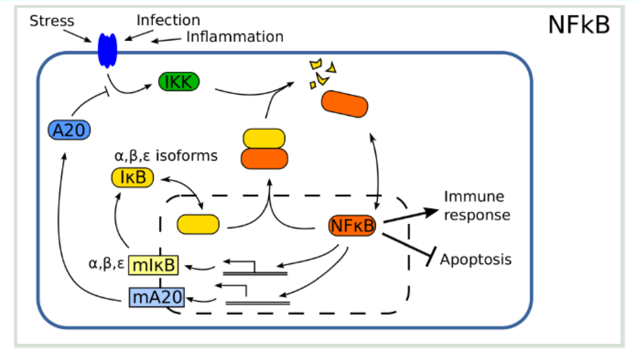
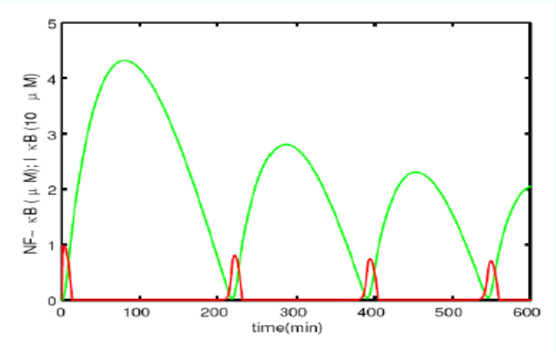
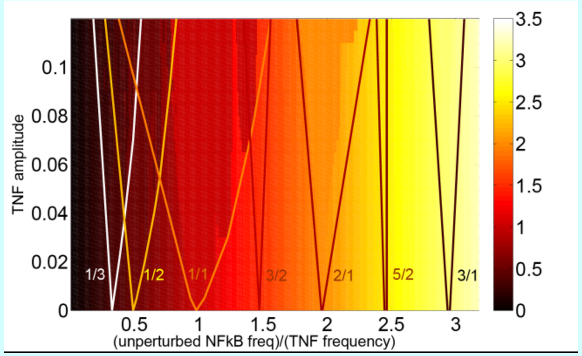
Coupled Oscillators and Arnold Tongues in Cell Dynamics

AV60, Rome , 22 Sep 2014

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 → Chaotic attractors

5. **Pulsatile extracellular signaling:**

A way to control cell dynamics ?

A way to control embryo segmentation ?

6. **Distinguish a non-linear from a linear, noisy systems:**

Occurrences of Arnold tongues ?

Collaborators:

- Sandeep Krishna, Uri Alon, Namiko Mitarai, Leo Kadanoff,

M.H. Jensen and S. Krishna, "Inducing phase-locking and chaos in cellular oscillators by modulating the driving stimuli", FEBS Letters 586, 1664-1668 (2012).

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 (2012)

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

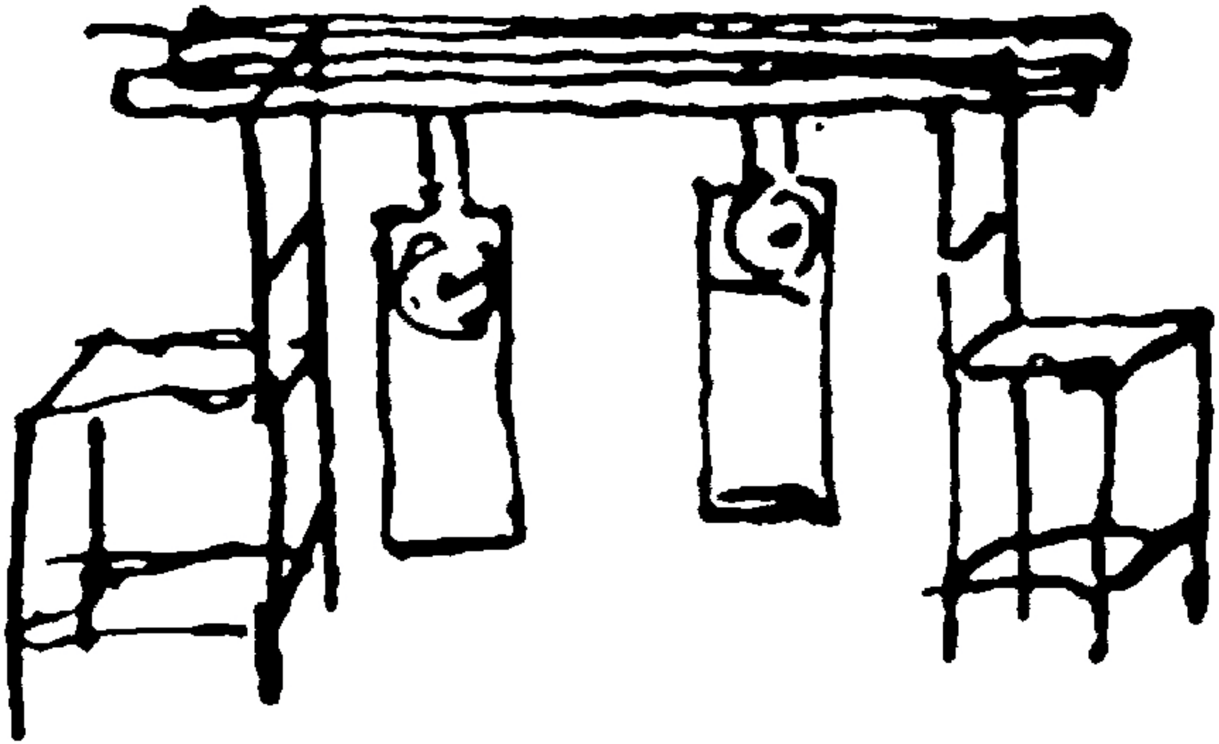
Congratulations Angelo !!

It has been a FANTASTIC experience to collaborate with you

Yours knowledge about dynamical systems and physics is truly amazing

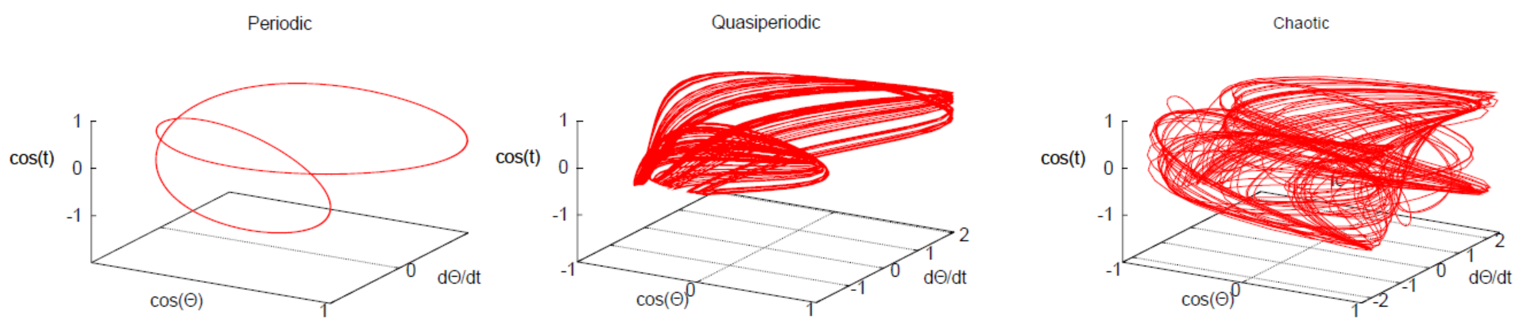
You are a true scholar !

