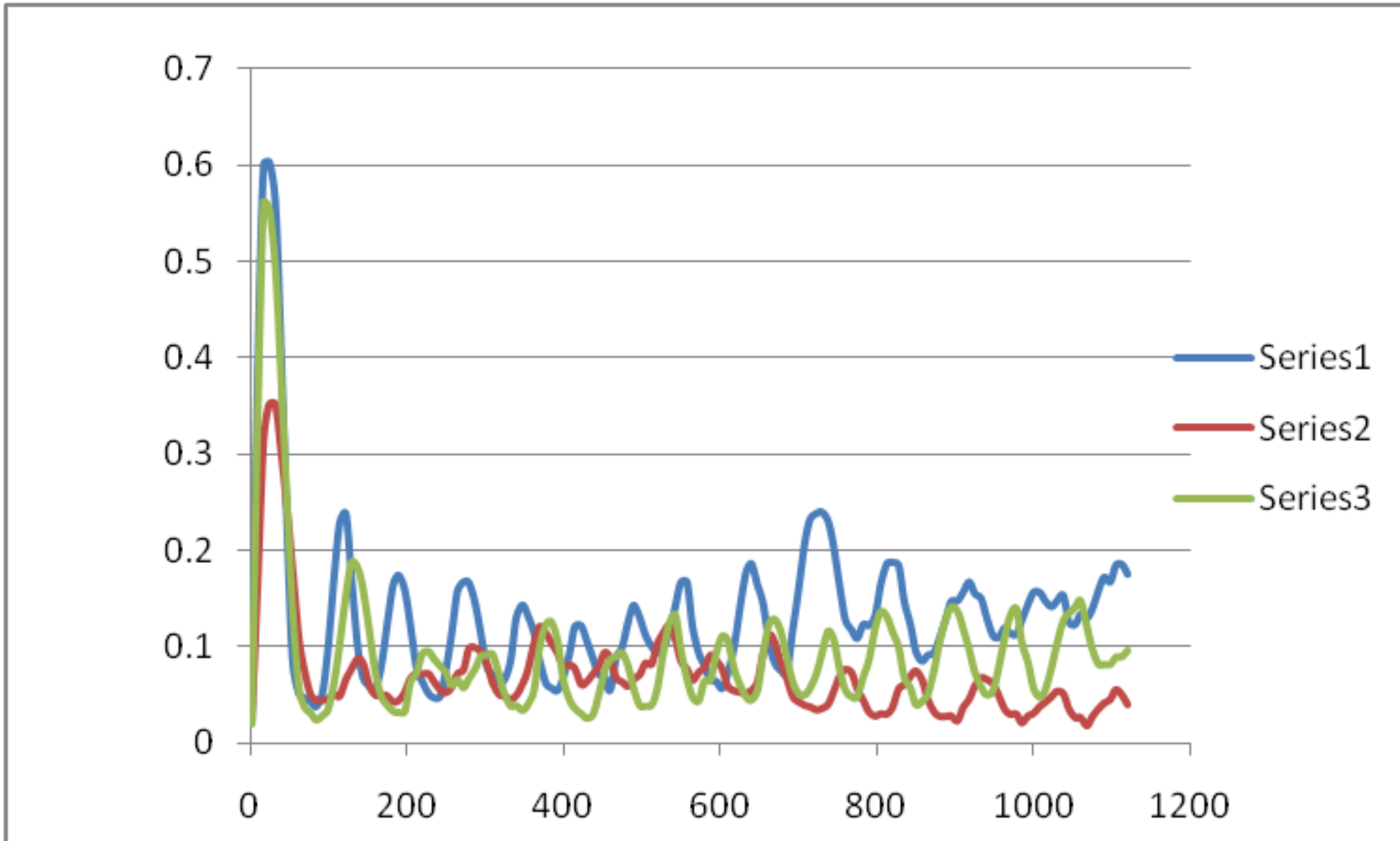
$$\frac{dI}{dt} = I_m - C\frac{(1-N_n)I}{\epsilon+I}.$$





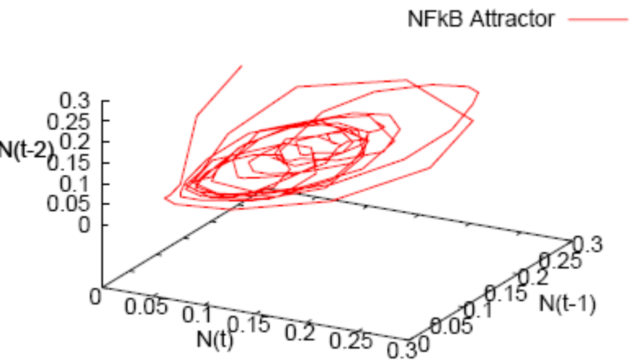
$$A = 0.007,\ B = 954.5,\ C = 0.035,$$
$$\delta = 0.029,\ \epsilon = 2\times 10^{-5}$$

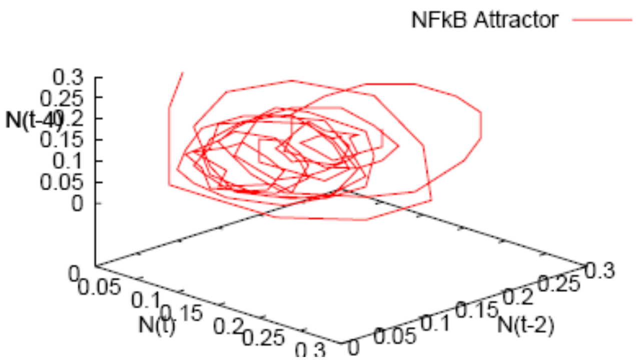
Oscillations of protein densities in a single cell

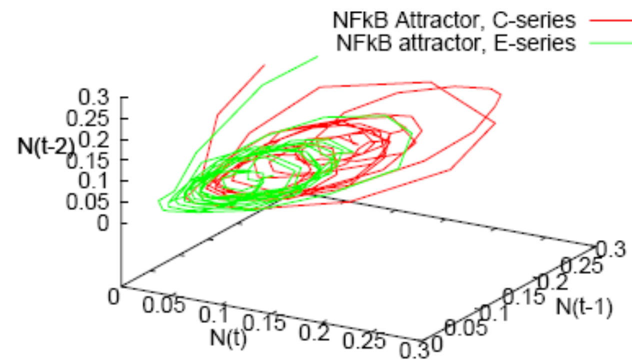


(M. Covert, Stanford, unpublished)
(Savas Tay, Zurich)

Embedded attractors:
Chaos ??

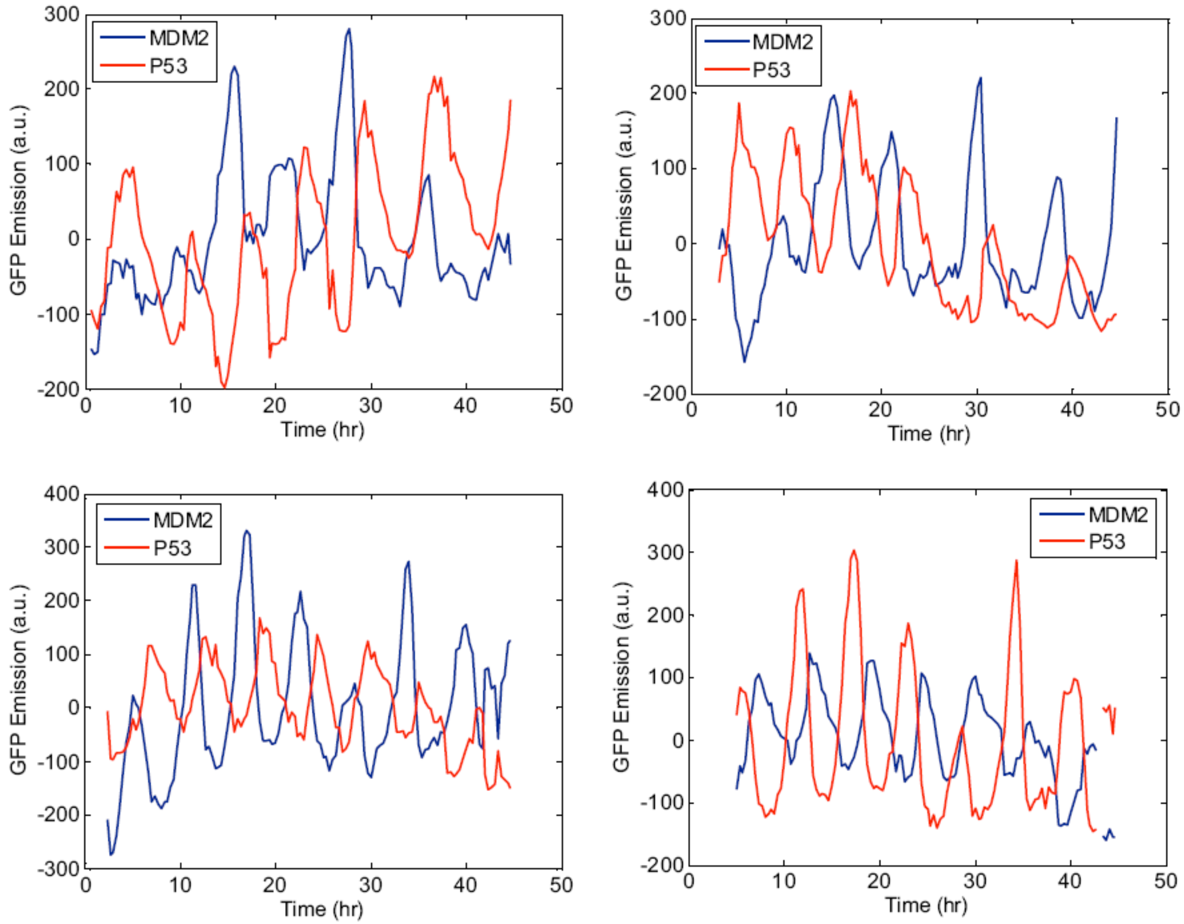






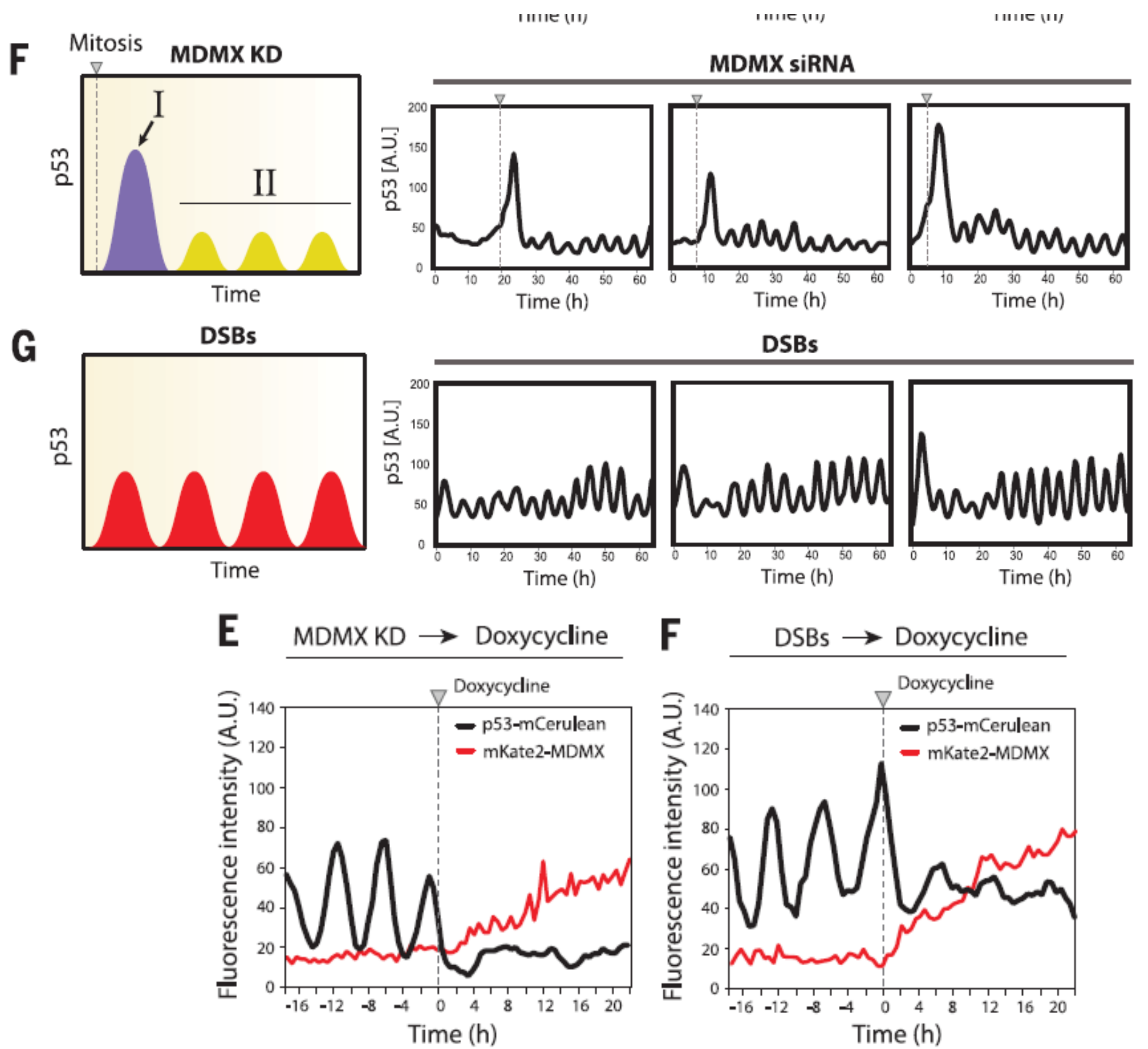
p53 – Mdm2 oscillations: Negative feedback loop

DNA damage (gamma)



Lahav, Alon, Geva-Zatorsky, Levine,..