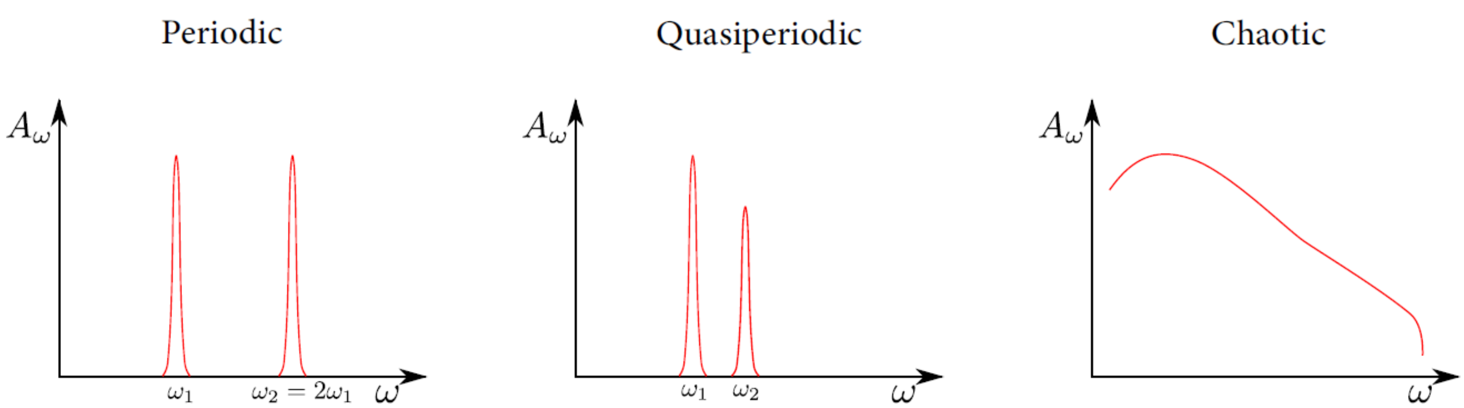
Synchronization of two oscillators



Huygens' clocks 1665

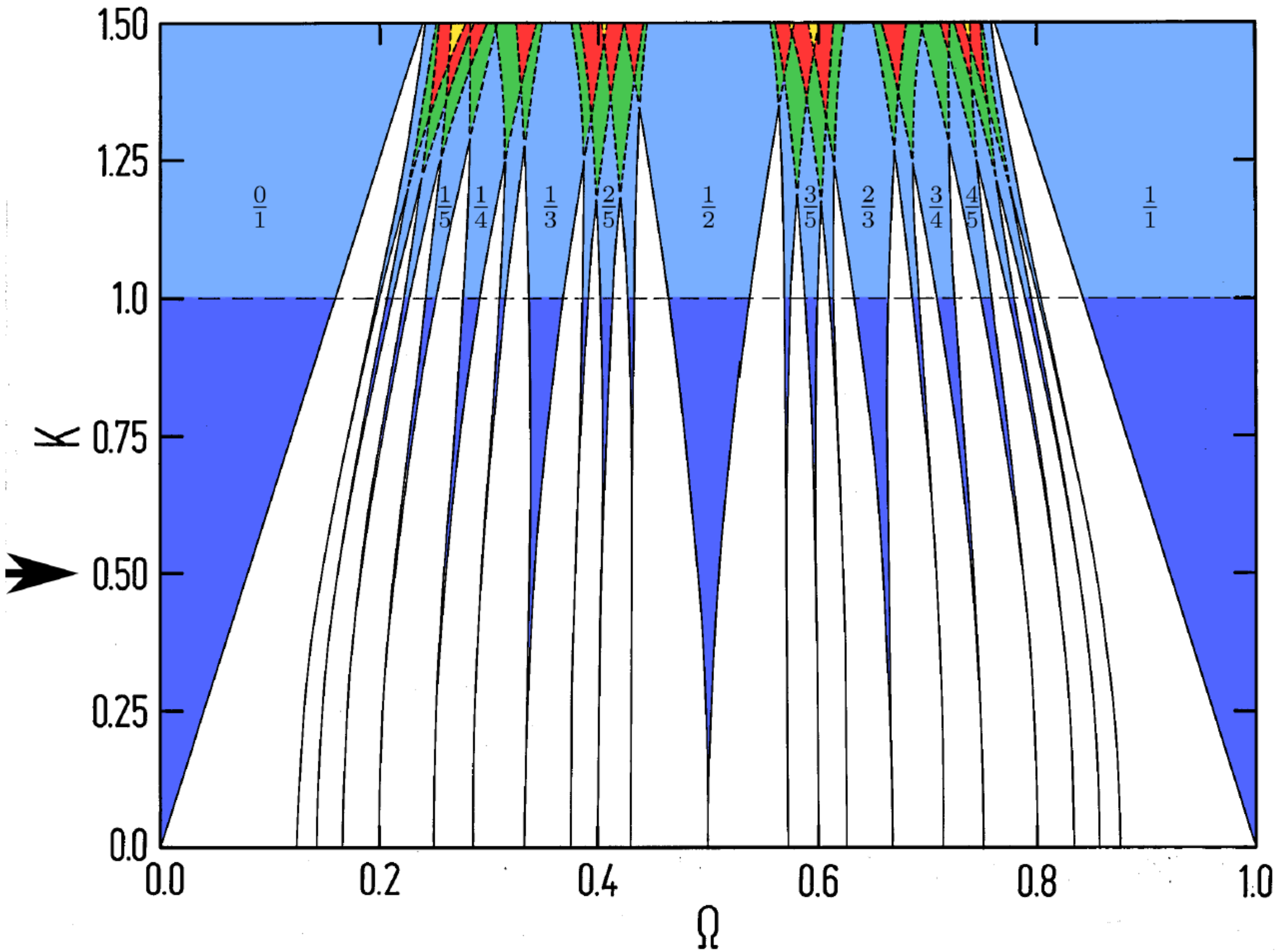
Three different non-linear dynamics



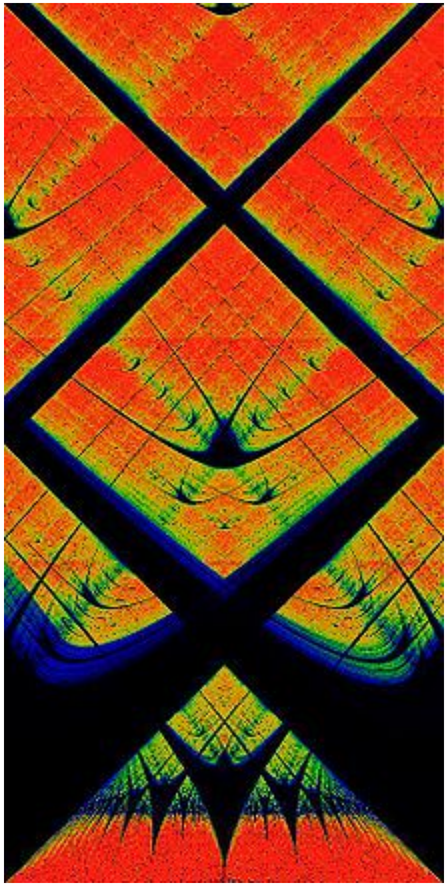


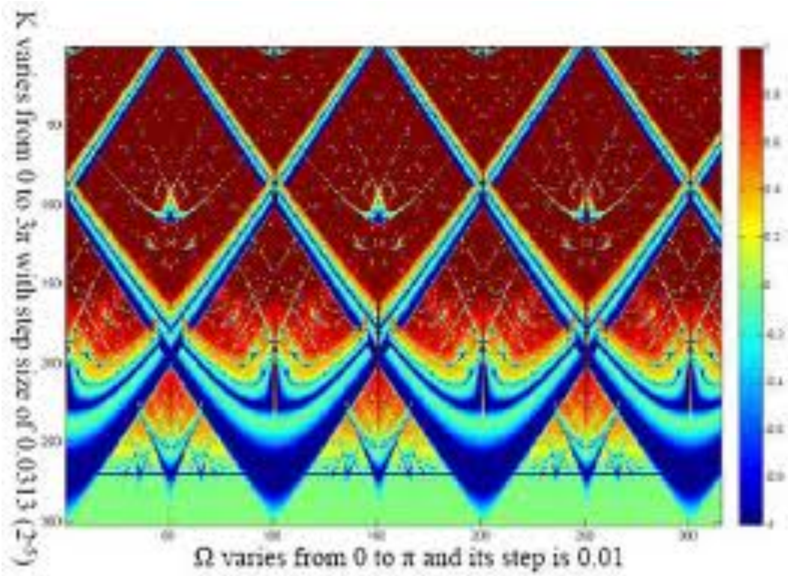
Two coupled oscillators: Arnold tongues

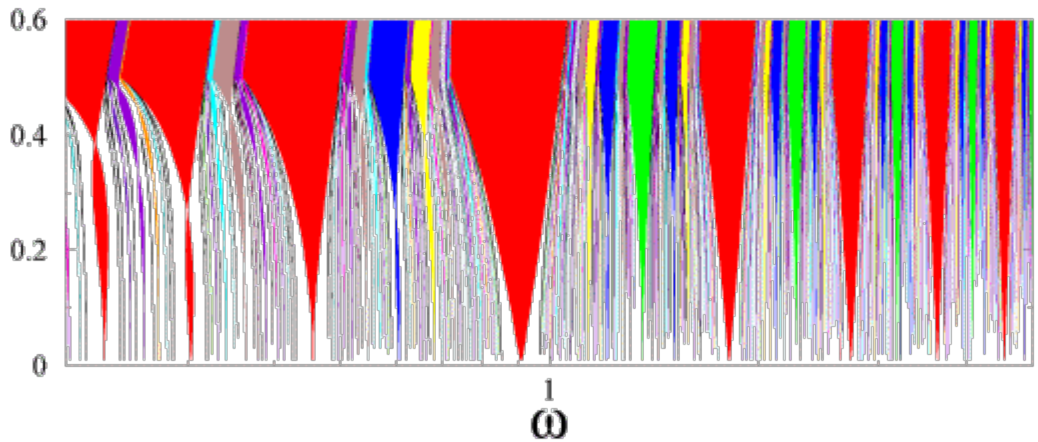
$$\omega/\Omega = P/Q$$



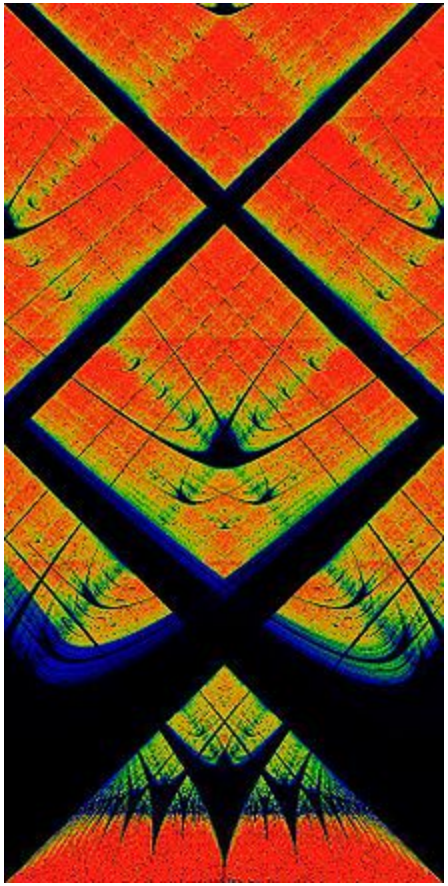
Examples of Arnold tongues !

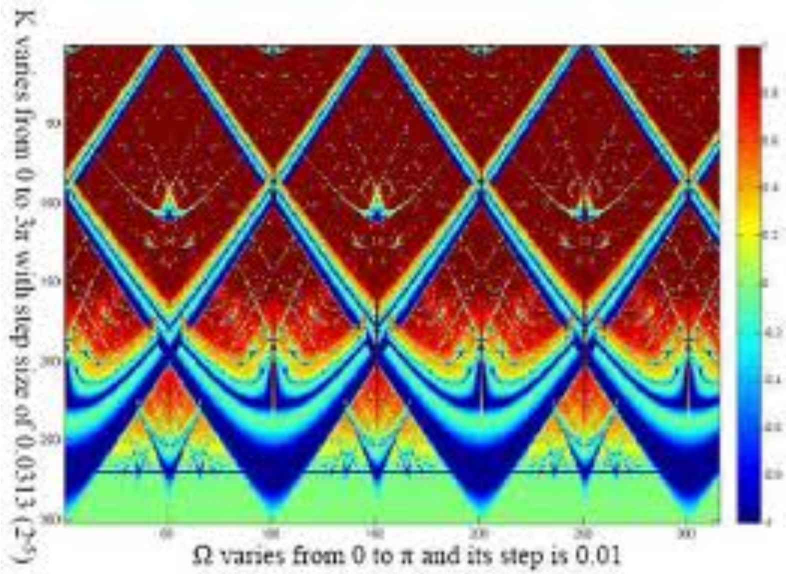


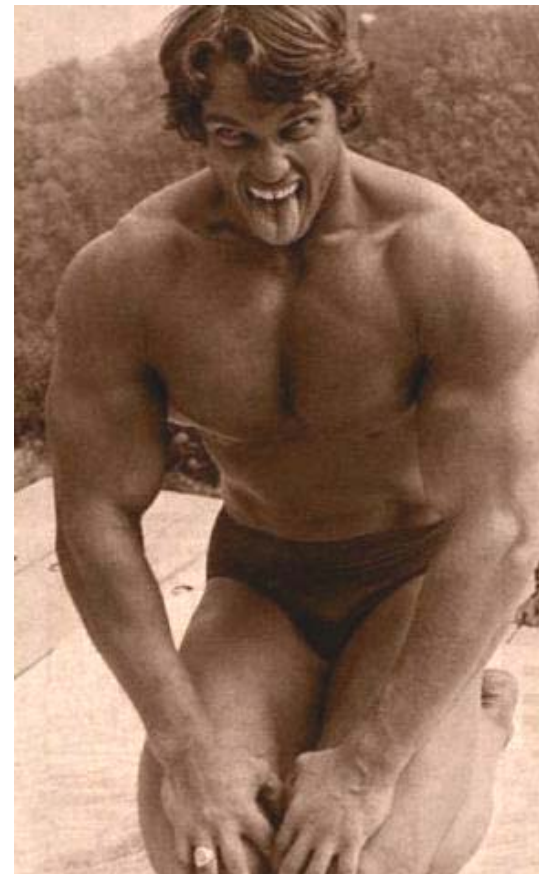


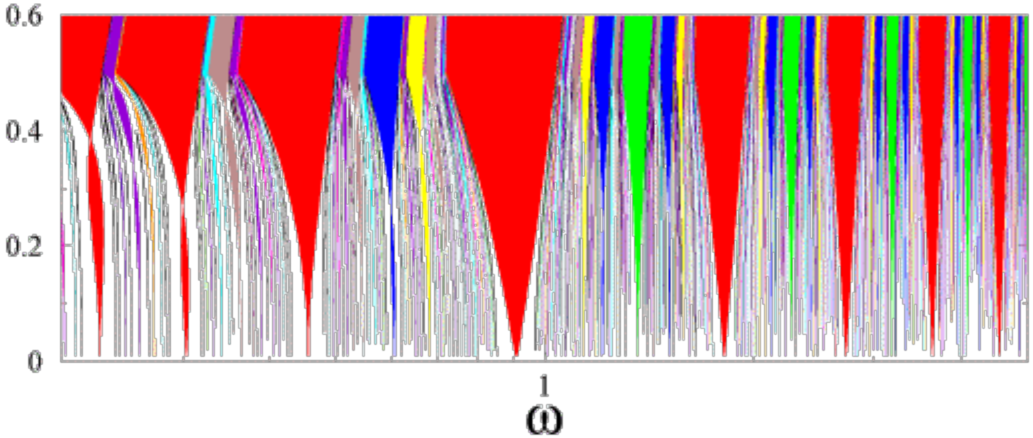


Examples of Arnold tongues !

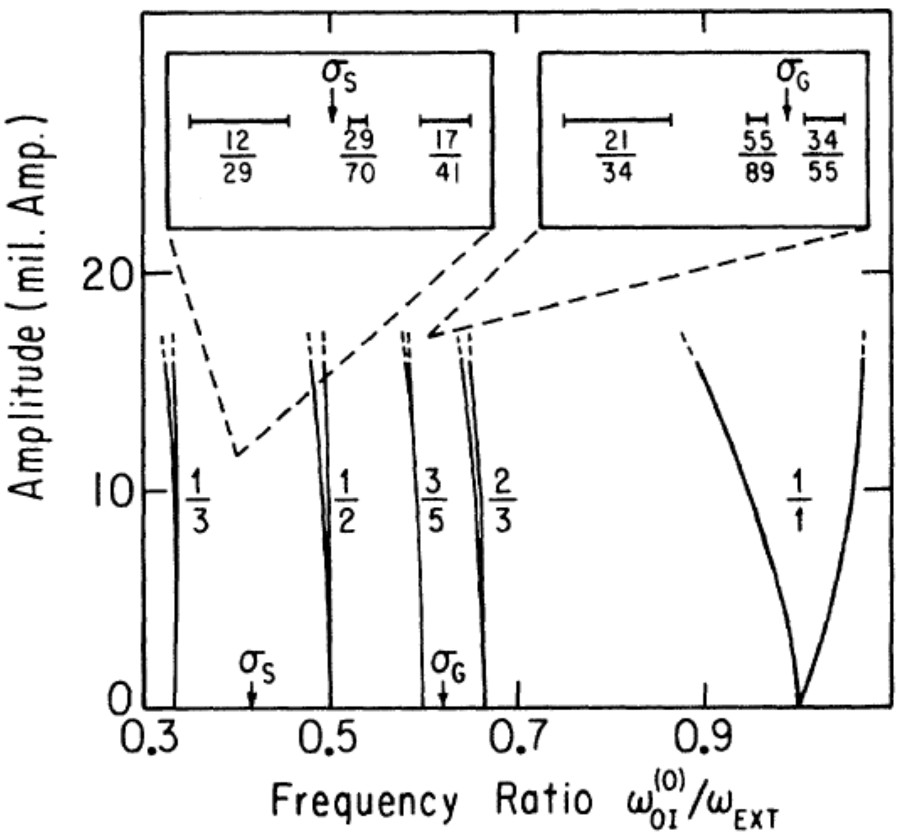




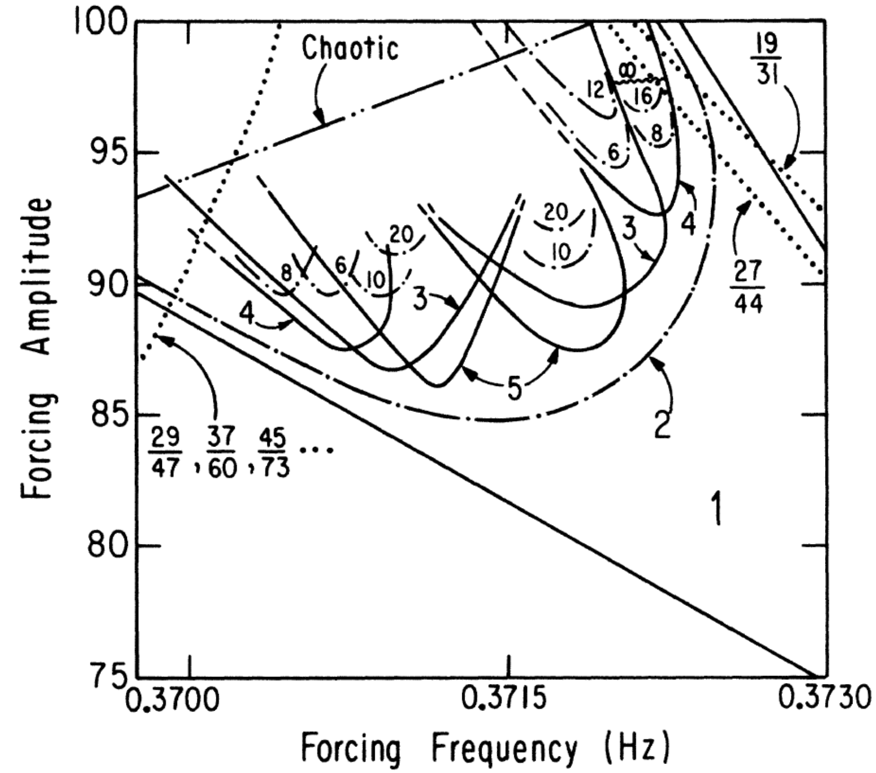




Chicago basement convection !

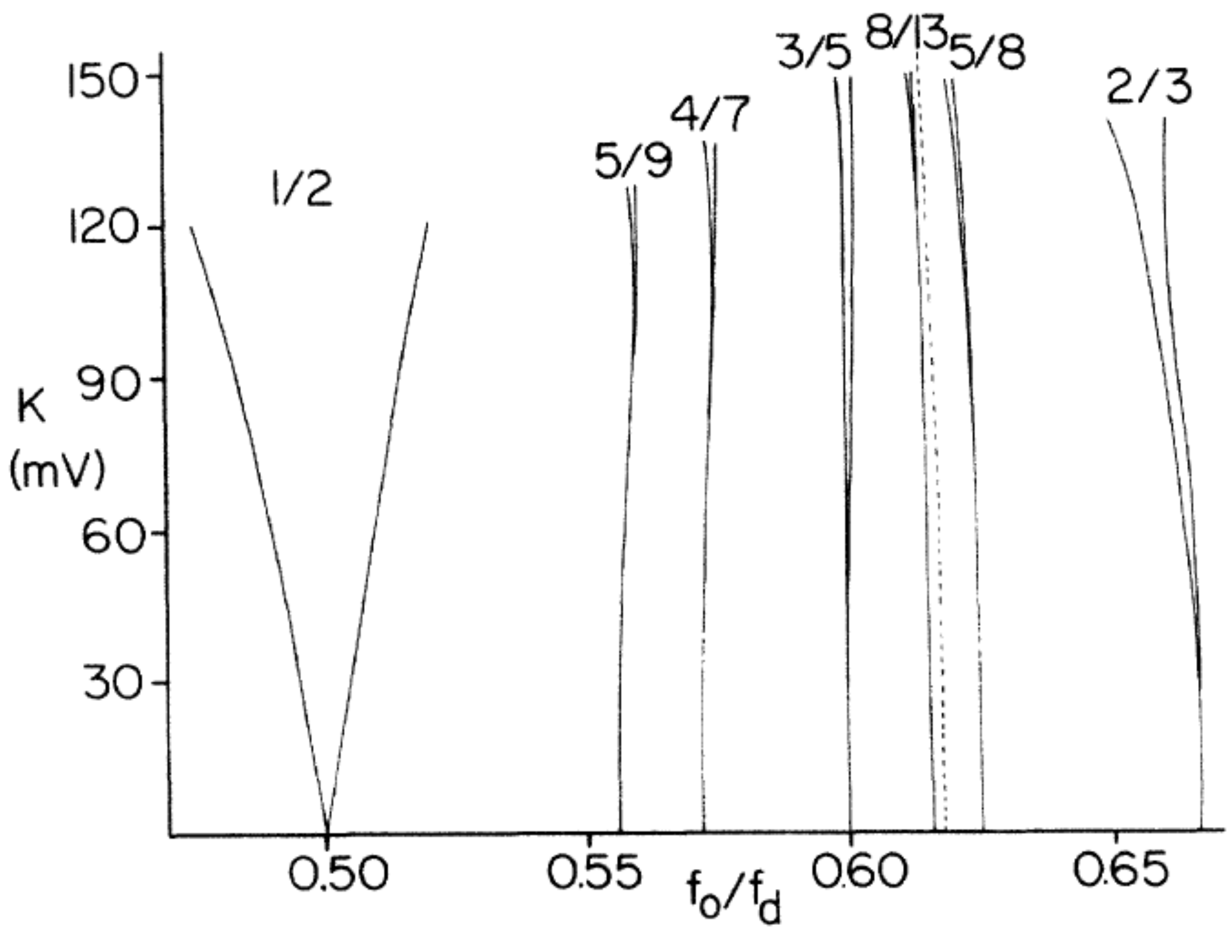


Stavans, Heslot, Libchaber



Glazier, Jensen, Libchaber, Stavans

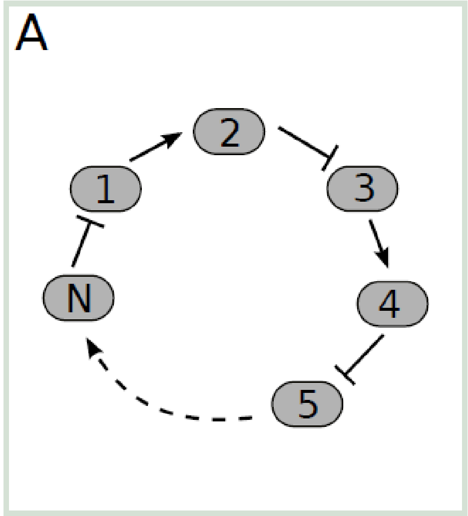
Electronic system, Gwinn, Westervelt, Harvard