MDMX knock-out induces p53 oscillations



Chen, Forrester, Lahav (2016); Heltberg, Jensen, Lahav et al (2018)

Externally ‘forced’ NF-κB system

External modulation of TNF cytokine signal

→ Transformed into IKK signal (C)

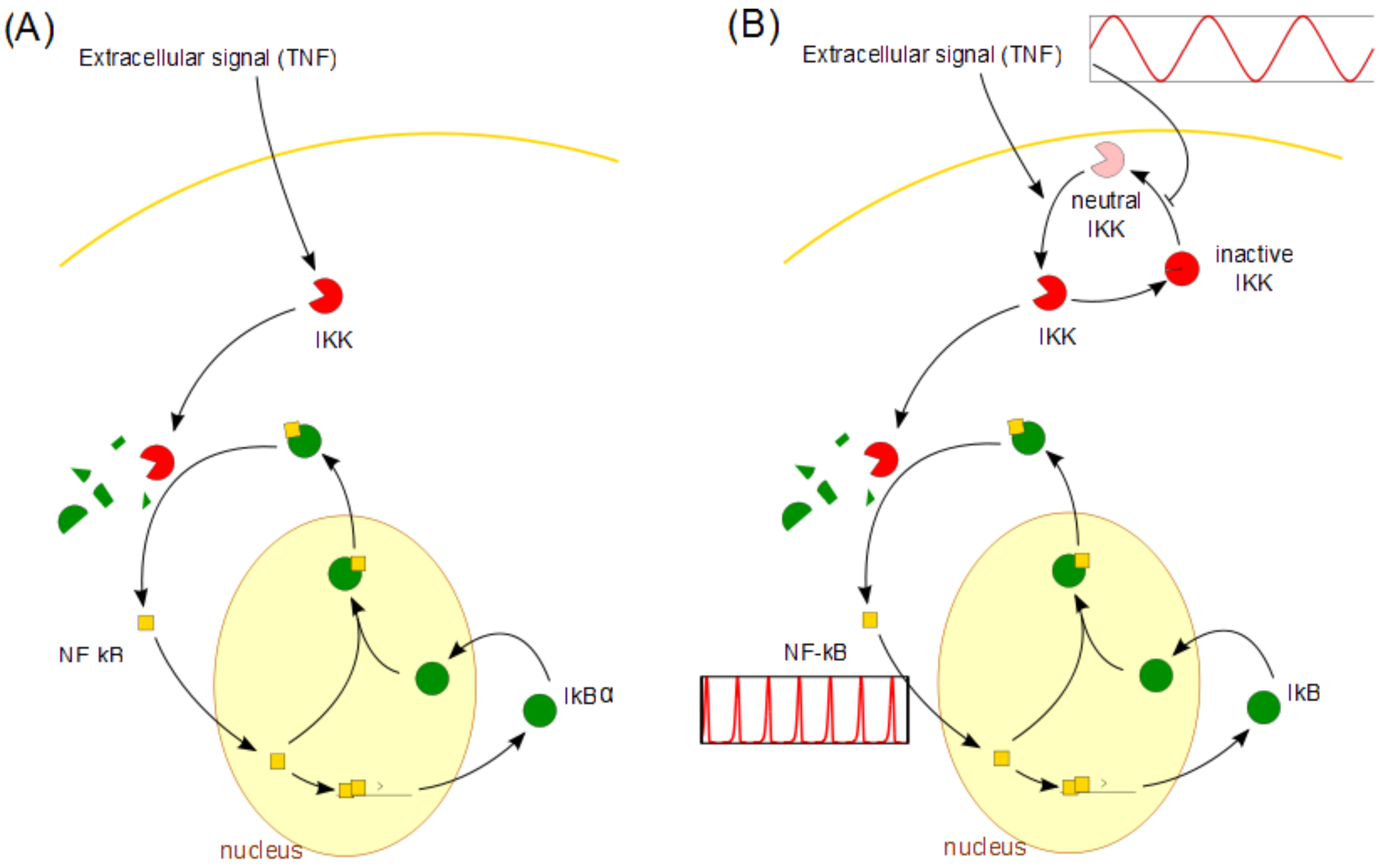
Arnold tongues:

Can synchronize the dynamics of a single cell:

Maybe a way to control DNA damage/DNA repair

(M. Heltberg, S. Krishna, 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

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

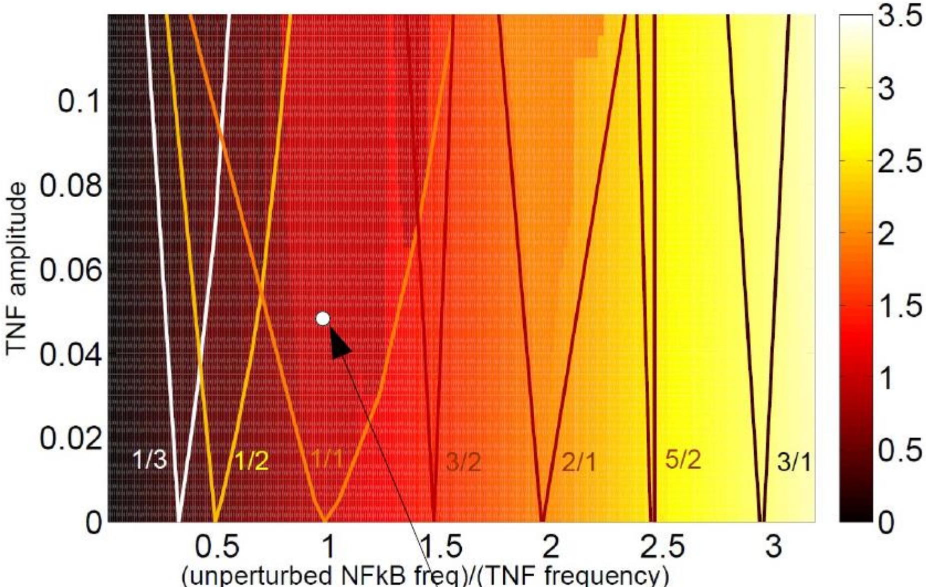
TNF

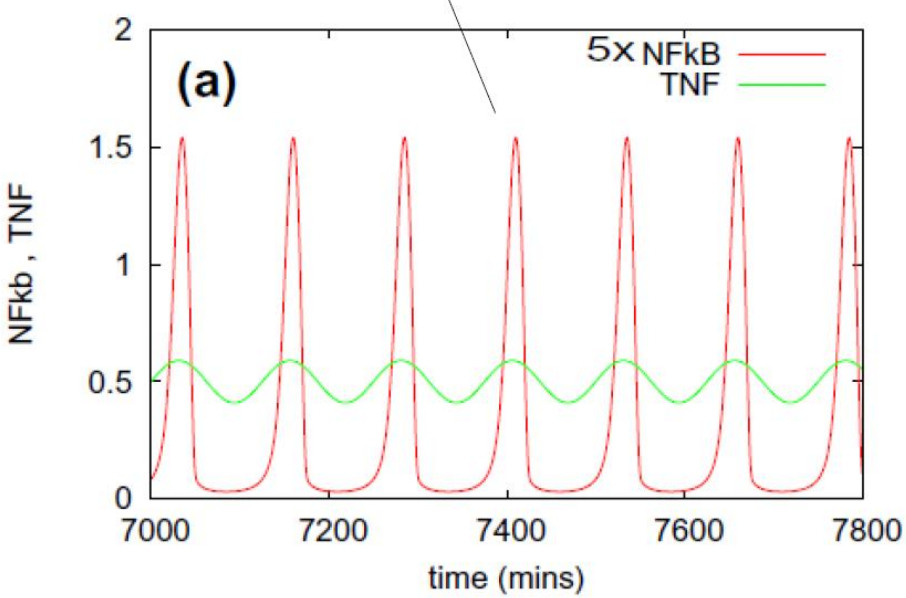
$$\frac{d[IKK]_i}{dt} = k_i[IKK]_a - k_p[IKK]_i\frac{k_{A20}}{k_{A20} + [A20][TNF]}$$