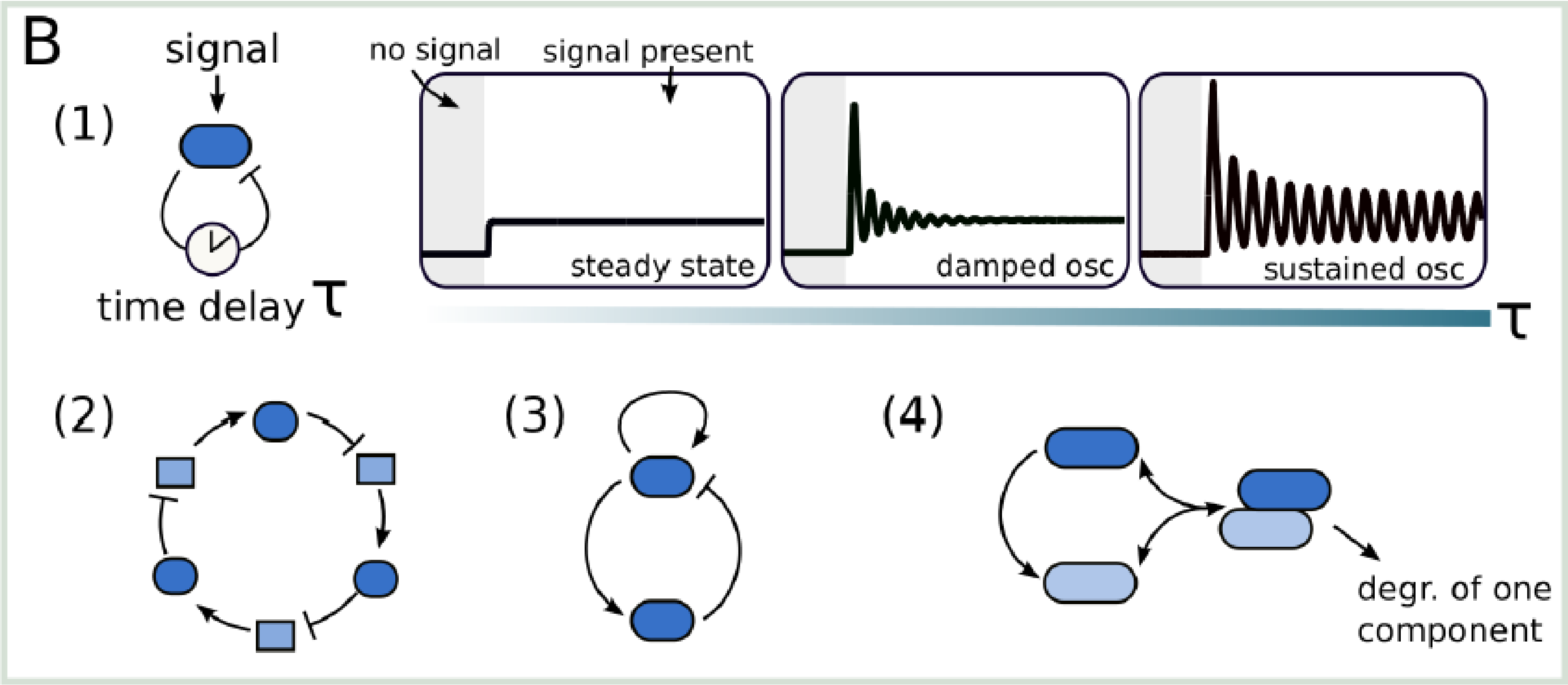


What about biology – many oscillators !

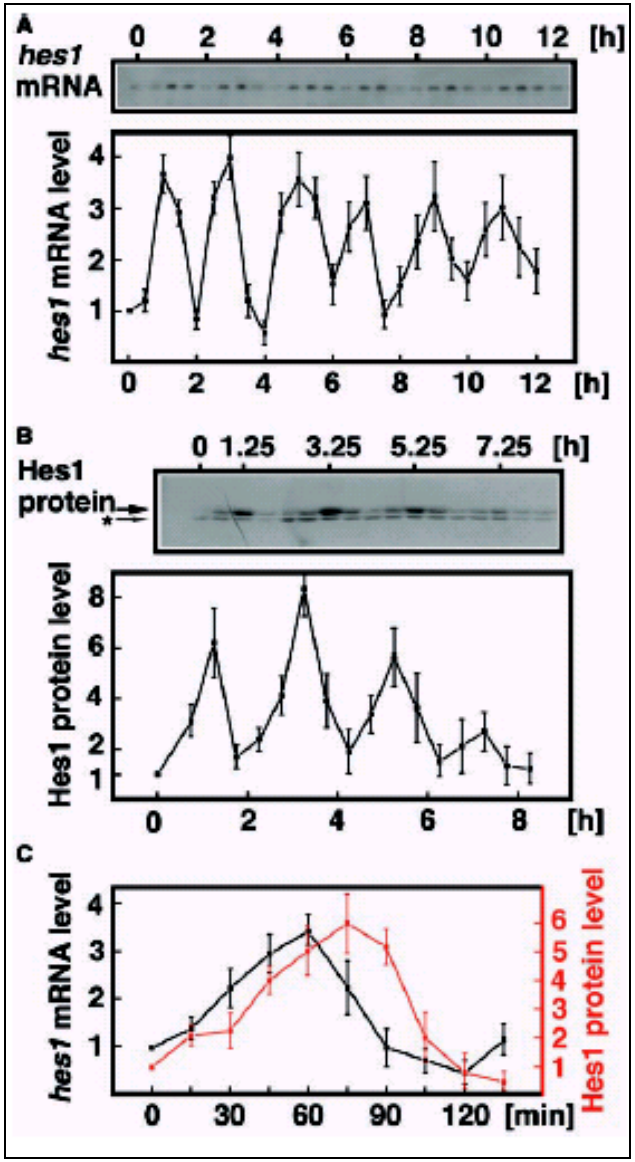
- Cell cycles
- Circadian clocks
- Calcium oscillators
- Embryos
- Pace maker cells
- Protein oscillations (DNA damage)
- Population dynamics

Basic oscillator: Negative Feed-Back loops:



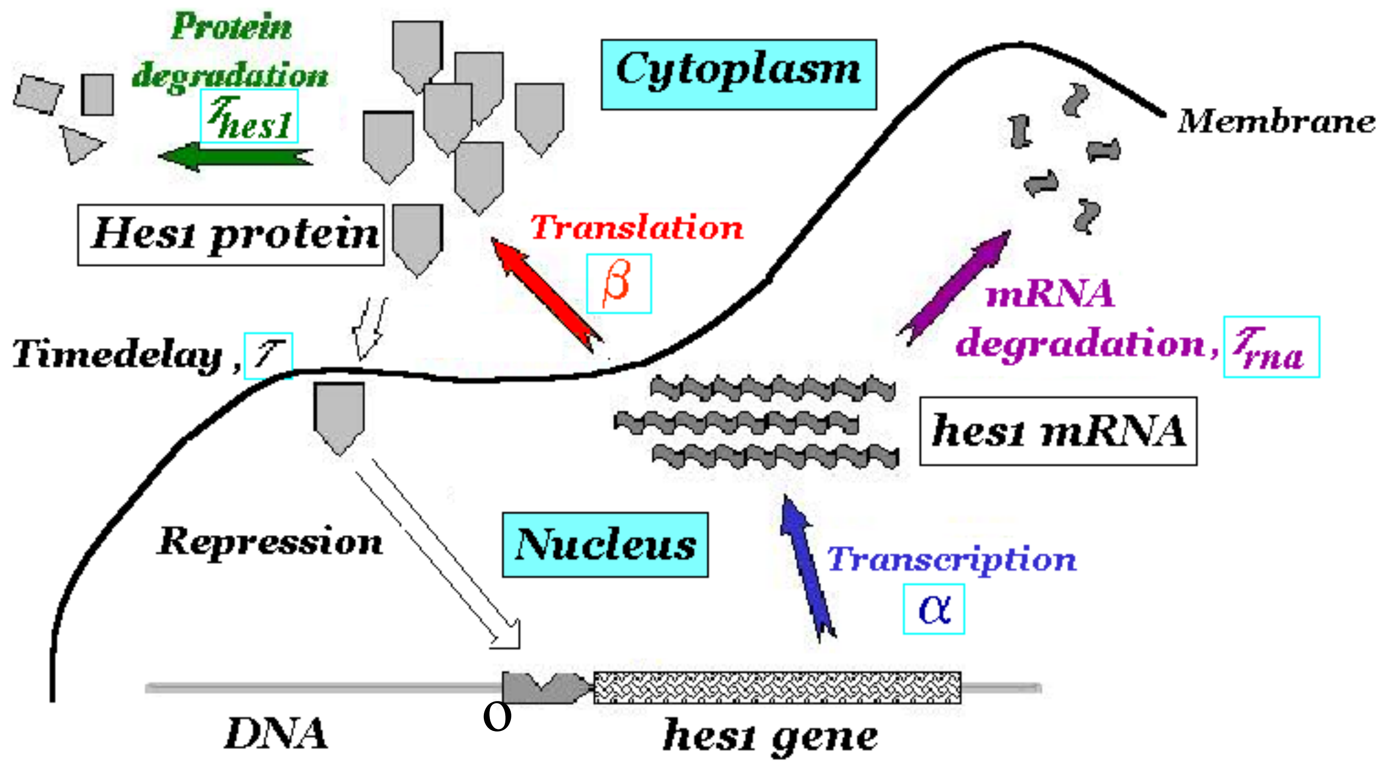


‘Typical’ Oscillating data: Hes1 - segmentation



(Hirata et al, 2002)

Simplest negative feed-back loop: Hes1



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

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

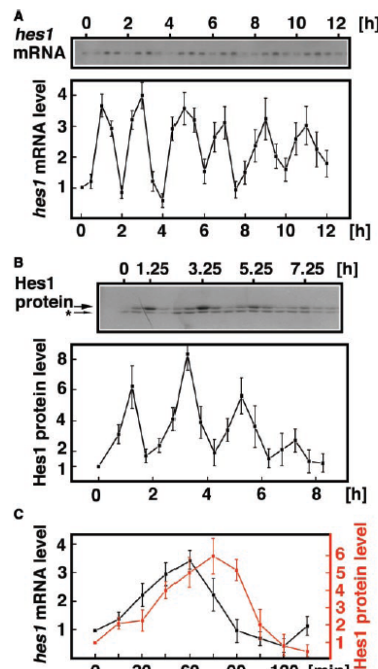
Jensen et al 2003

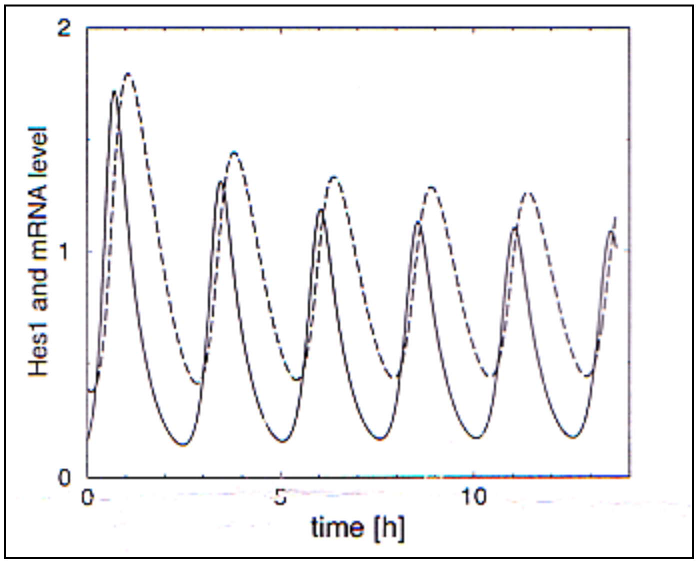
$$\frac{d[mRNA]}{dt} = \alpha \cdot \frac{K_M}{K_M + [Hes1(t-\tau)]^n} - \frac{[mRNA(t)]}{\tau_{rna}}$$

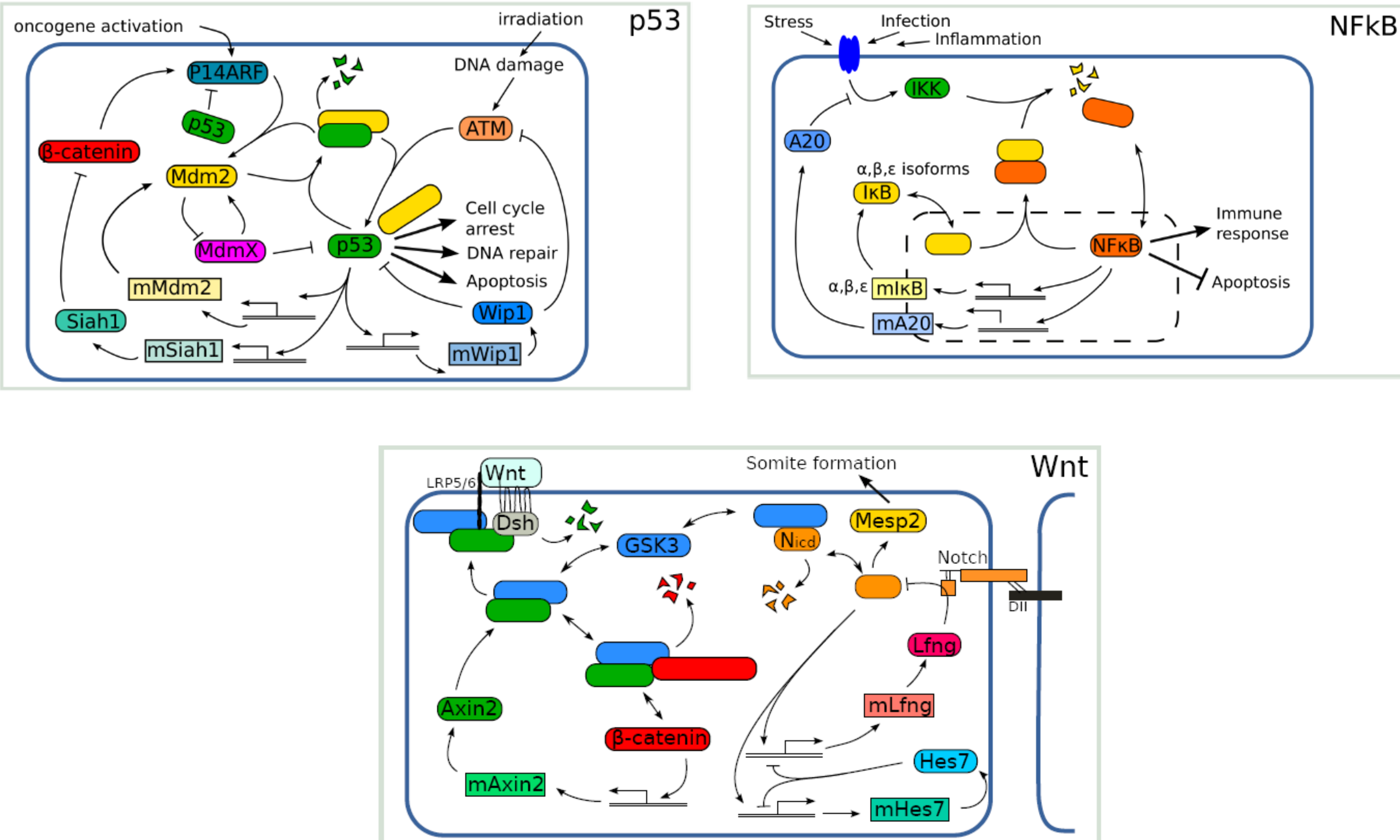
$$\frac{d[Hes1]}{dt} = \beta \cdot [mRNA(t)] - \frac{[Hes1(t)]}{\tau_{hes1}}$$

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

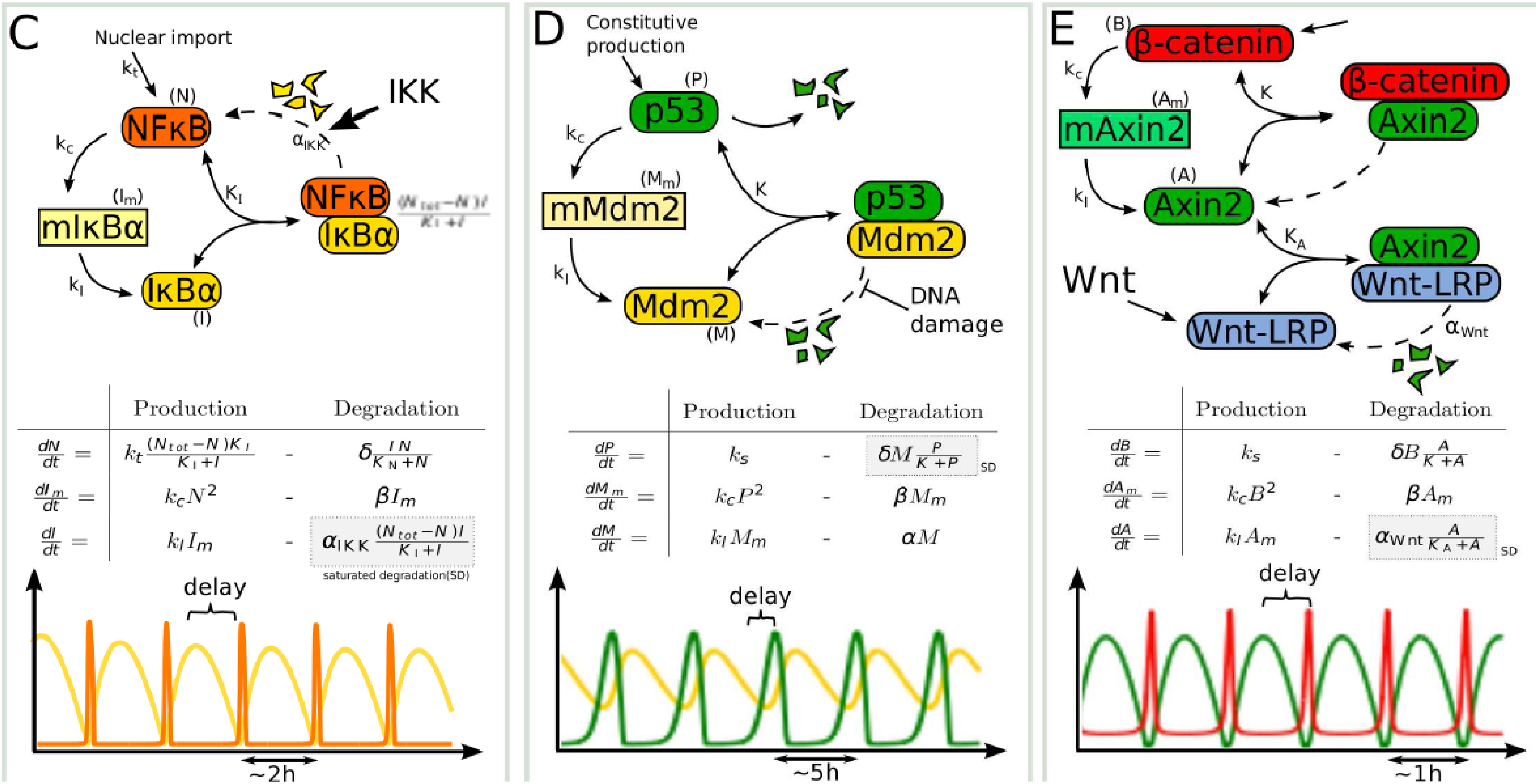
- τ_{rna} = 24.1 min
- τ_{hes1} = 22.3 min
- τ = 24 min
- α = 20 $[R]_0$ min^{-1}
- β = 1/20 min^{-1}
- $K_M = (0.1[R]_0)^n$
- n = 4



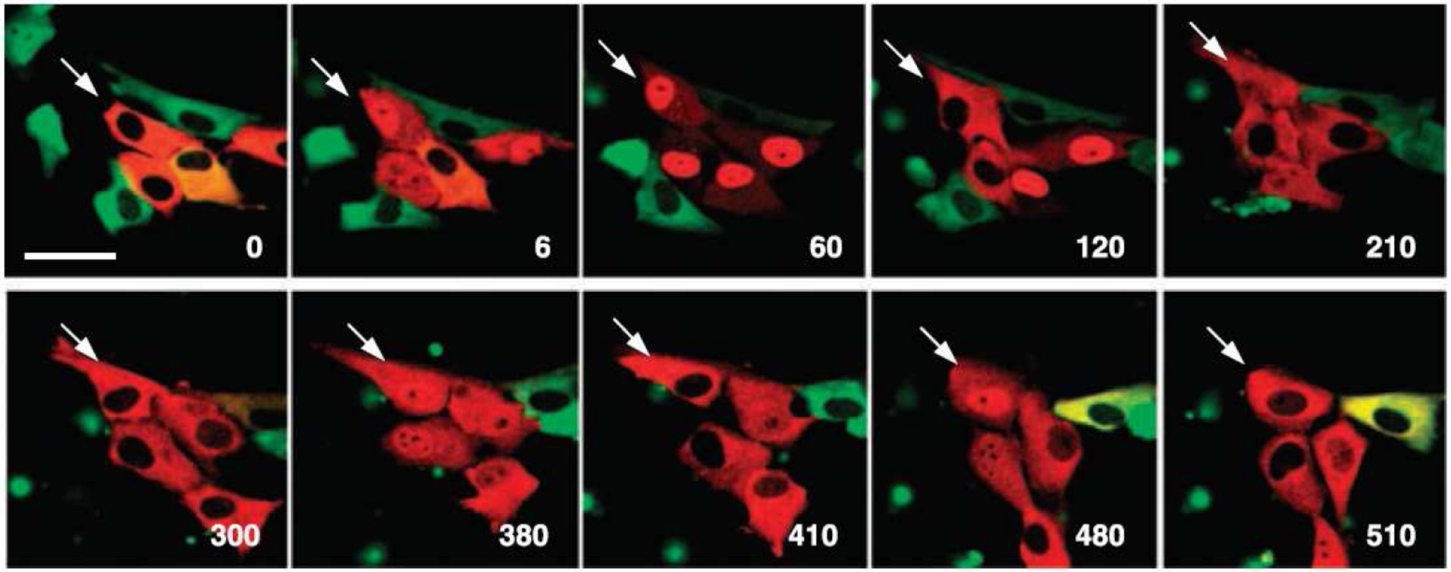




p53
oncogene activation
irradiation
DNA damage
P14ARF
p53
ATM
β-catenin
Mdm2
MdmX
p53
Cell cycle arrest
DNA repair
Apoptosis
mMdm2
Wip1
Siah1
mSiah1
mWip1
NFkB
Stress
Infection
Inflammation
IKK
A20
α,β,ε isoforms
IκB
NFκB
Immune response
Apoptosis
α,β,ε mIκB
mA20
Wnt
Somite formation
Wnt
LRP5/6
Dsh
GSK3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


C
Nuclear import
NFκB
mIκBα
IκBα
NFκB
IκBα
IKK
Production
Degradation
$\frac{dN}{dt} = k_t \frac{(N_{tot}-N)K_I}{K_I+I} - \delta \frac{IN}{K_N+N}$
$\frac{dI_m}{dt} = k_c N^2 - \beta I_m$
$\frac{dI}{dt} = k_I I_m - \alpha_{IKK} \frac{(N_{tot}-N)I}{K_I+I}$
saturated degradation(SD)
delay
~2h
D
Constitutive production
p53
mMdm2
Mdm2
p53
Mdm2
DNA damage
Production
Degradation
$\frac{dP}{dt} = k_s - \delta M \frac{P}{K+P}$ SD
$\frac{dM_m}{dt} = k_c P^2 - \beta M_m$
$\frac{dM}{dt} = k_I M_m - \alpha M$
delay
~5h
E
β-catenin
mAxin2
Axin2
β-catenin
Axin2
Axin2
Wnt-LRP
Wnt
Wnt-LRP
Production
Degradation
$\frac{dB}{dt} = k_s - \delta B \frac{A}{K+A}$
$\frac{dA_m}{dt} = k_c B^2 - \beta A_m$
$\frac{dA}{dt} = k_I A_m - \alpha_{Wnt} \frac{A}{K_A+A}$ SD
delay
~1h

‘Direct’ observations of oscillations in nucleus



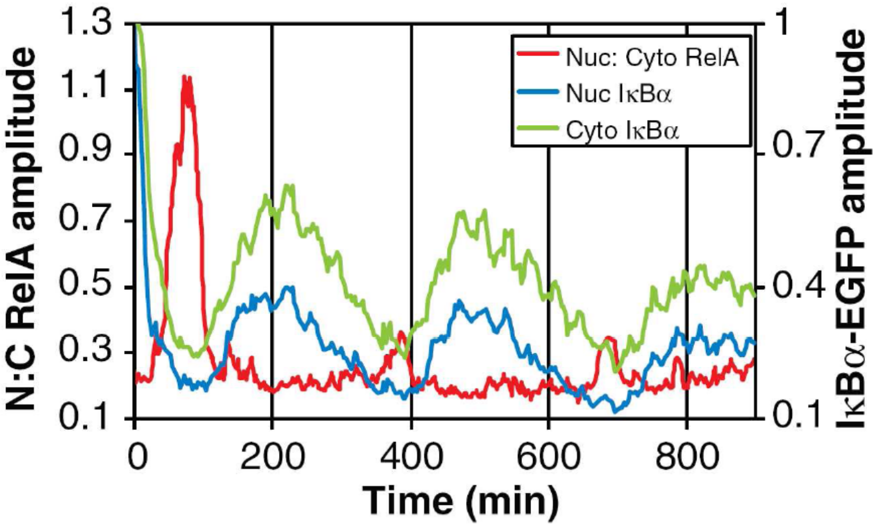
Oscillations in the nuclear localization of an NF-κB transcription factor in human cells

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

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.

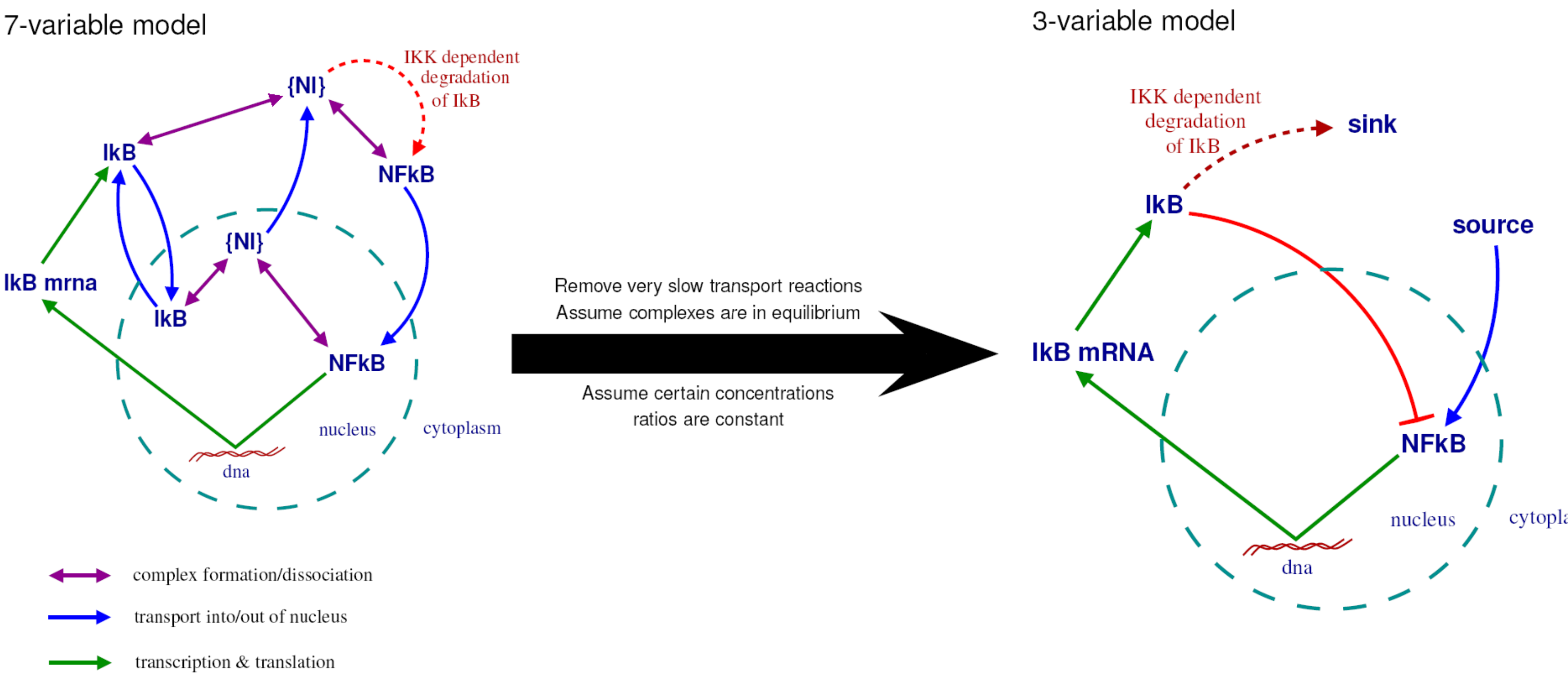
Nelson et al. (2004) Science 306, 704.