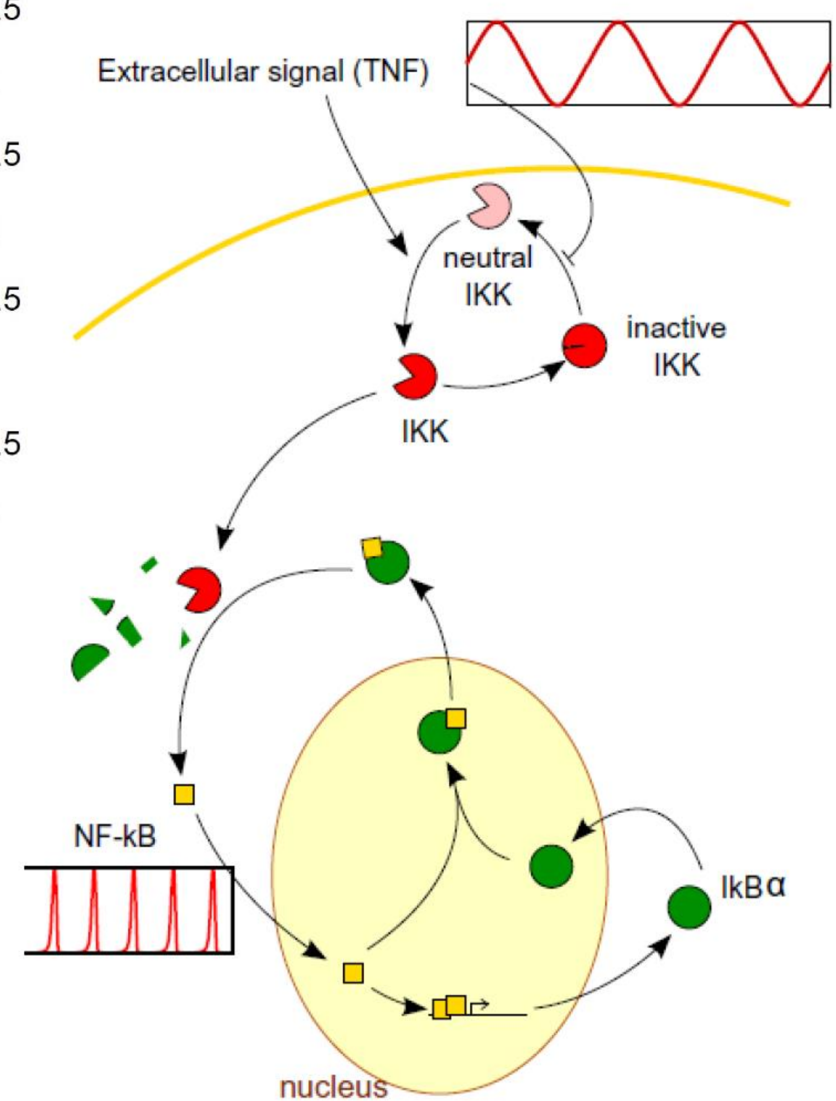
A20

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

Sinusoidally driven NF-kB oscillations

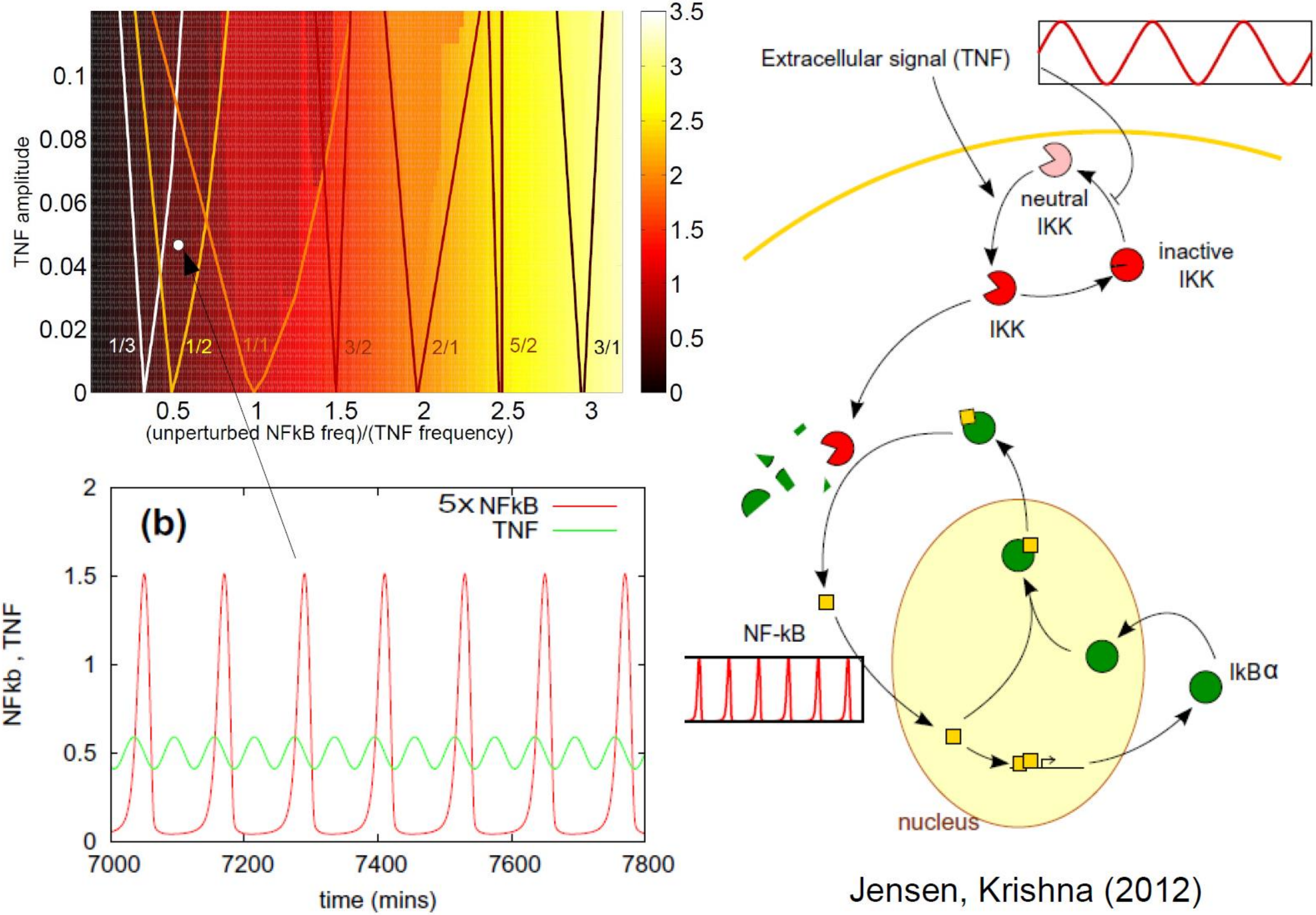






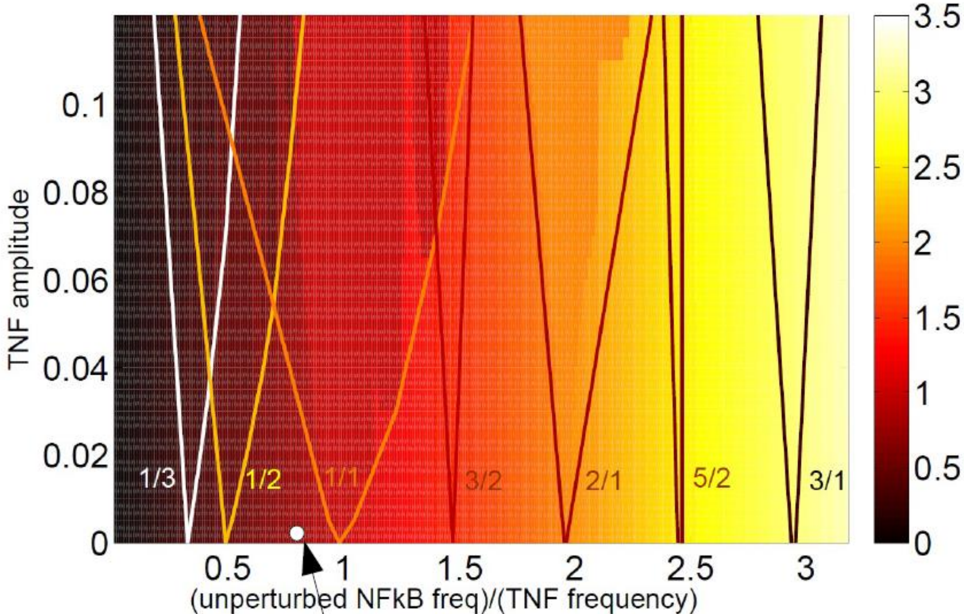
Jensen, Krishna (2012)

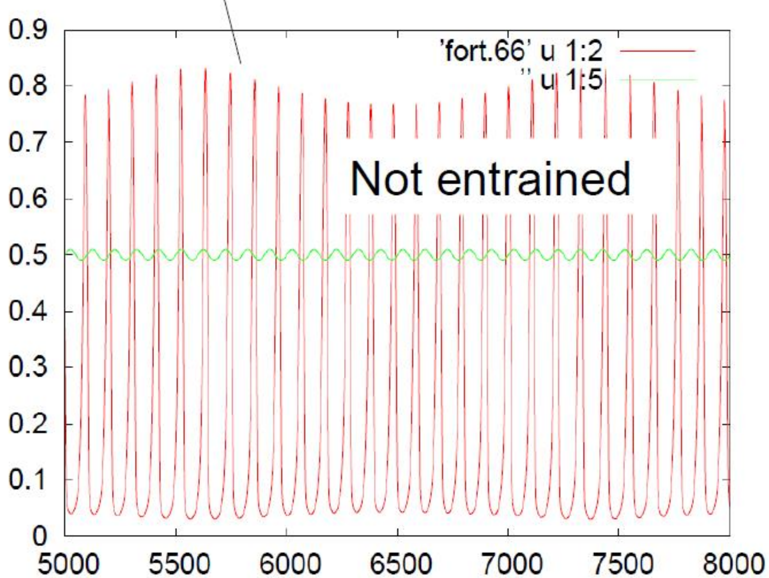
Sinusoidally driven NF-kB oscillations

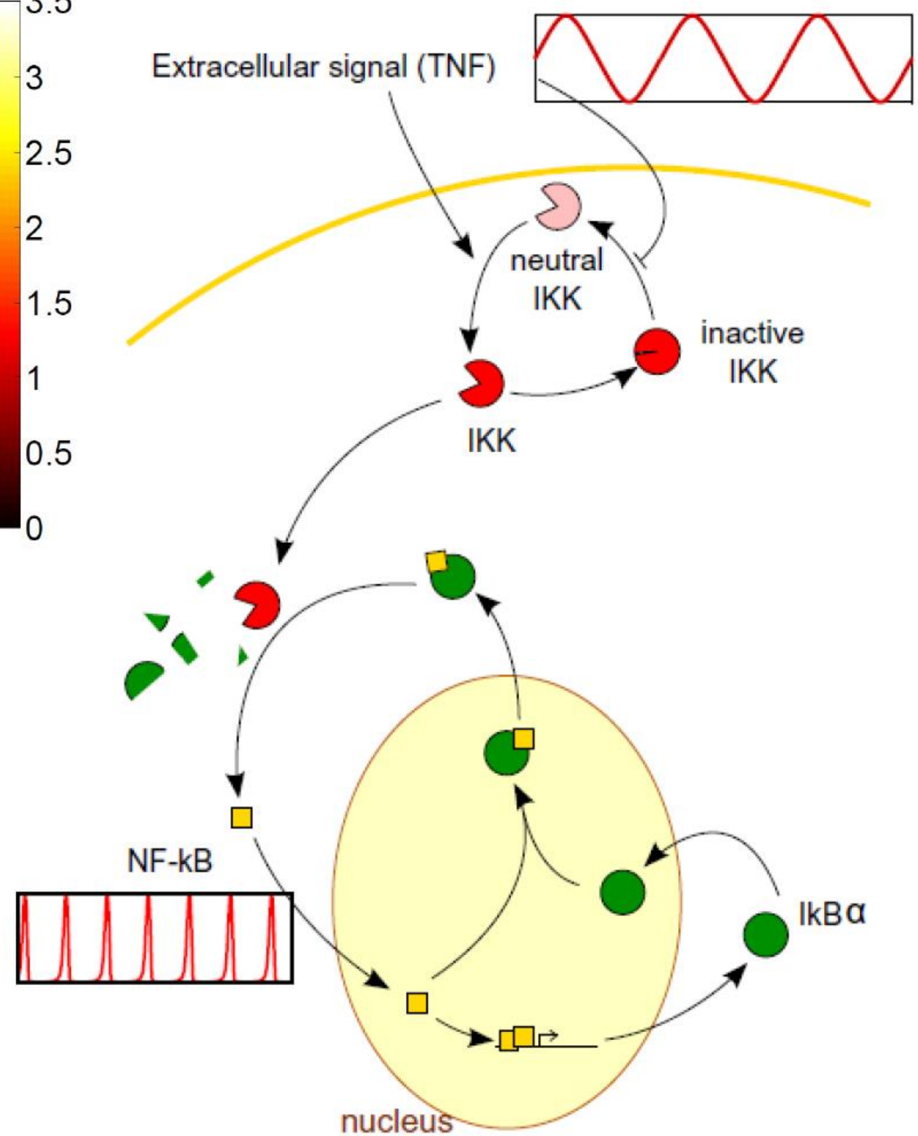


Jensen, Krishna (2012)

Sinusoidally driven NF-kB oscillations

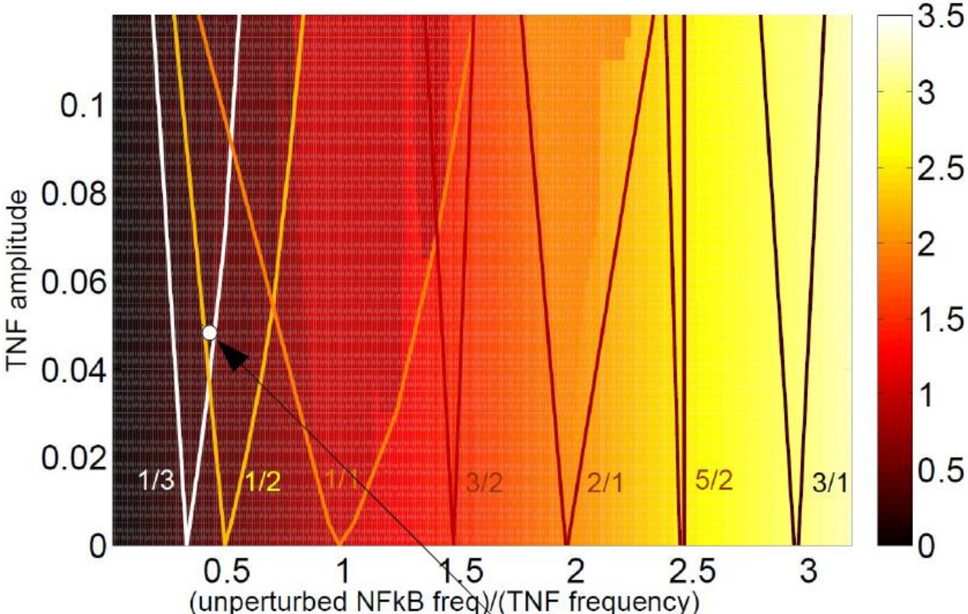






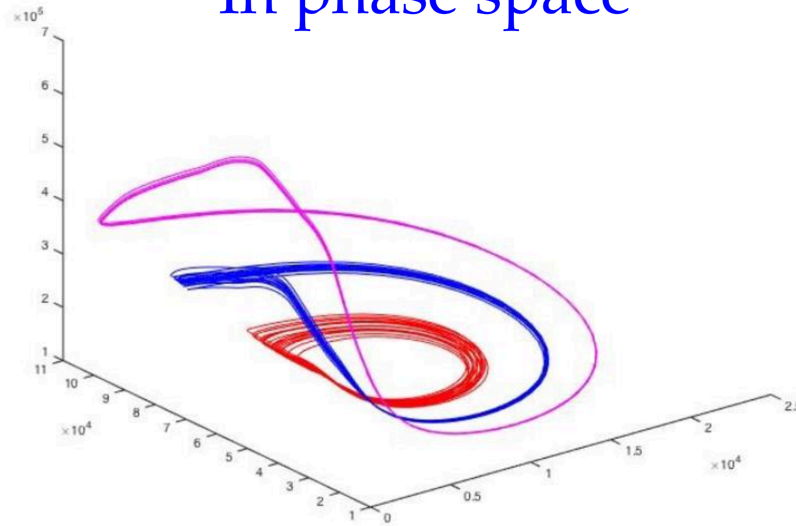
Jensen, Krishna (2012)

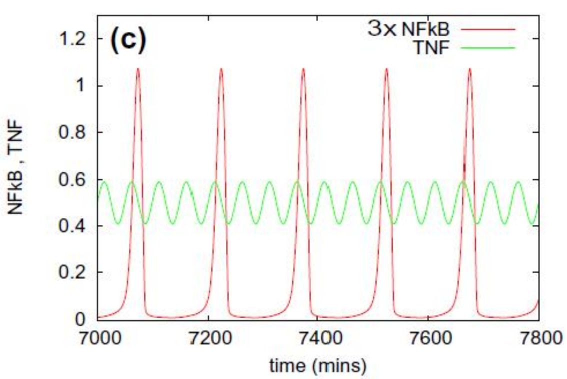
Sinusoidally driven NF-kB oscillations

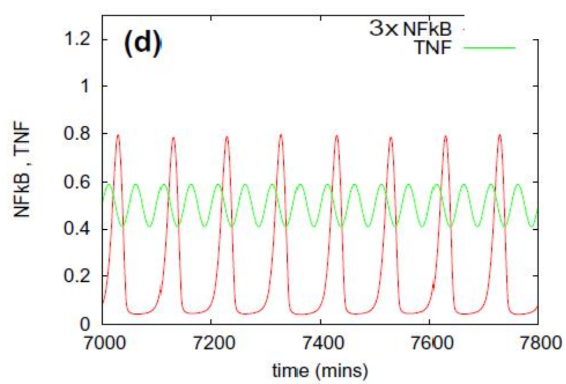


Tongues overlap !