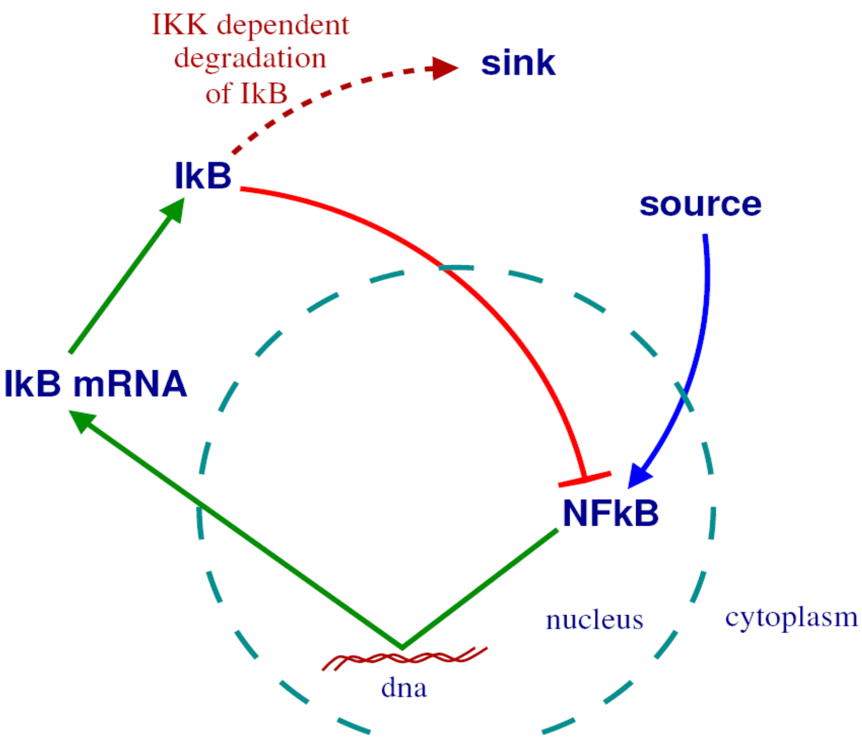
How does the network produce oscillations?

Why does the cell need the oscillations?

Reduction of the NF-κB system



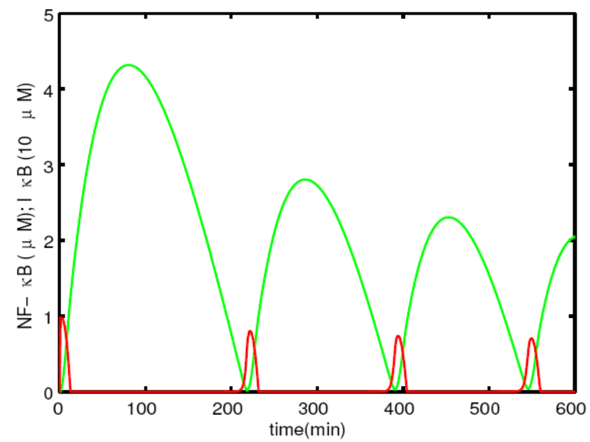
Simple Model for Protein Oscillations



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

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

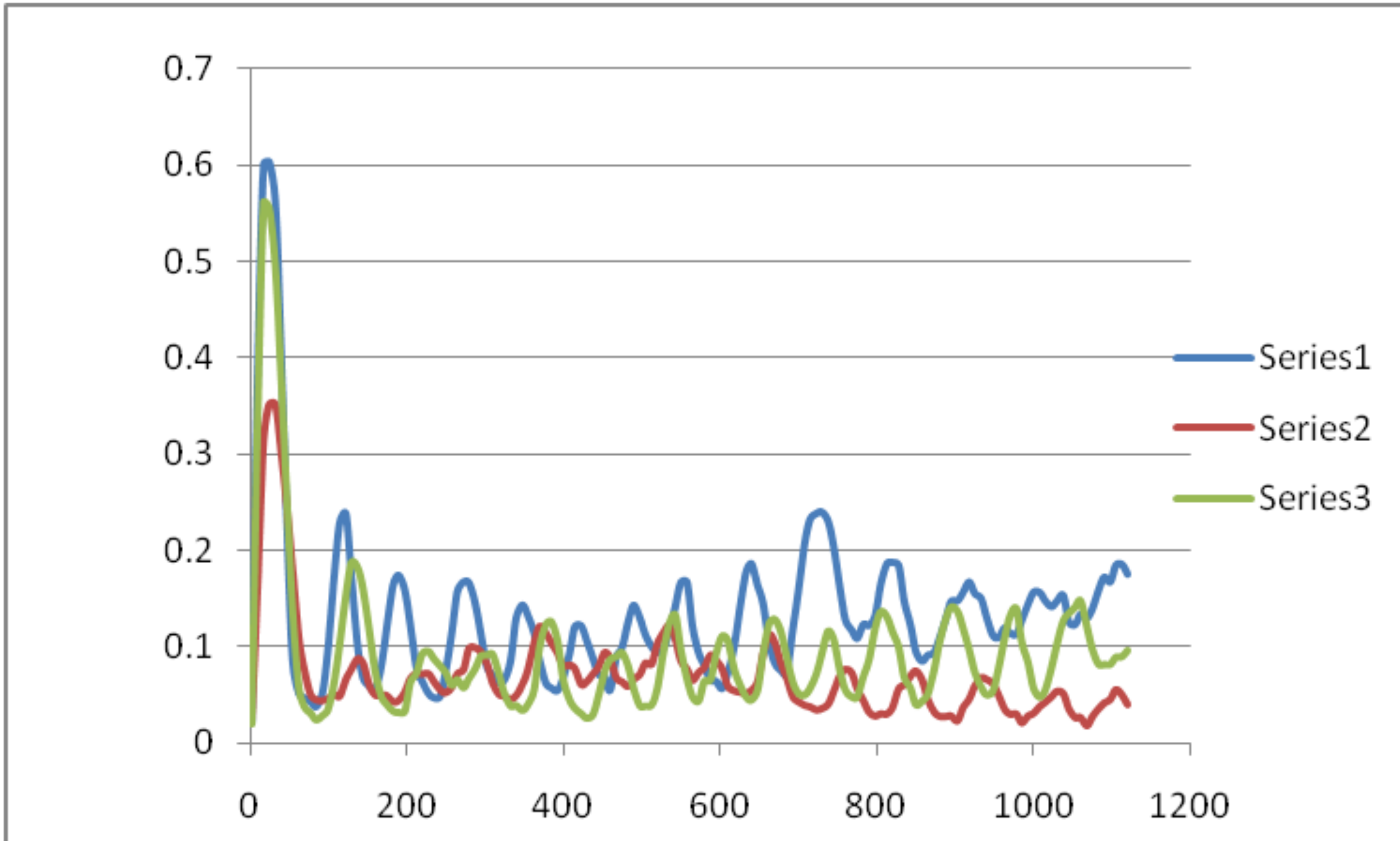
$$\frac{dI}{dt} = I_m - C\frac{(1-N_n)I}{\epsilon + I}.$$



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

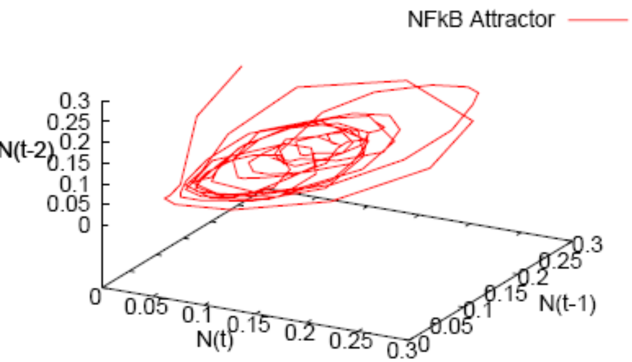
$$\delta = 0.029,\ \epsilon = 2 \times 10^{-5}$$

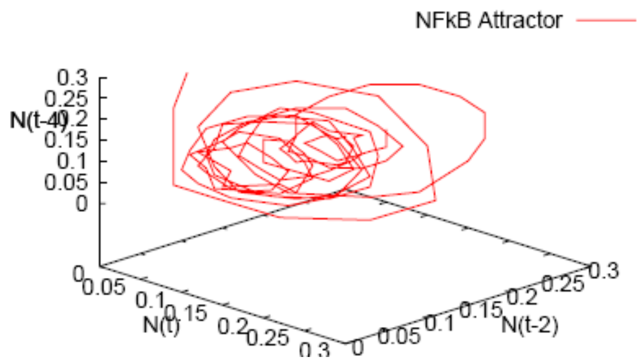
Oscillations of protein densities in a single cell

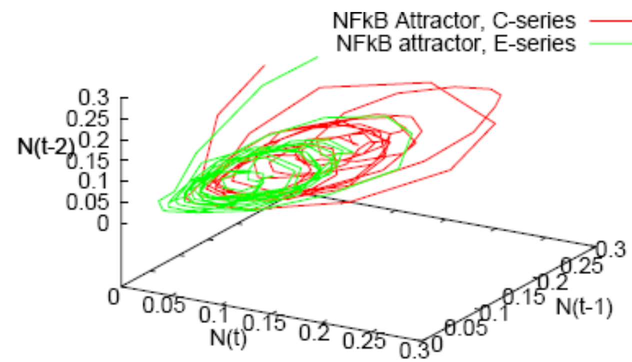


(M. Covert, Stanford, unpublished)
(Savas Tay, Zurich)

Embedded attractors:
Chaos ??







Externally ‘forced’ NF-κB system

External modulation of TNF cytokine signal

→ Transformed into IKK signal (C)

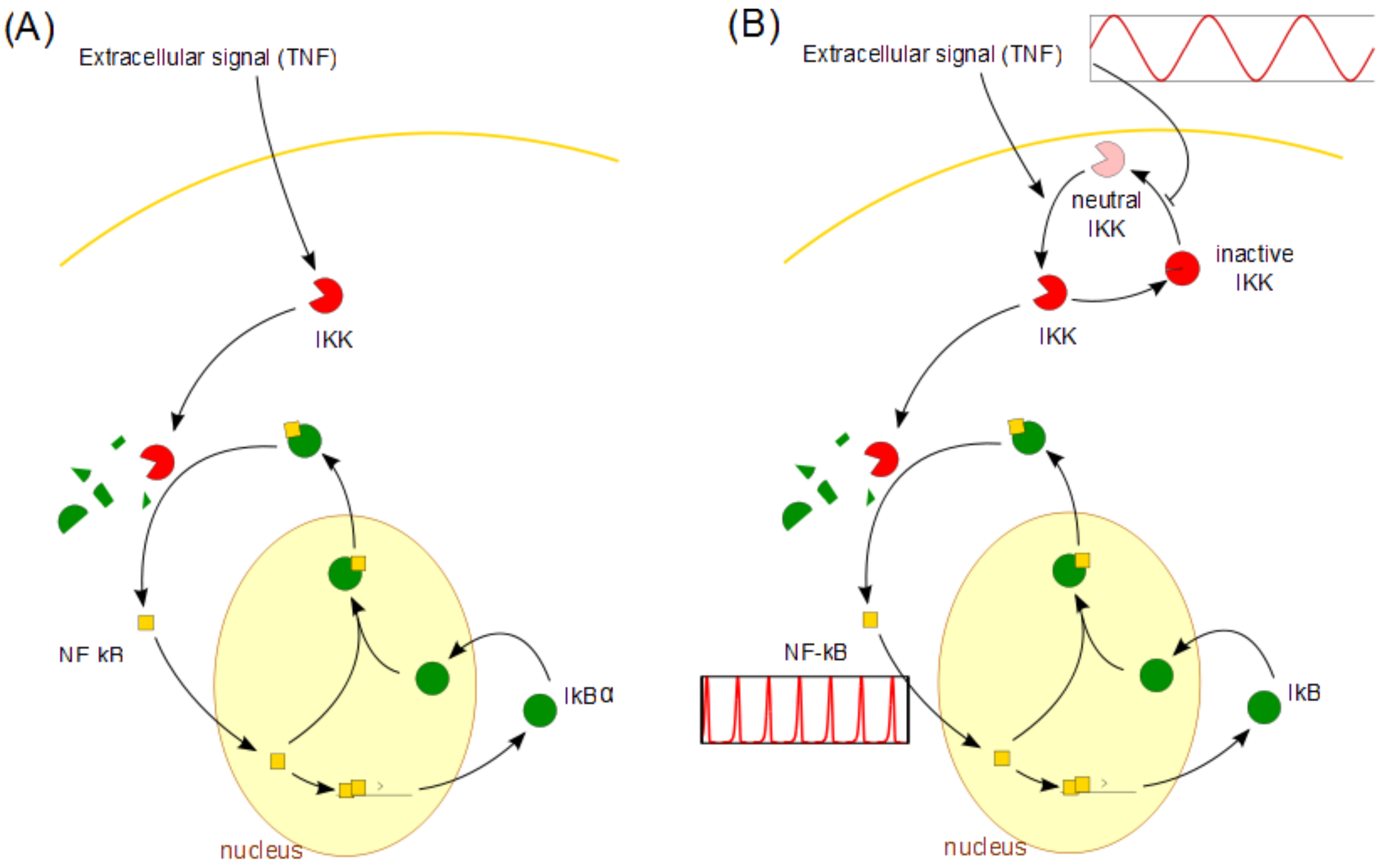
Arnold tongues:

Can synchronize the dynamics of a single cell:

Maybe a way to control DNA damage/DNA repair

(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

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

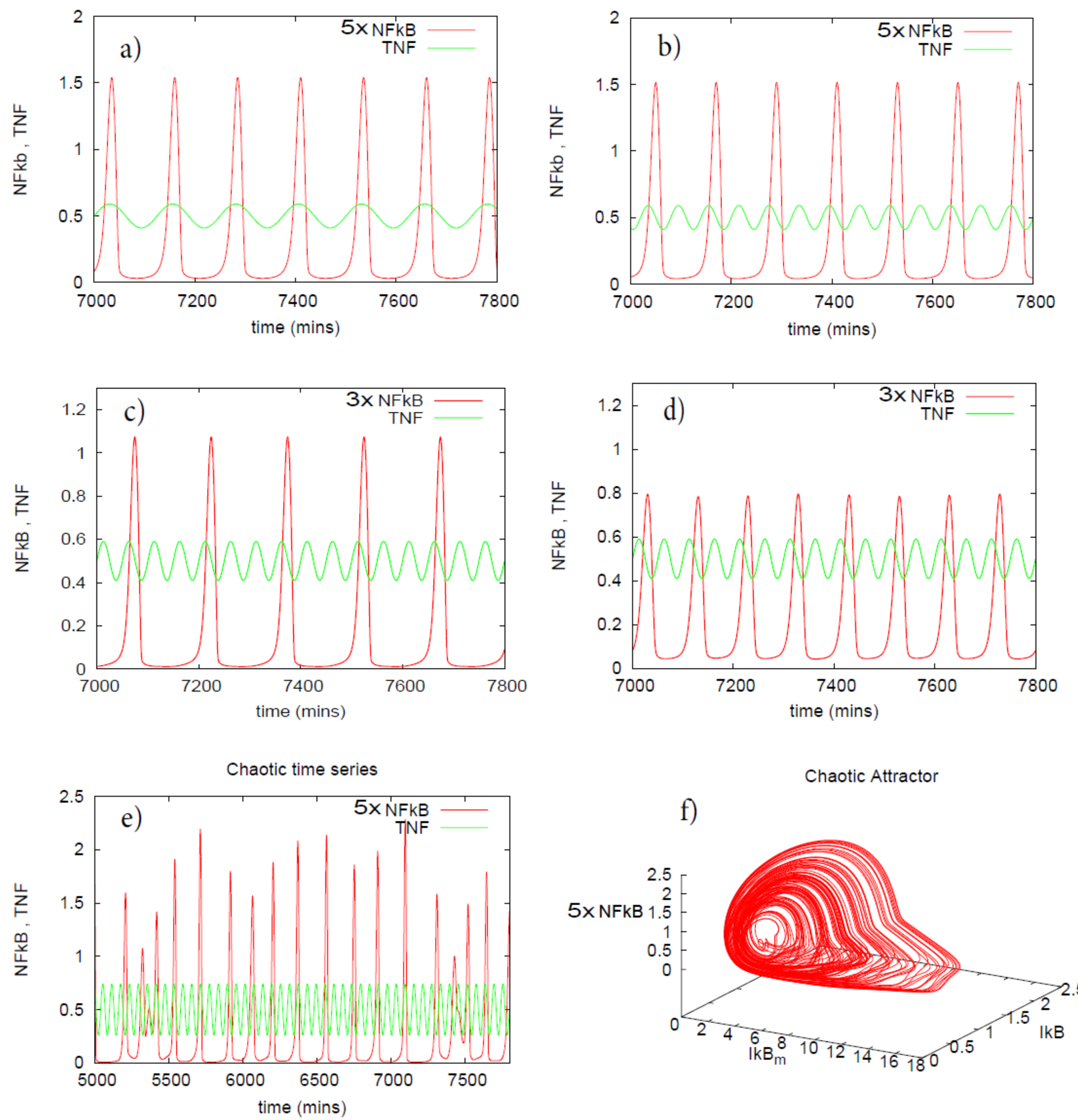
TNF

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

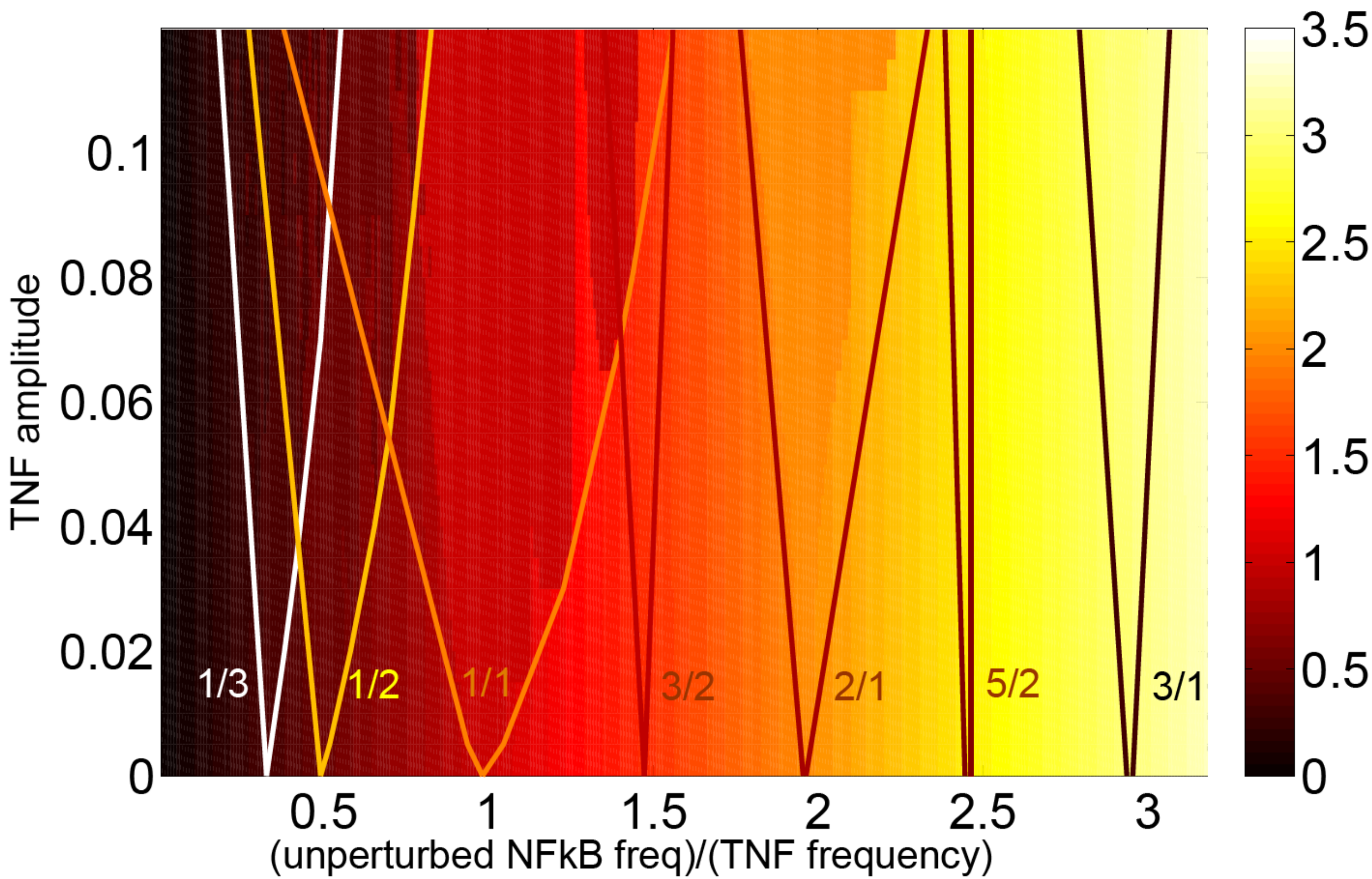
A20

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

Sinusoidal TNF stimulus

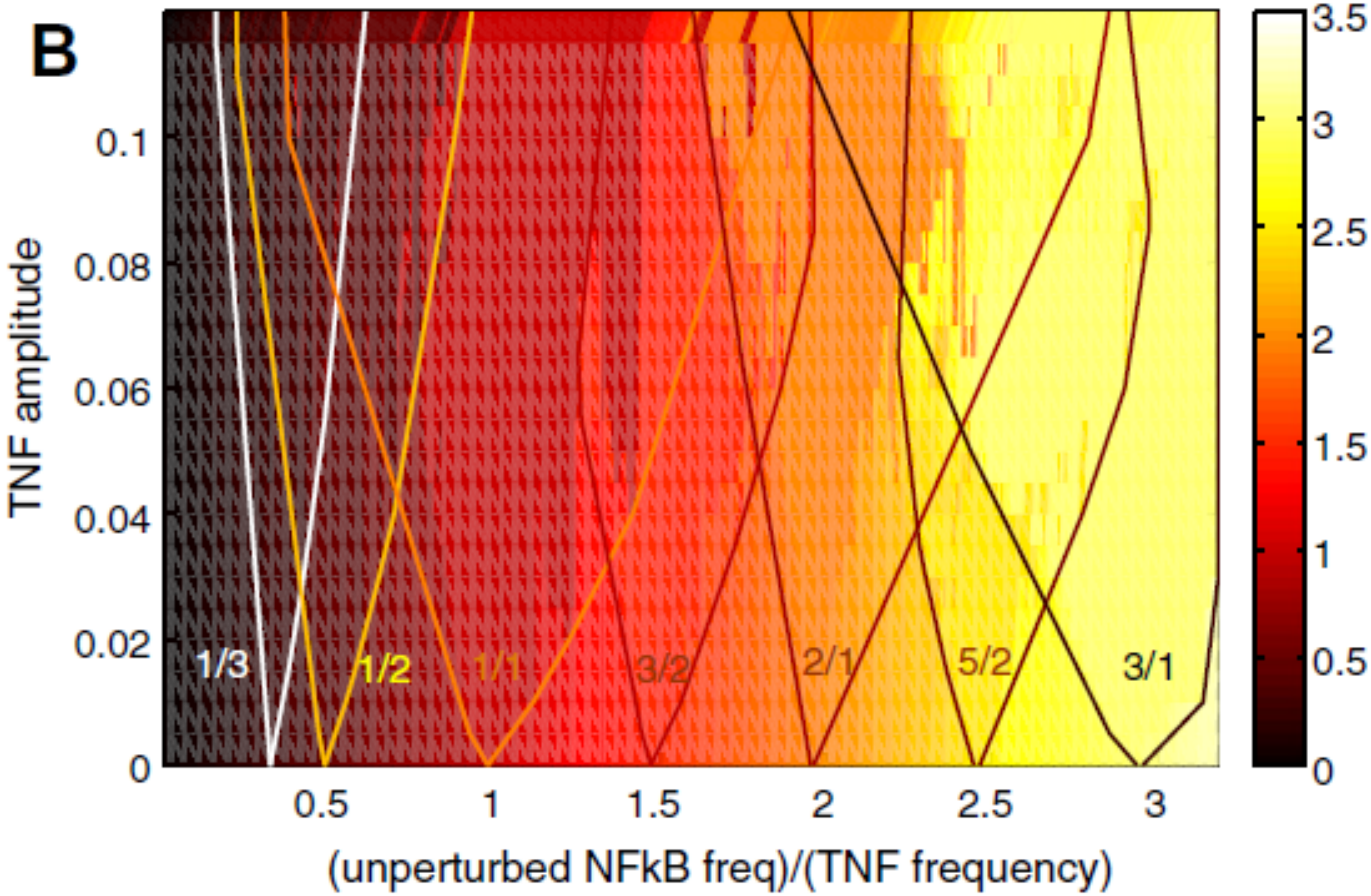


Arnold tongues for NF-kB/TNF system

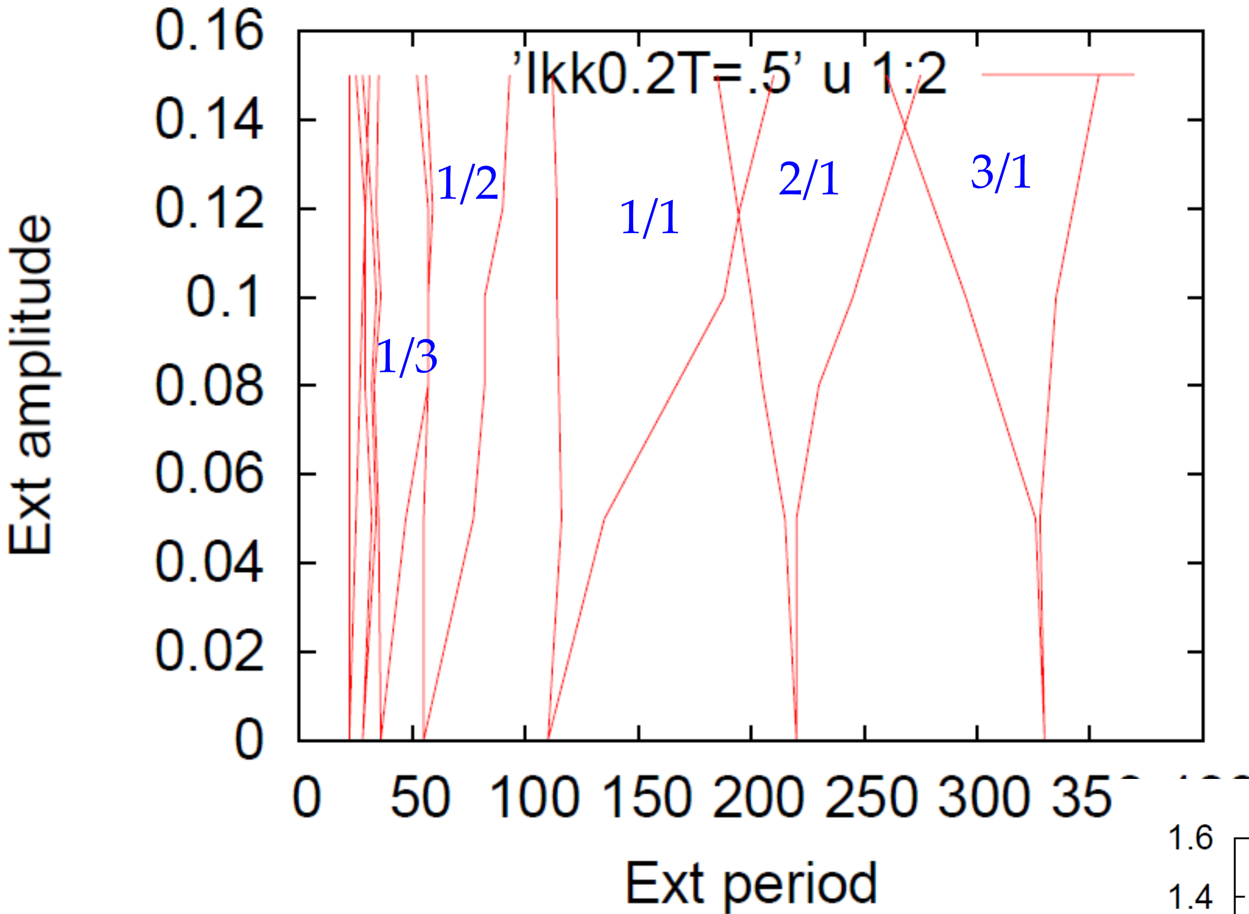


External sine wave

(Savas Tay, Zurich, - several tongues)

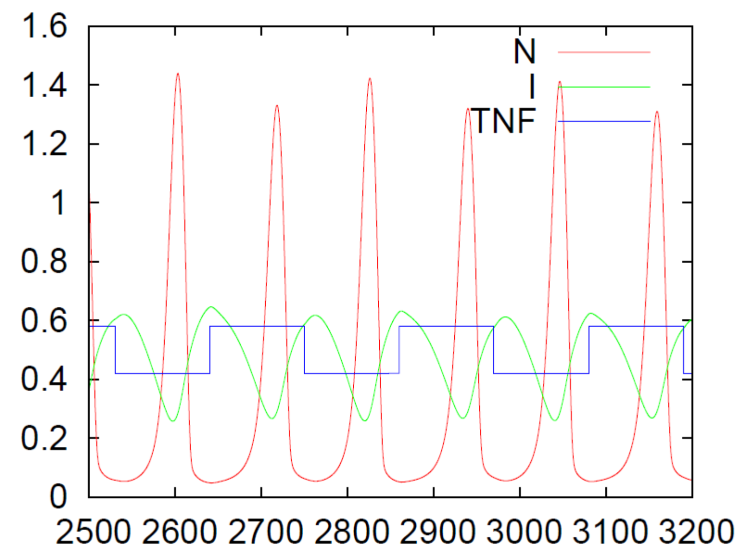


External square wave

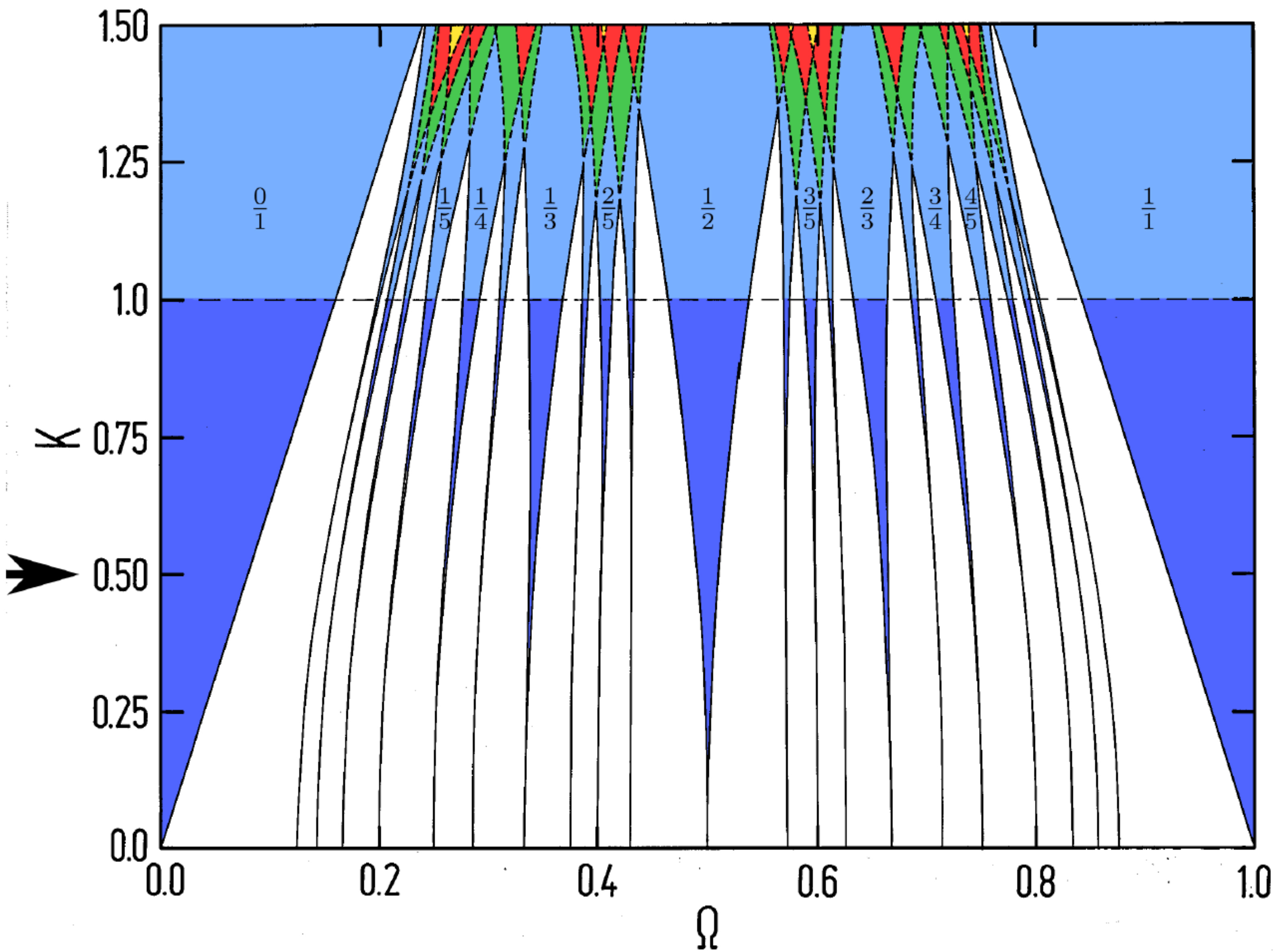


Square external TNF wave

$$
\begin{aligned}
\frac{dN_n}{dt} &= A\frac{(1-N_n)}{\epsilon+I} - B\frac{IN_n}{\delta+N_n}, \\
\frac{dI_m}{dt} &= N_n^2 - I_m, \\
\frac{dI}{dt} &= I_m - C\frac{(1-N_n)I}{\epsilon+I}.
\end{aligned}
$$



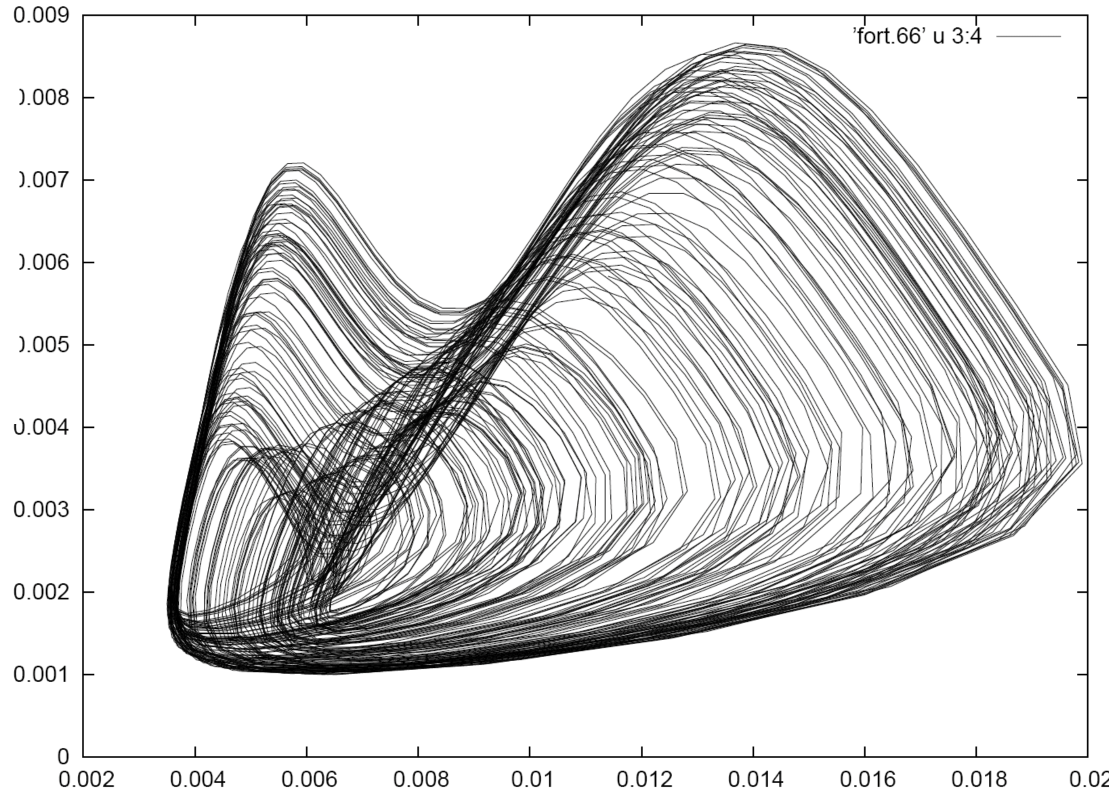
Two coupled oscillators: Arnold tongues



Strange attractor of periodically 'forced' NF-κB system

$$\frac{dN_n}{dt} = A\frac{(1-N_n)}{\epsilon + I} - B\frac{IN_n}{\delta + N_n},$$
$$\frac{dI_m}{dt} = N_n^2 - I_m,$$
$$\frac{dI}{dt} = I_m - C\frac{(1-N_n)I}{\epsilon + I}.$$

$$C \to C(1 + sin2\pi\omega t)$$



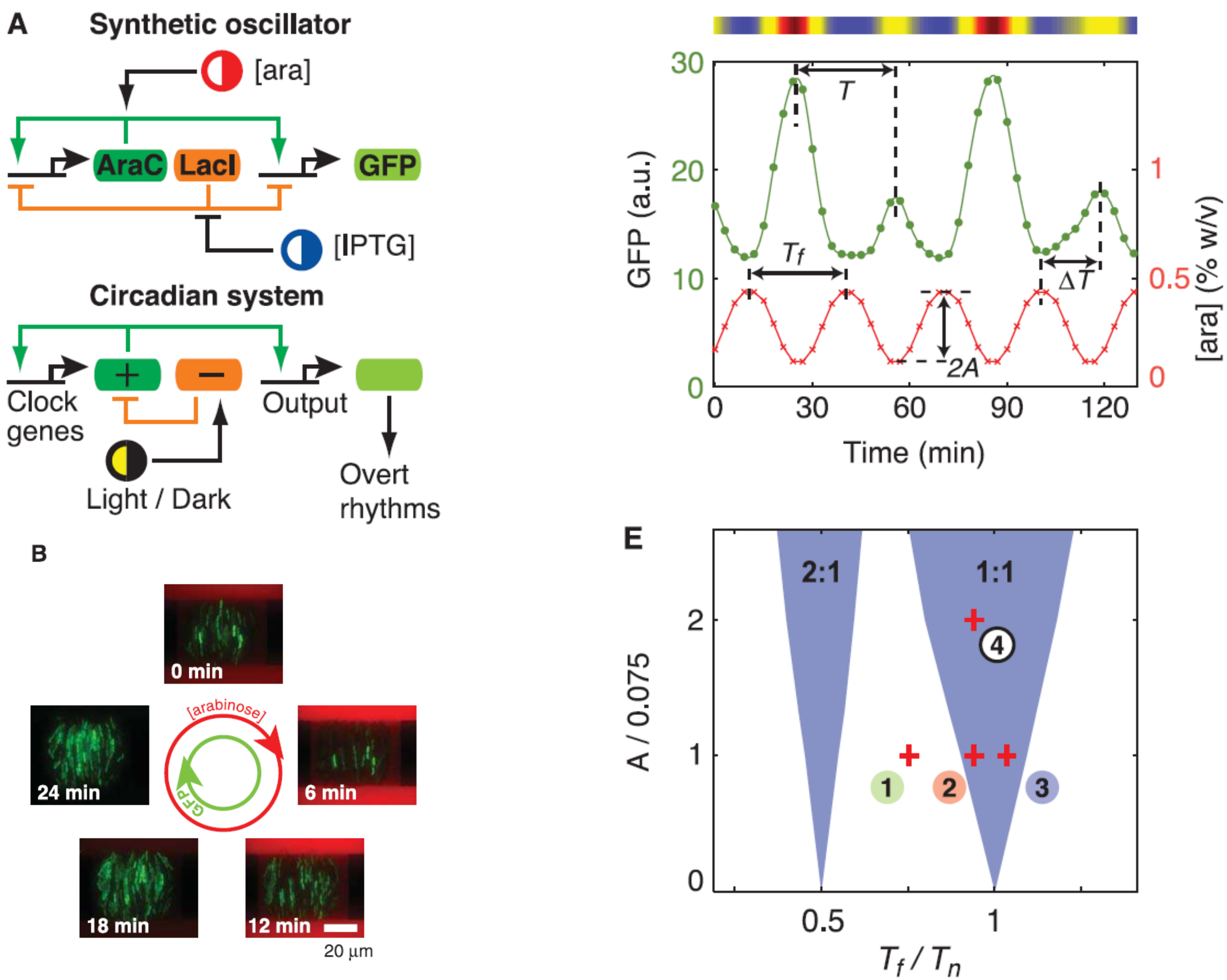
ω=1

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

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

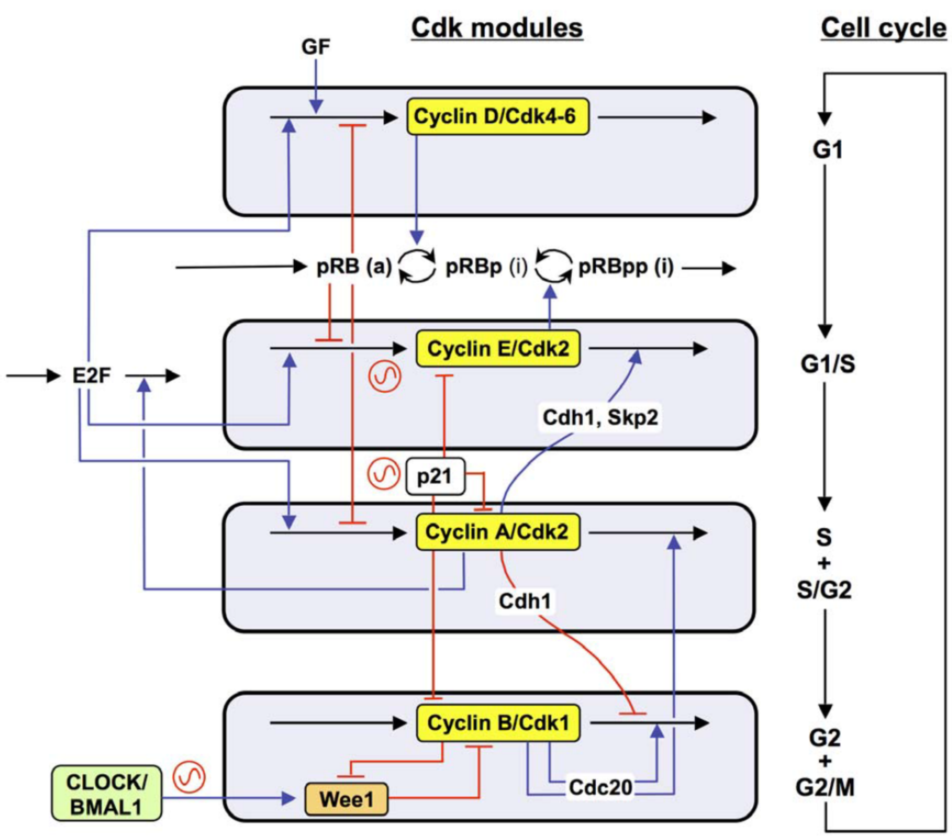
(2-3 hour period)