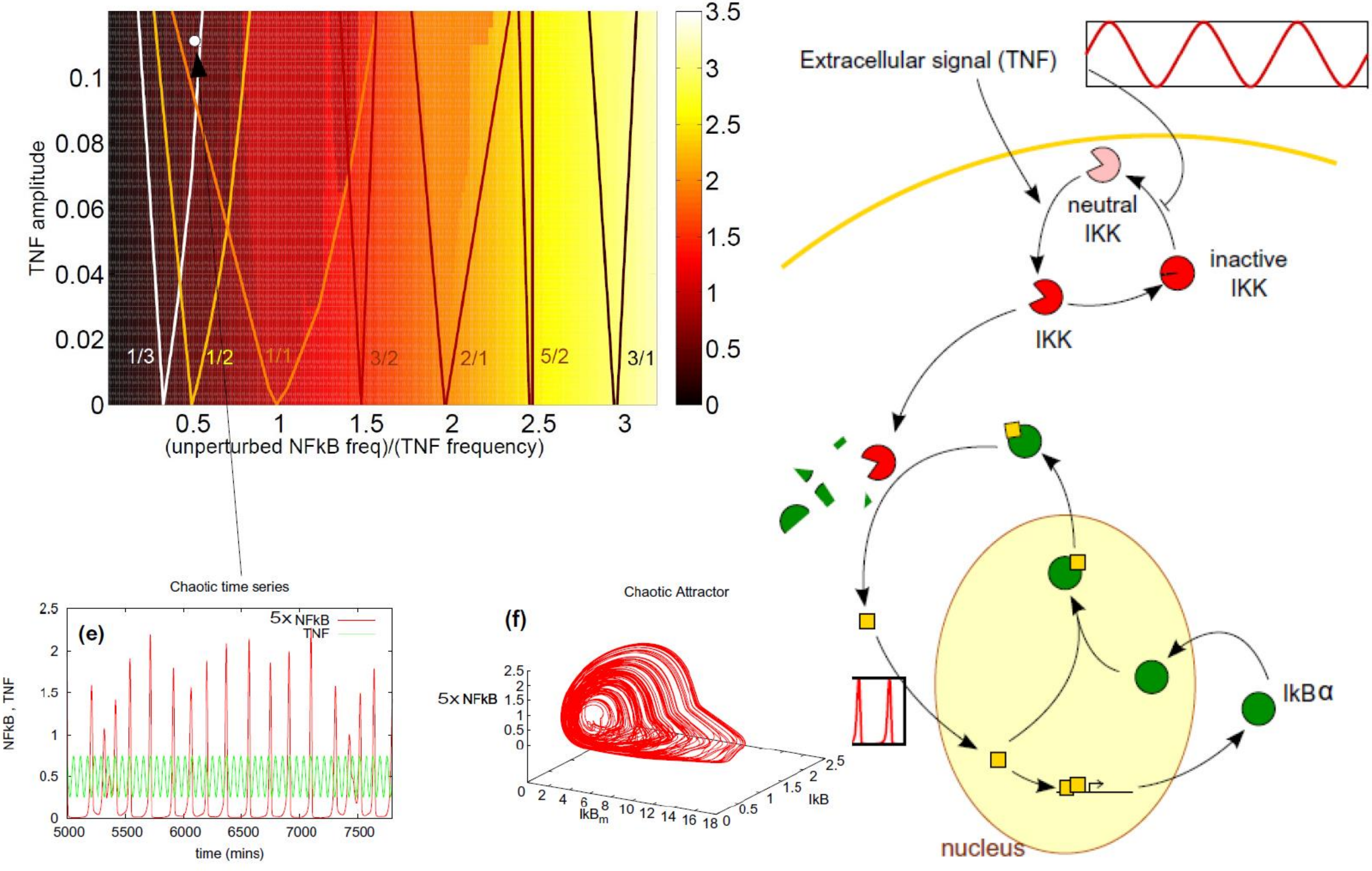
In phase space





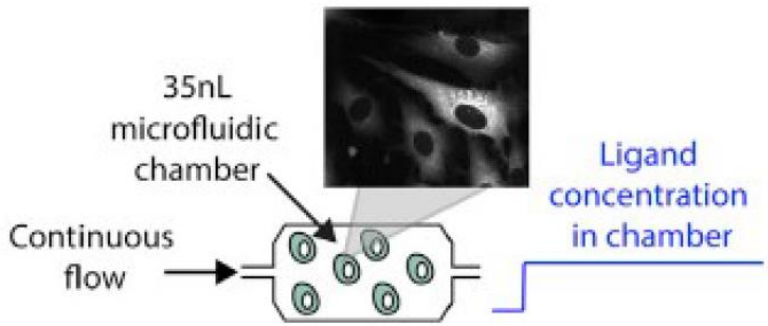


Sinusoidally driven NF-kB oscillations



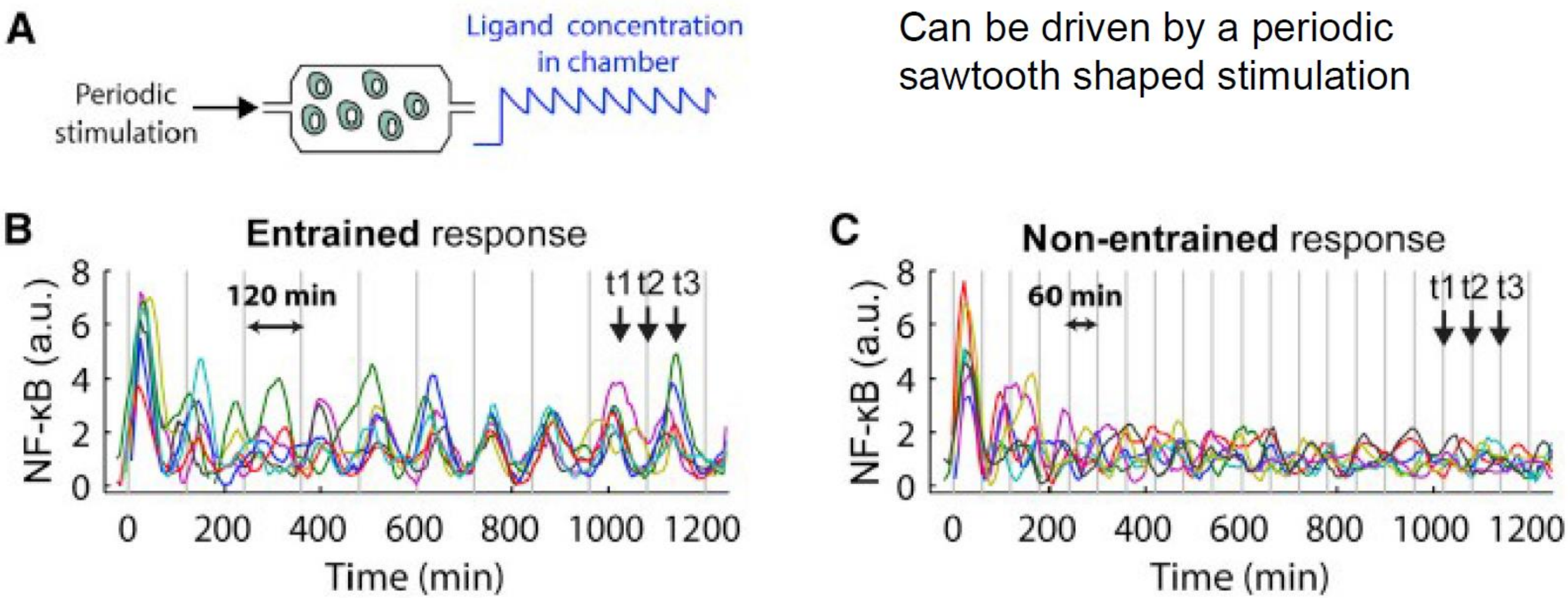
Jensen, Krishna (2012)

Sinusoidally driven NF-kB oscillations

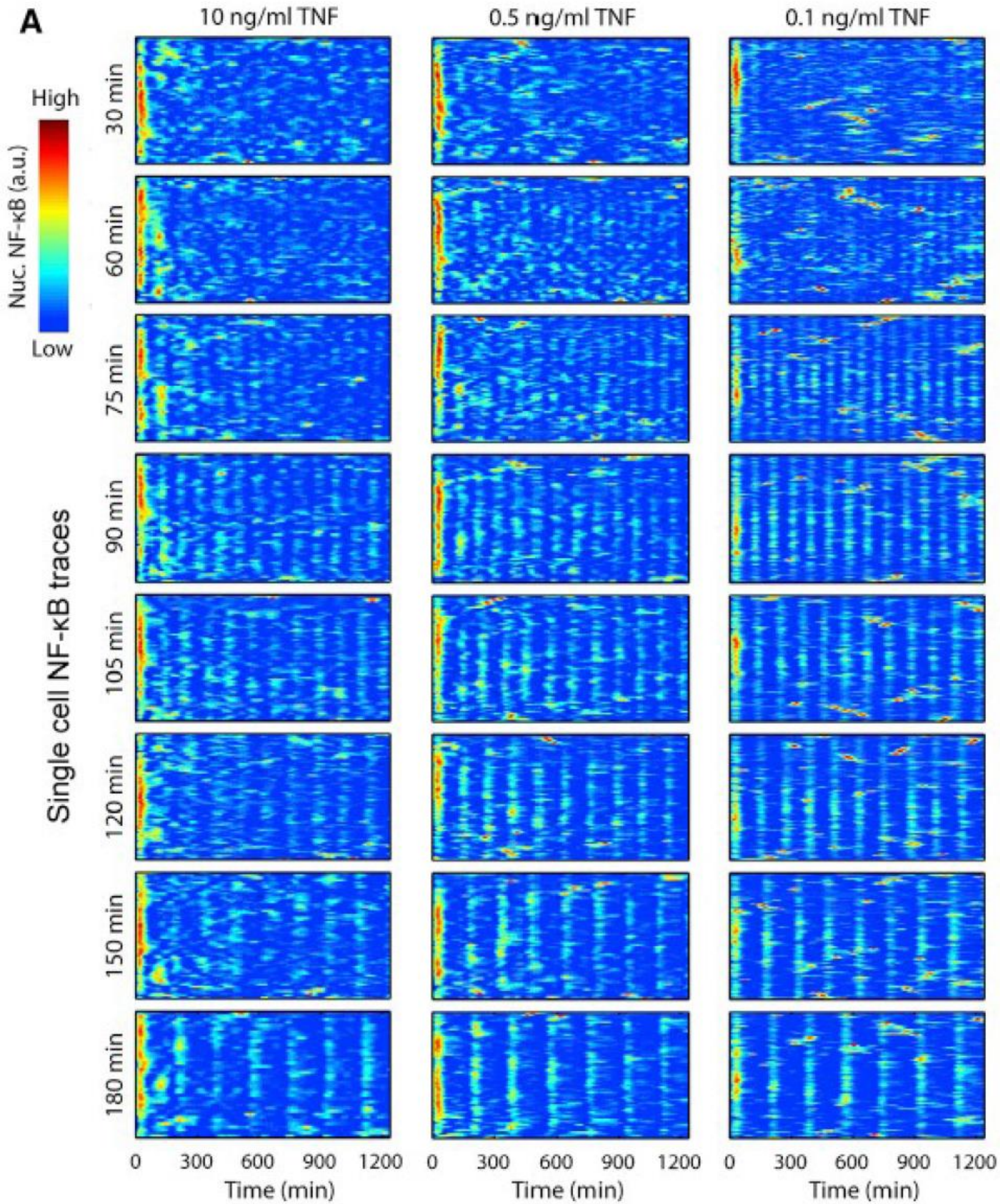


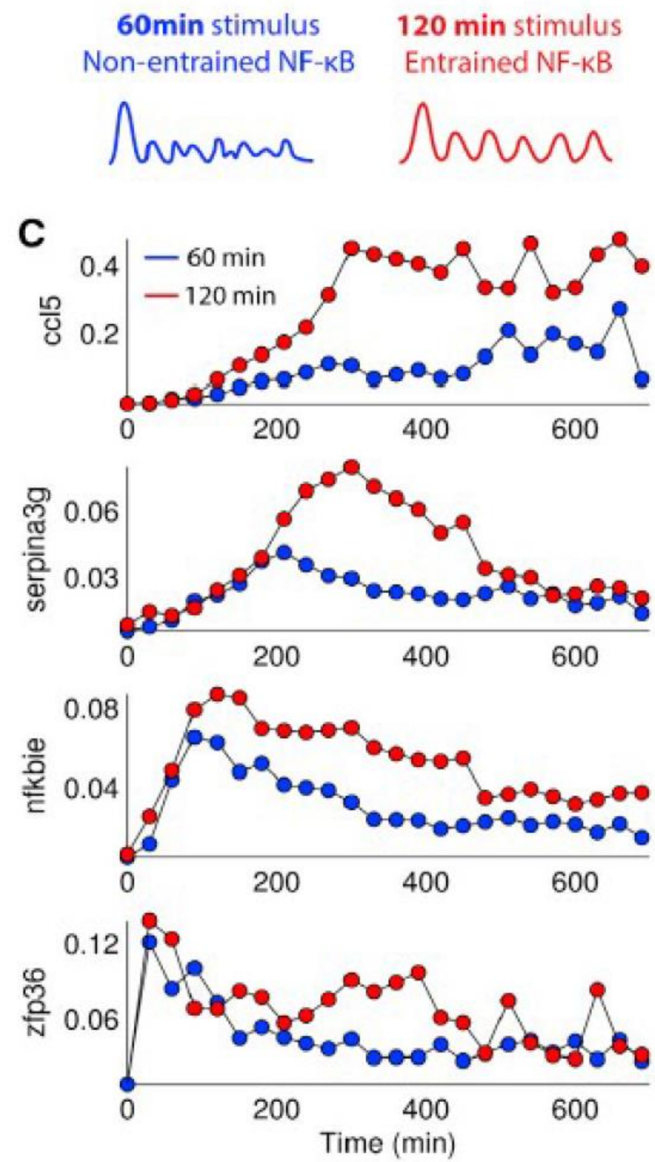
Ryan Kellog, Savas Tay (2015)

Microfluidic chamber with mouse fibroblast cells



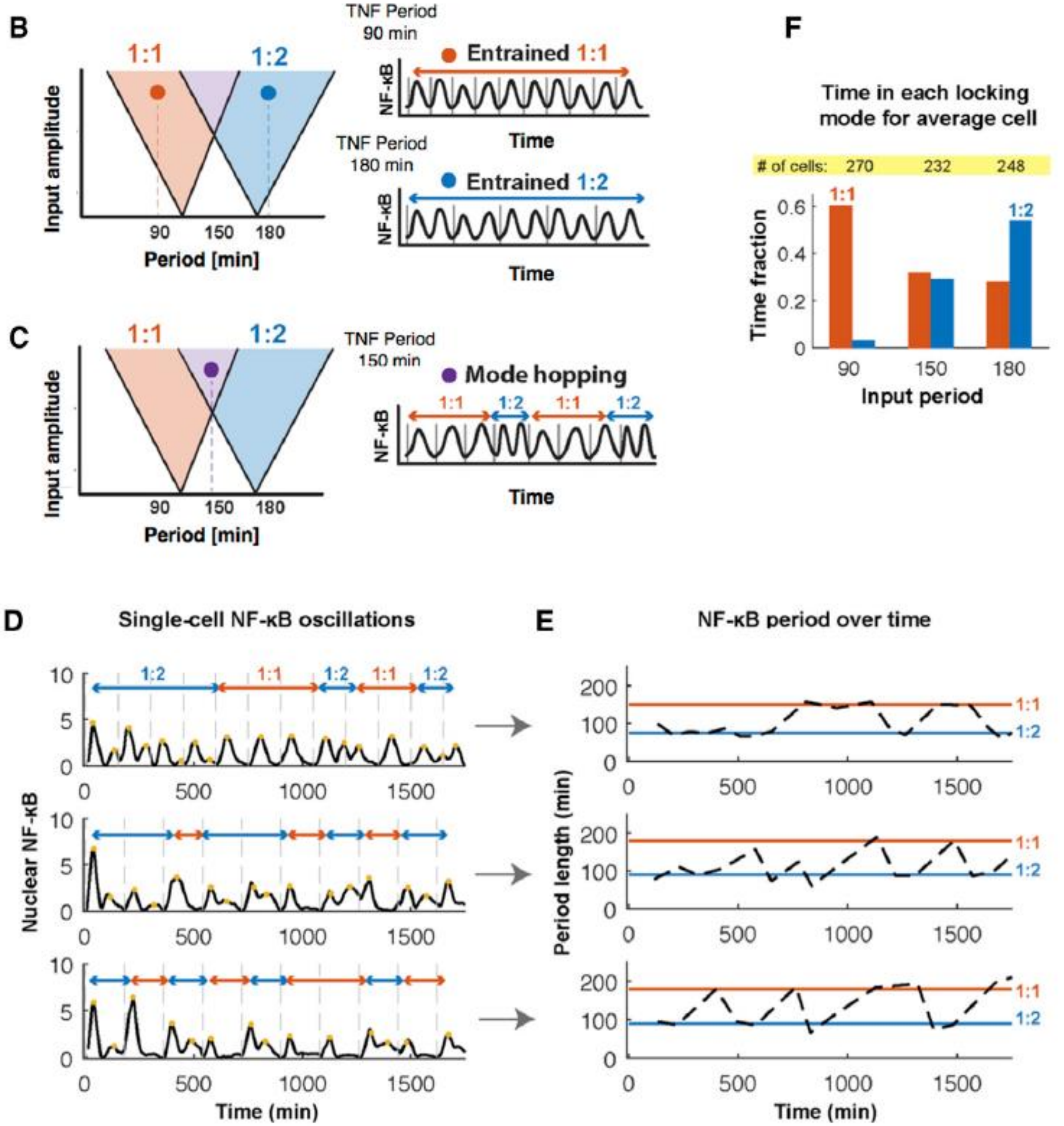
Can be driven by a periodic sawtooth shaped stimulation



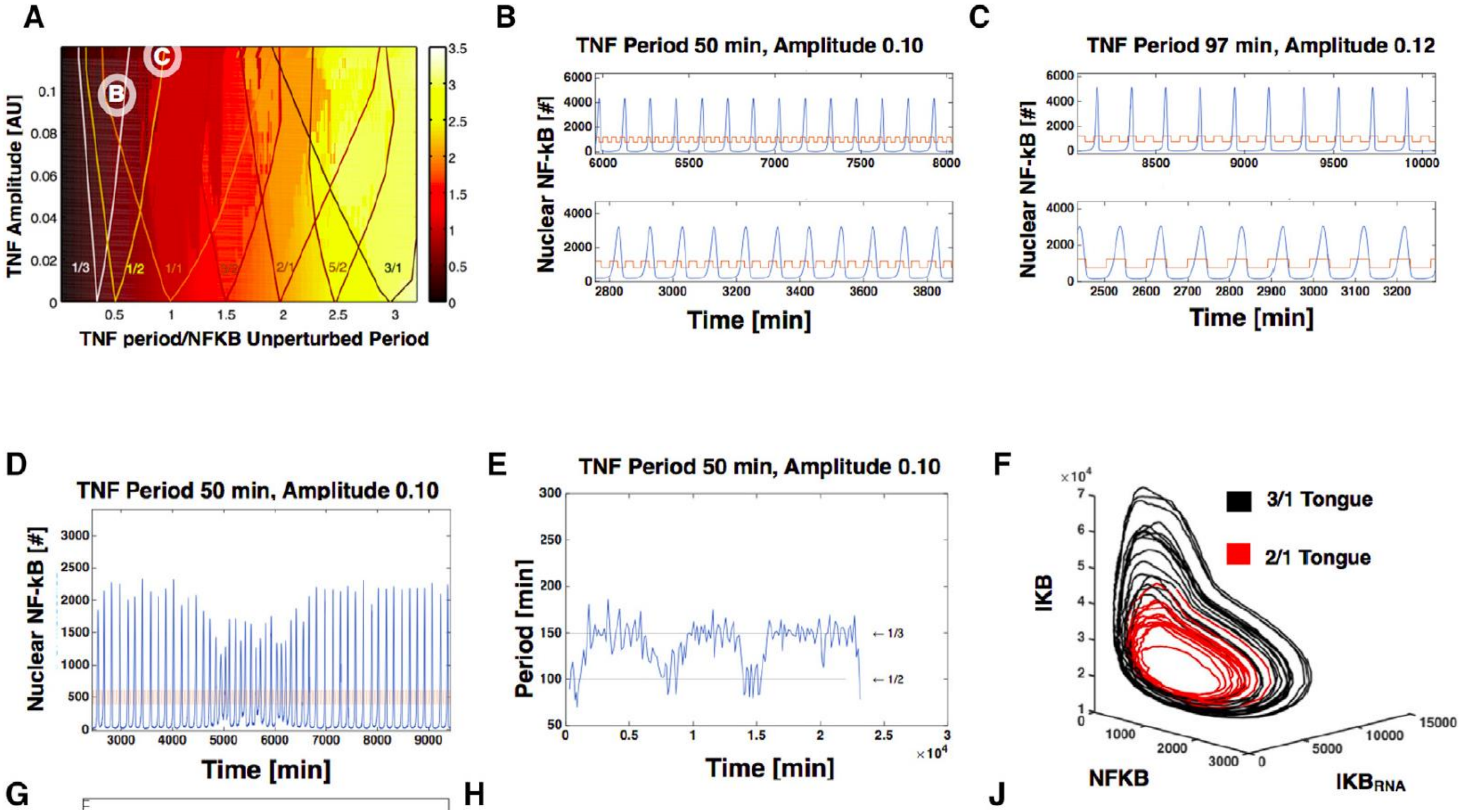


Entrained NF-kB seems to aid expression of certain genes

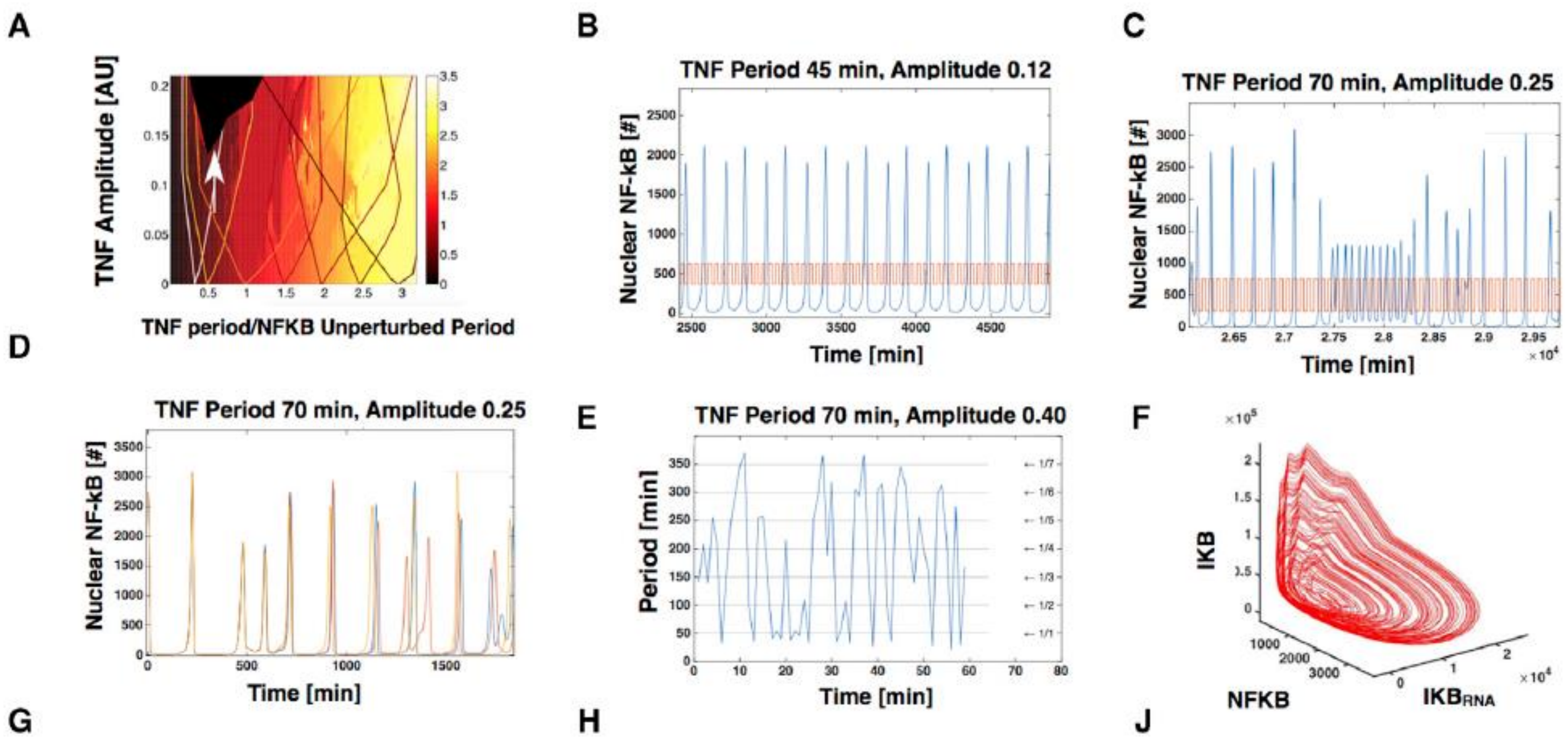
When tongues overlap:
Experimentally observed mode hopping between entrained states



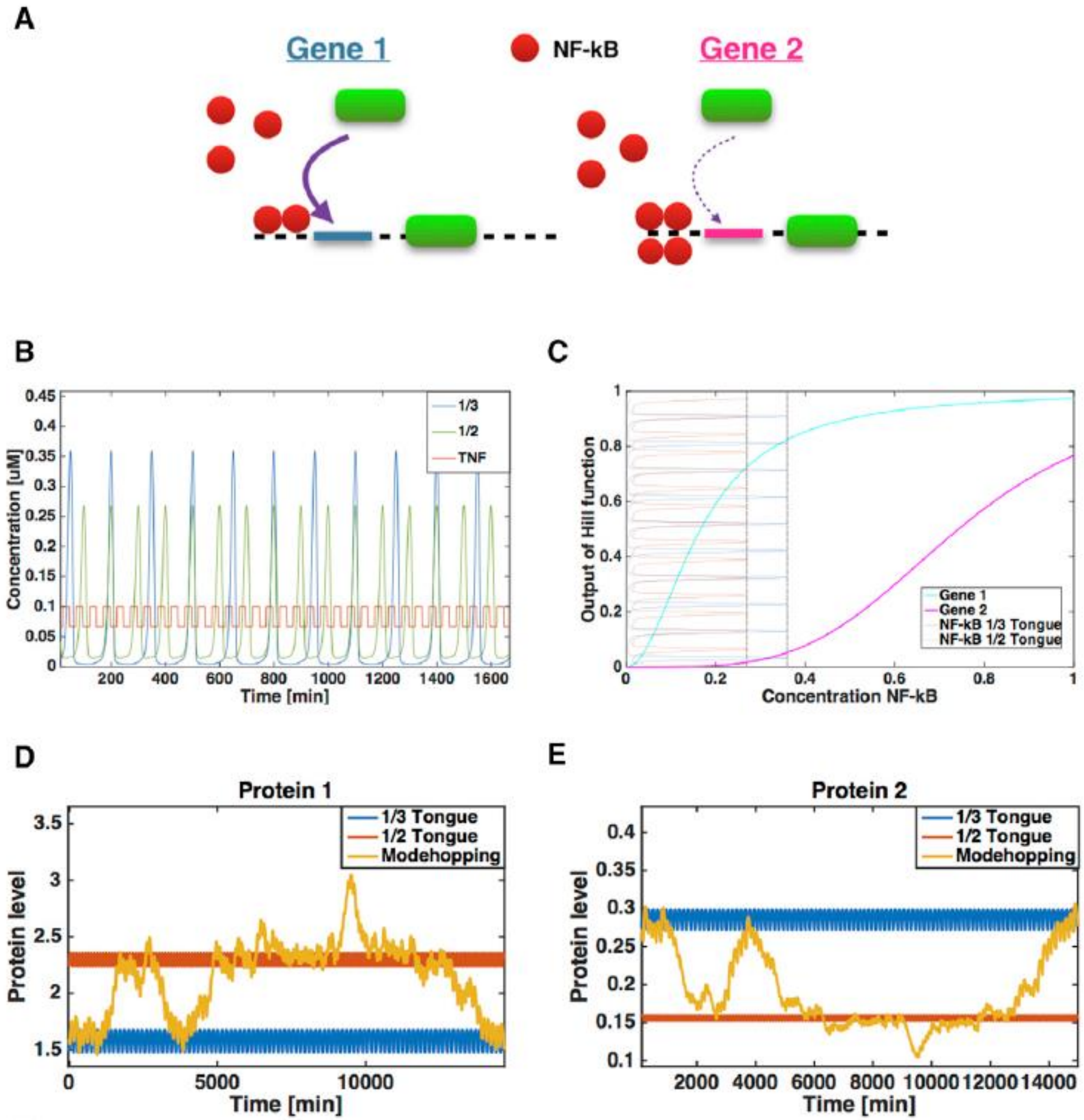
Stochastic Gillespie simulations: manifest as modehopping between entrained states



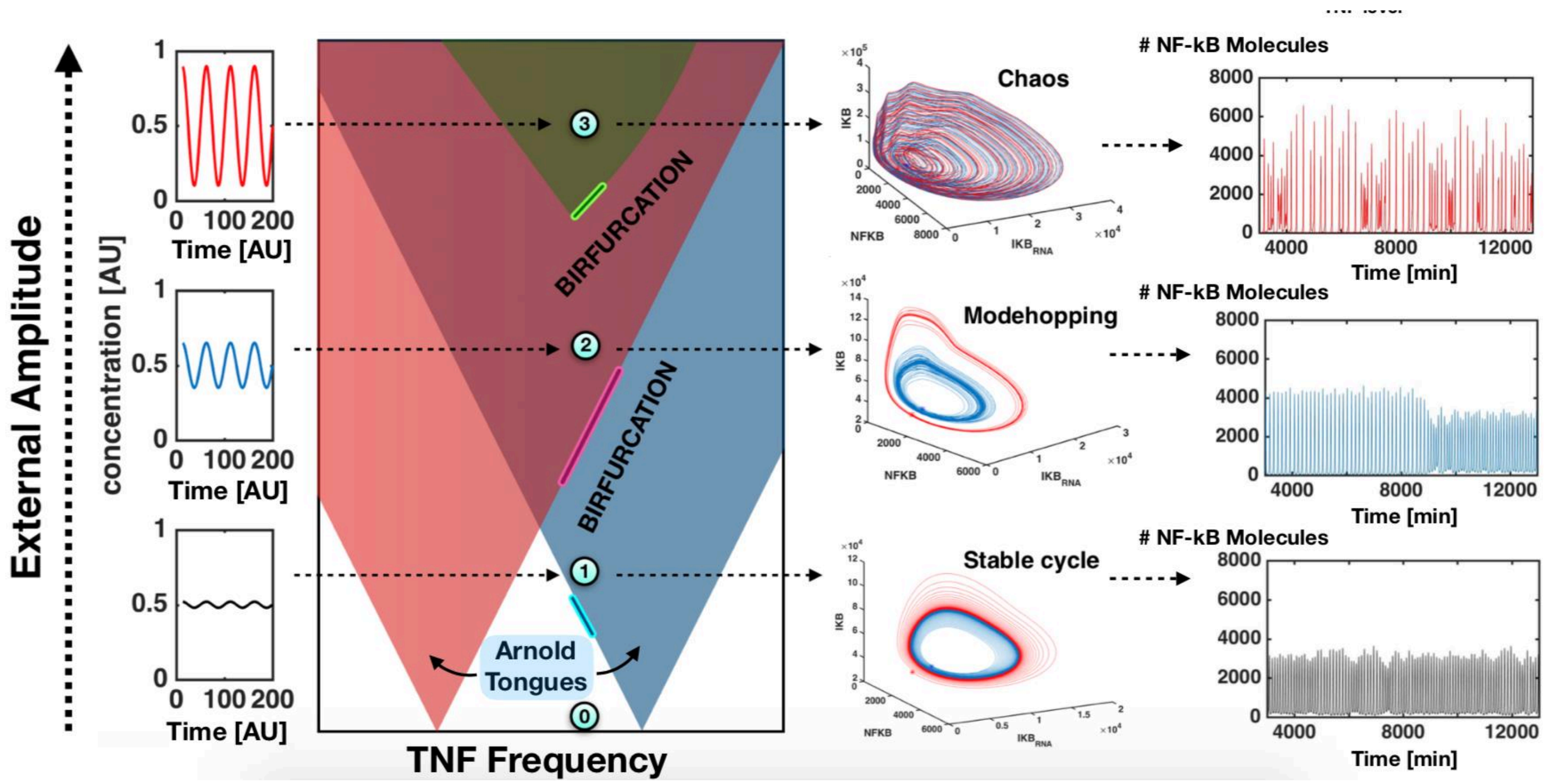
Deterministic chaos:
Mode hopping between several entrained states



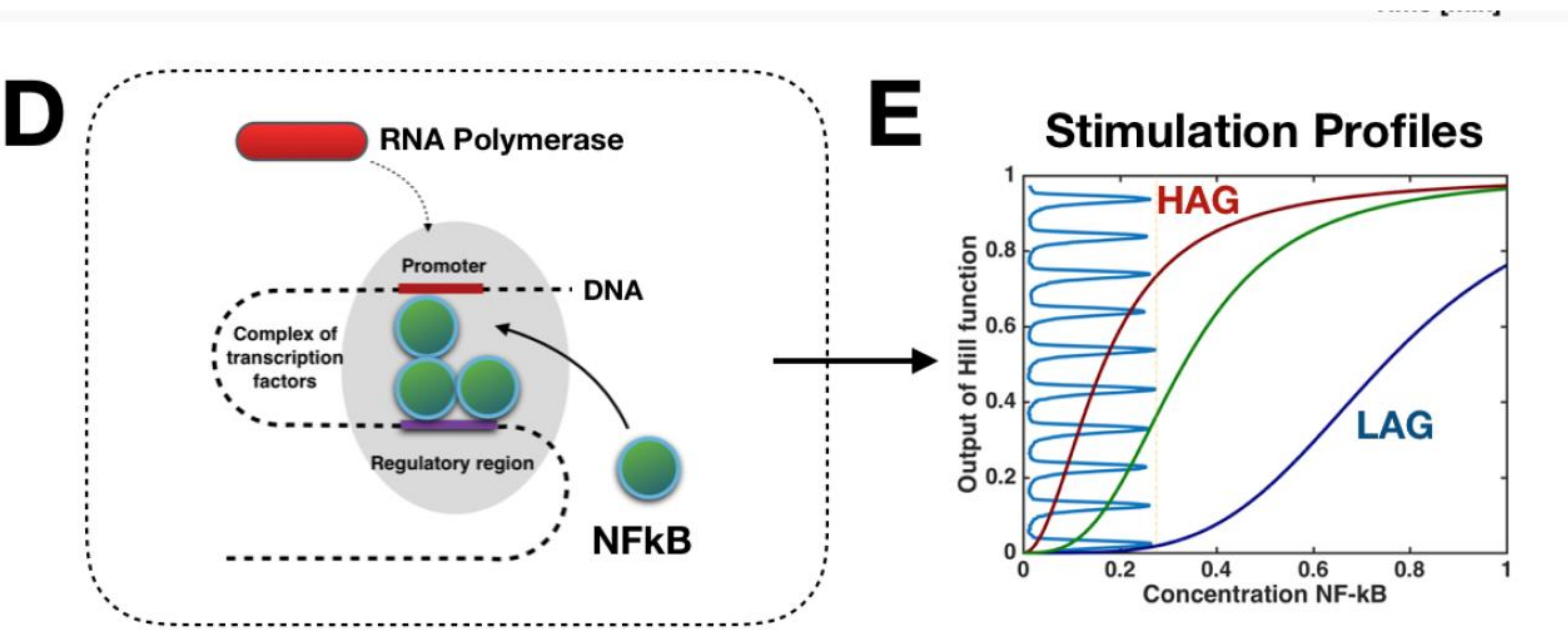
Mode hopping switches between high and low gene production states: Multiplexing!



Strongly coupled oscillations: Overlap of tongues ! Transitions to chaos !



Is chaos relevant for gene production ?

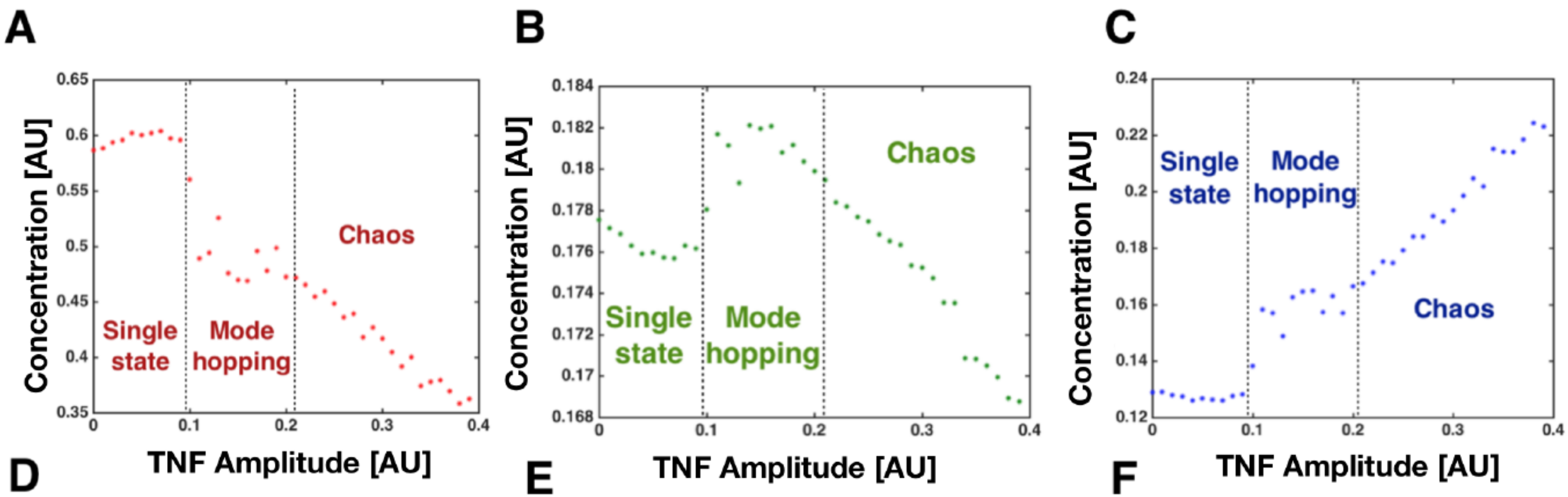


Hill function –
h cooperativity,
K affinity:

$$\dot{m}_i = \gamma_i \frac{N^{h_i}}{N^{h_i} + K_i^{h_i}} - \delta_i m_i,$$

$$\dot{P}_i = \Gamma_i m_i - \Delta_i P_i.$$

For low affinity: High gene production in chaos!

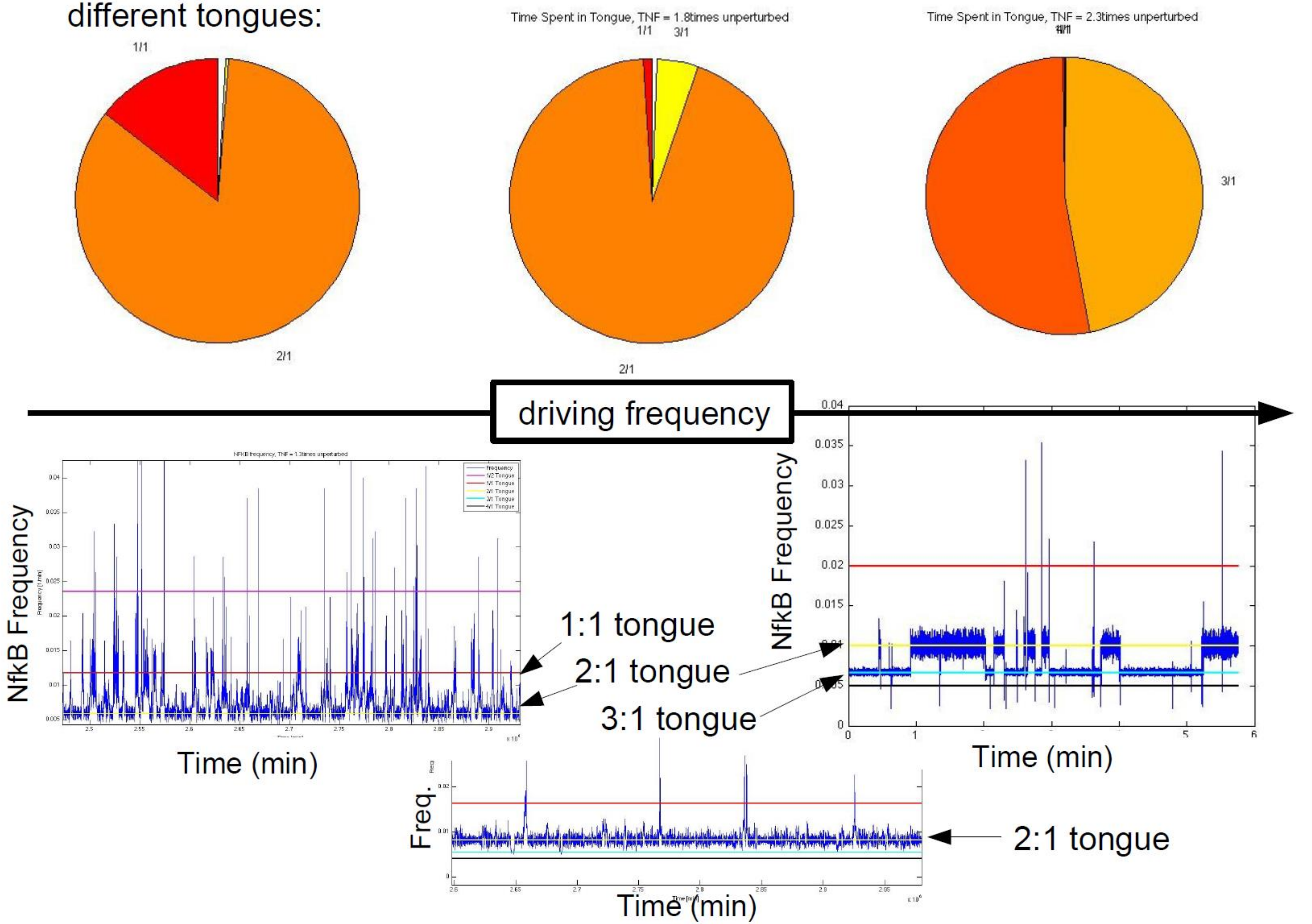


Medium cooperativity
High affinity
(h=2, K=1)

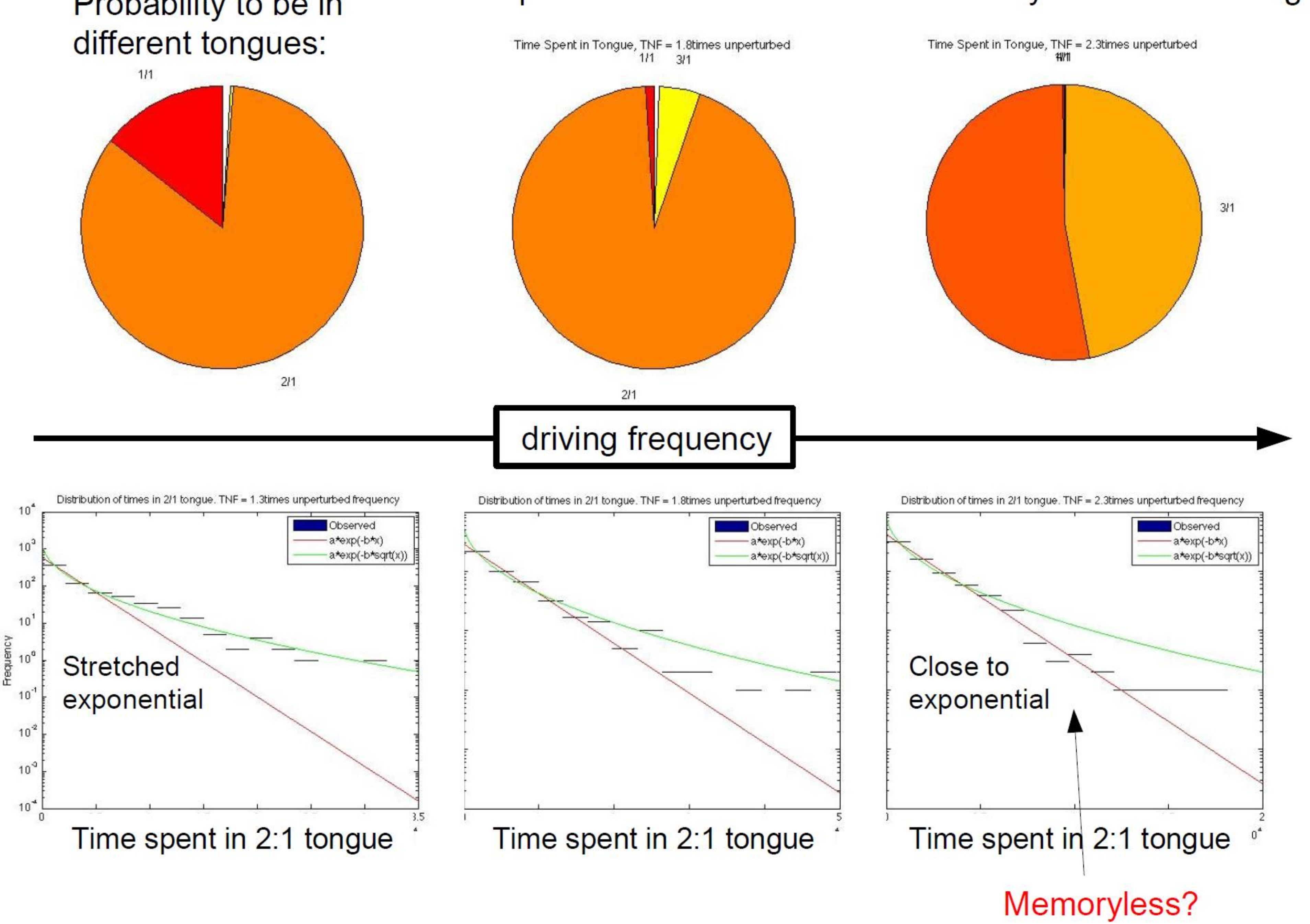
High cooperativity
Low affinity
(h=4, K=4.5)

Gillespie simulations of NF-kB network by Mathias Heltberg

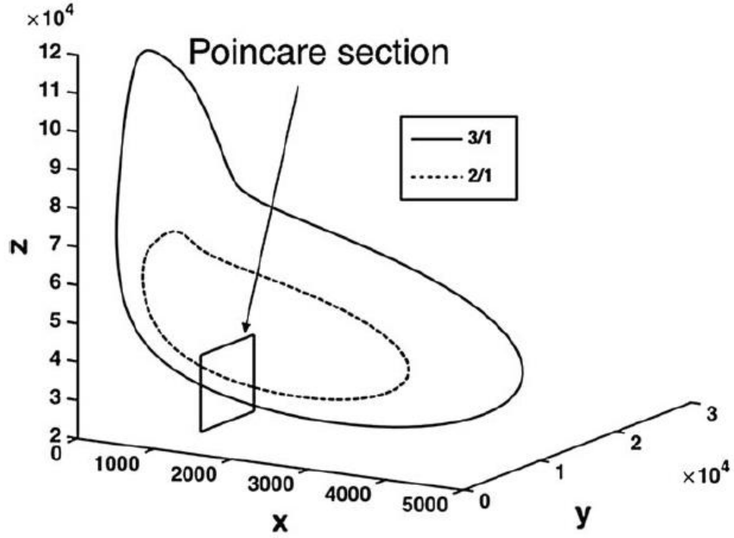
Probability to be in different tongues:

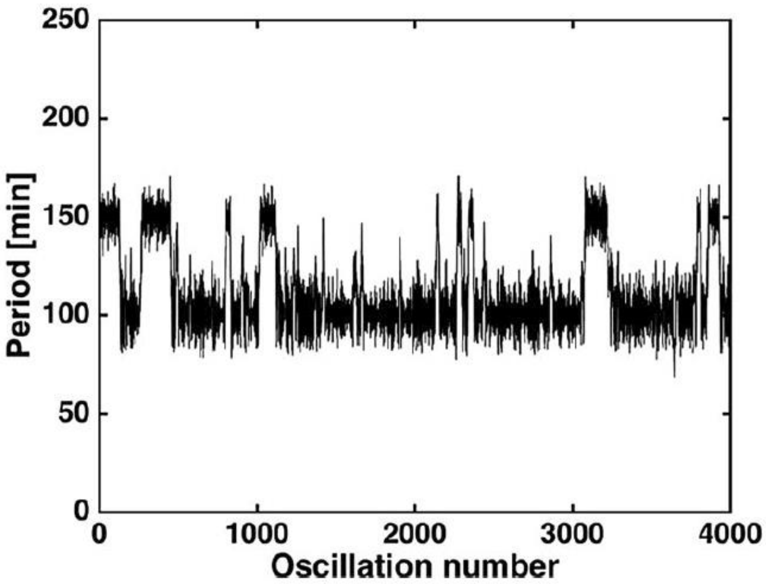


Gillespie simulations of NF-kB network by Mathias Heltberg



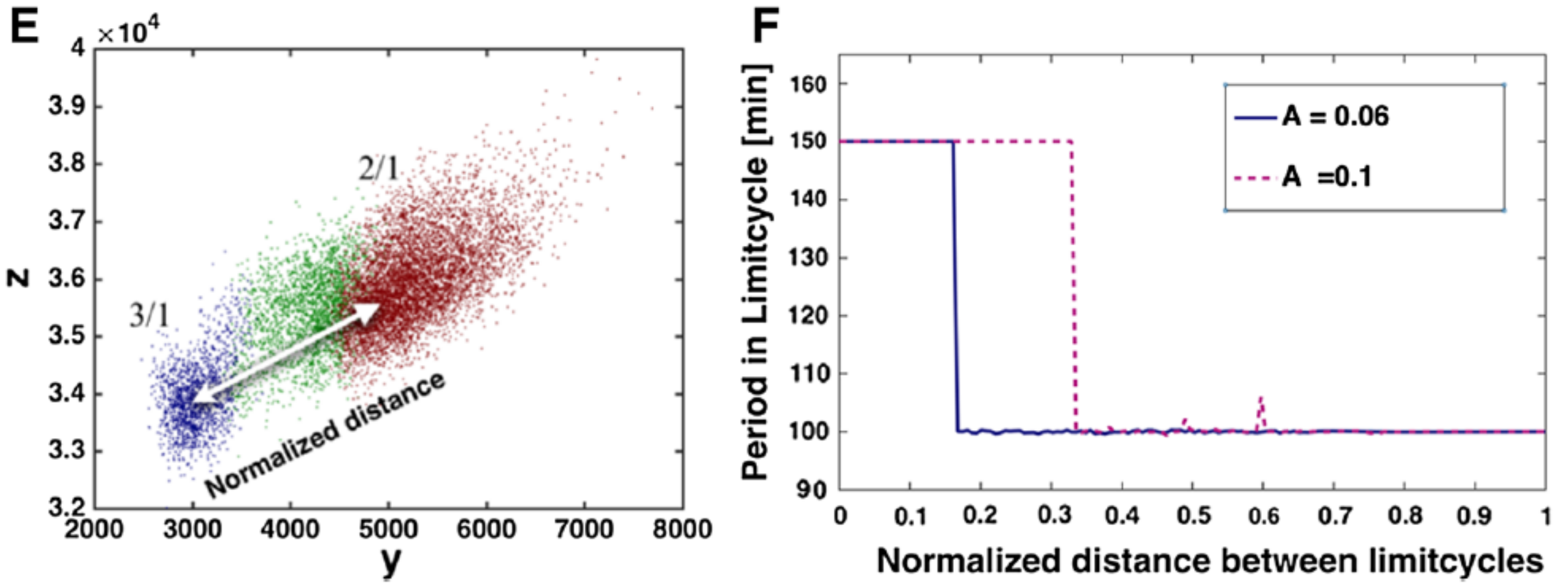
To simplify: Make a Poincare cut



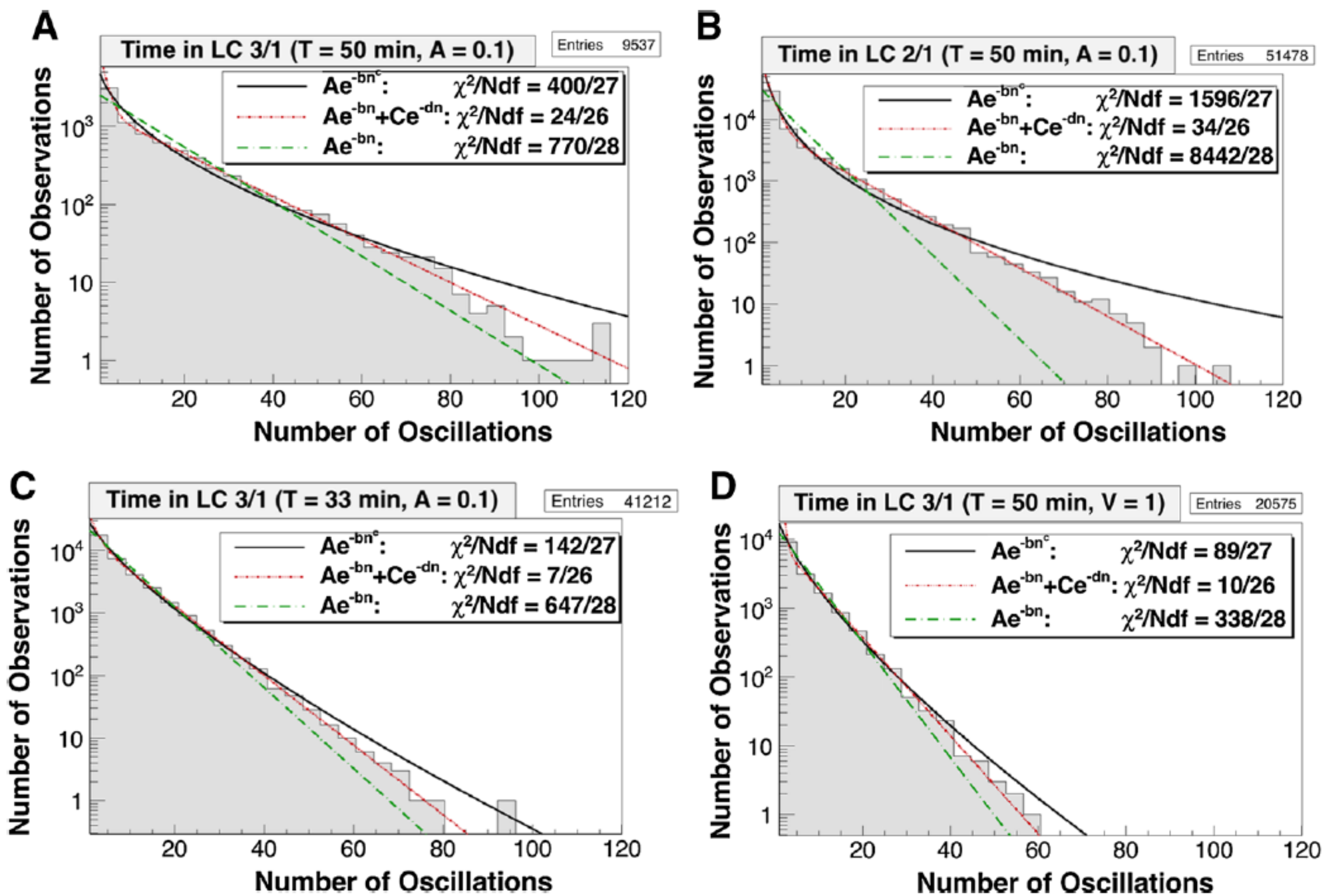


Stochastic simulation: Jumps between the tongues !

Basin of attraction for the two tongues

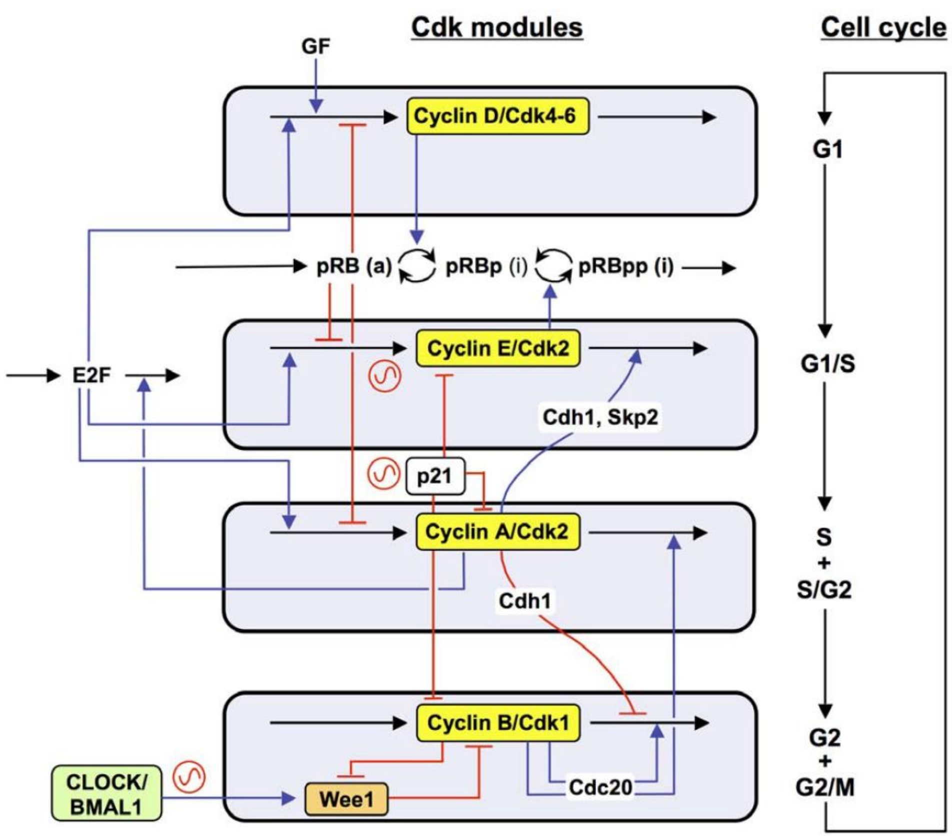


Number of oscillations before leaving a tongue



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

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



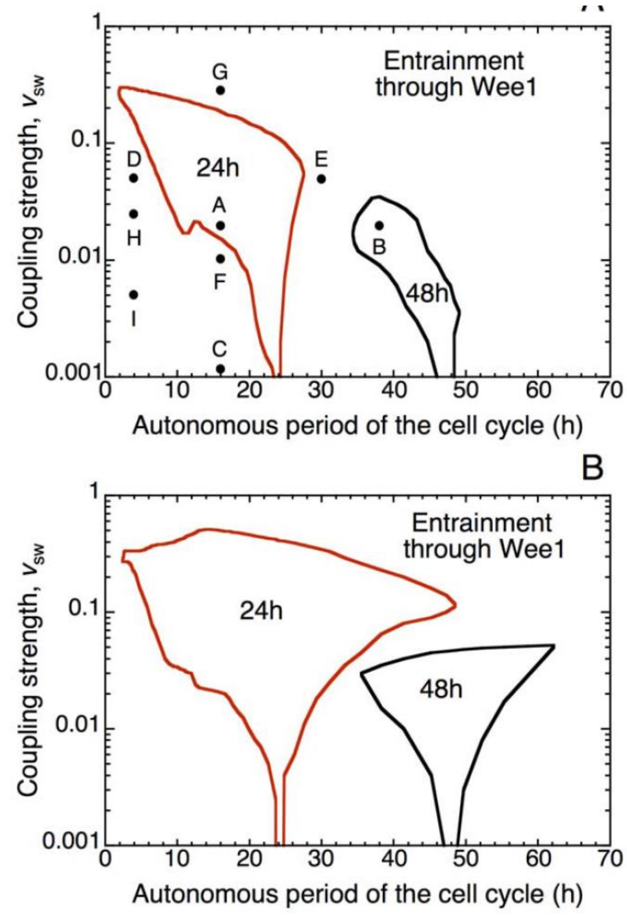
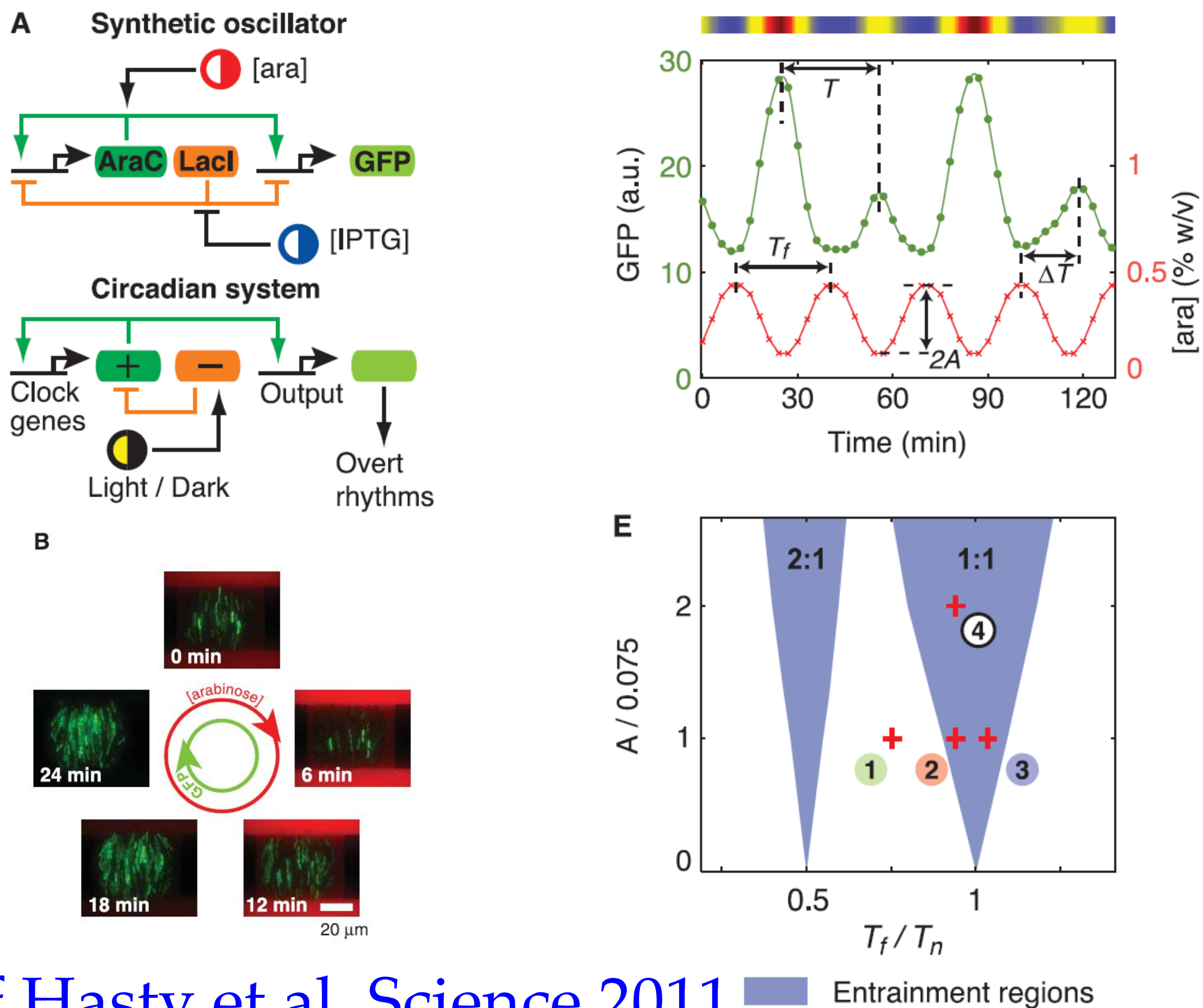


Figure 4. Domains of entrainment of the cell cycle by the circadian clock via circadian control of the kinase Wee1. The

Gerard and Goldbeter, May, 2012

Populations of genetic oscillators



Jeff Hasty et al, Science 2011