Populations of genetic oscillators



Jeff Hasty et al, Science 2011

Cell cycle and circadian clock



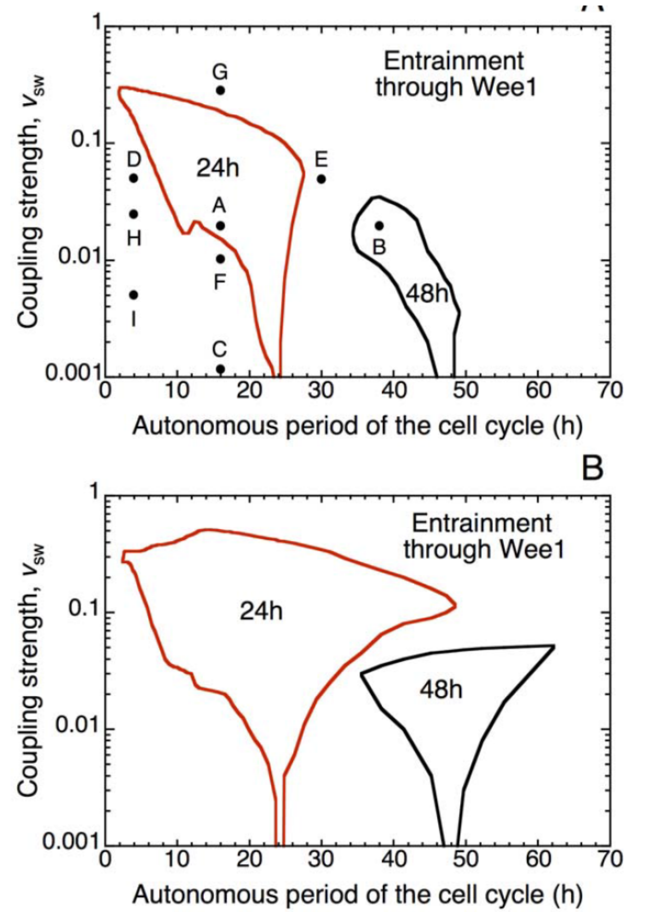
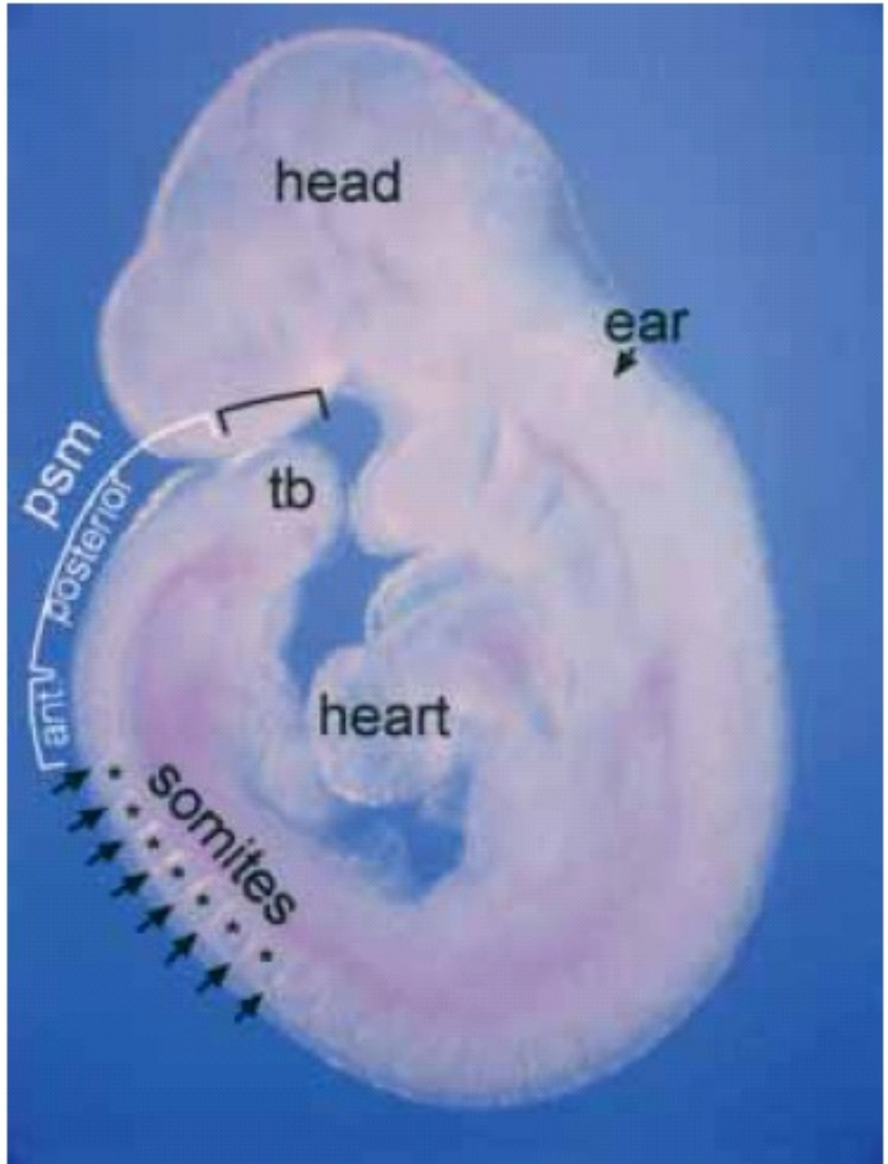
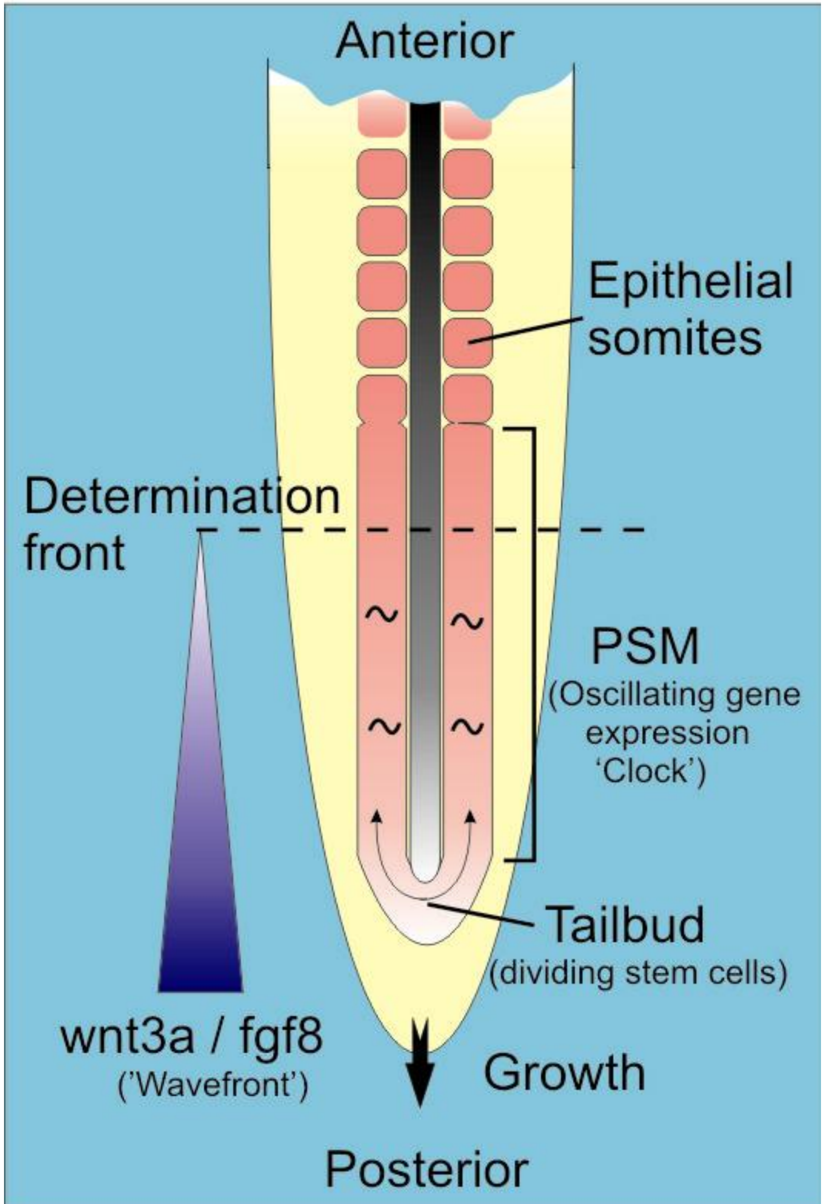


Figure 4. Domains of entrainment of the cell cycle by the circadian clock via circadian control of the kinase Wee1. The

Gerard and Goldbeter, May, 2012


head
ear
psm
posterior
ant
tb
heart
somites



A clock and wavefront

(Cooke and Zeeman 1976)

The presomitic mesoderm (PSM) segments anterior-posterior as somites bud off from the anterior end

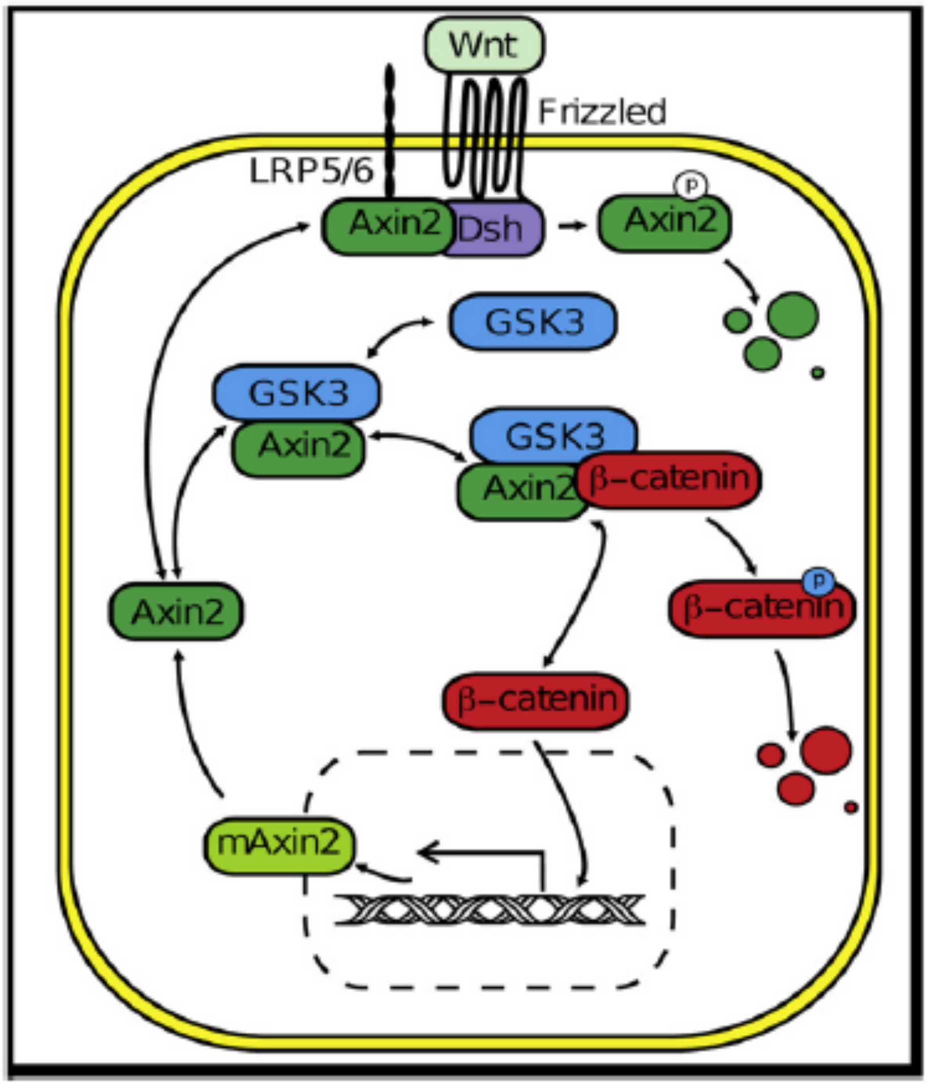
Dividing stem cells in the tailbud supply cells to posterior PSM and elongates the embryo

PSM cells have locally syncronized oscillating expression patterns with periods matching somite formation (90 min in chick) – **Clock**

A morphogen gradient (**Wavefront**) determines onset of segmentation program

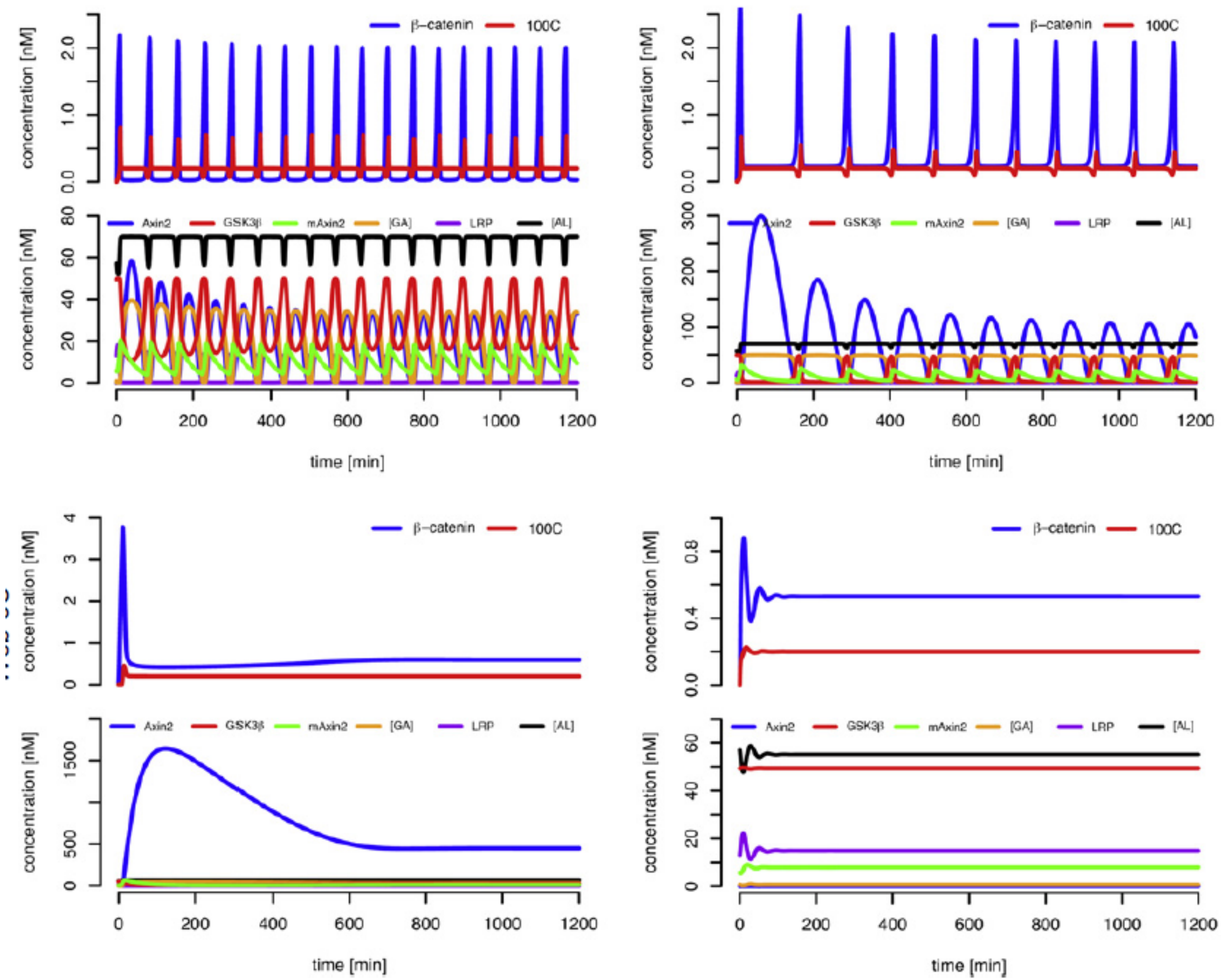
Clock determines susceptibility to **wavefront**, which ensures groupwise incorporation into somites

The Wnt systems



Goldbeter, Pourquie

P. B. Jensen, L. Pedersen, S. Krishna, MHJ, Biophys. Journ (2010)



β−catenin
100C
concentration [nM]
0.0
1.0
2.0
Axin2
GSK3β
mAxin2
[GA]
LRP
[AL]
0
20
40
60
80
0
200
400
600
800
1000
1200
time [min]
β−catenin
100C
concentration [nM]
0.0
1.0
2.0
Axin2
GSK3β
mAxin2
[GA]
LRP
[AL]
0
100
200
300
time [min]
β−catenin
100C
concentration [nM]
0
1
2
3
4
Axin2
GSK3β
mAxin2
[GA]
LRP
[AL]
0
500
1500
time [min]
β−catenin
100C
concentration [nM]
0.0
0.4
0.8
Axin2
GSK3β
mAxin2
[GA]
LRP
[AL]
0
20
40
60
time [min]

External periodic variation of Wnt:

$$\frac{dB}{dt} = k_s - \delta B \frac{A}{K + A},$$

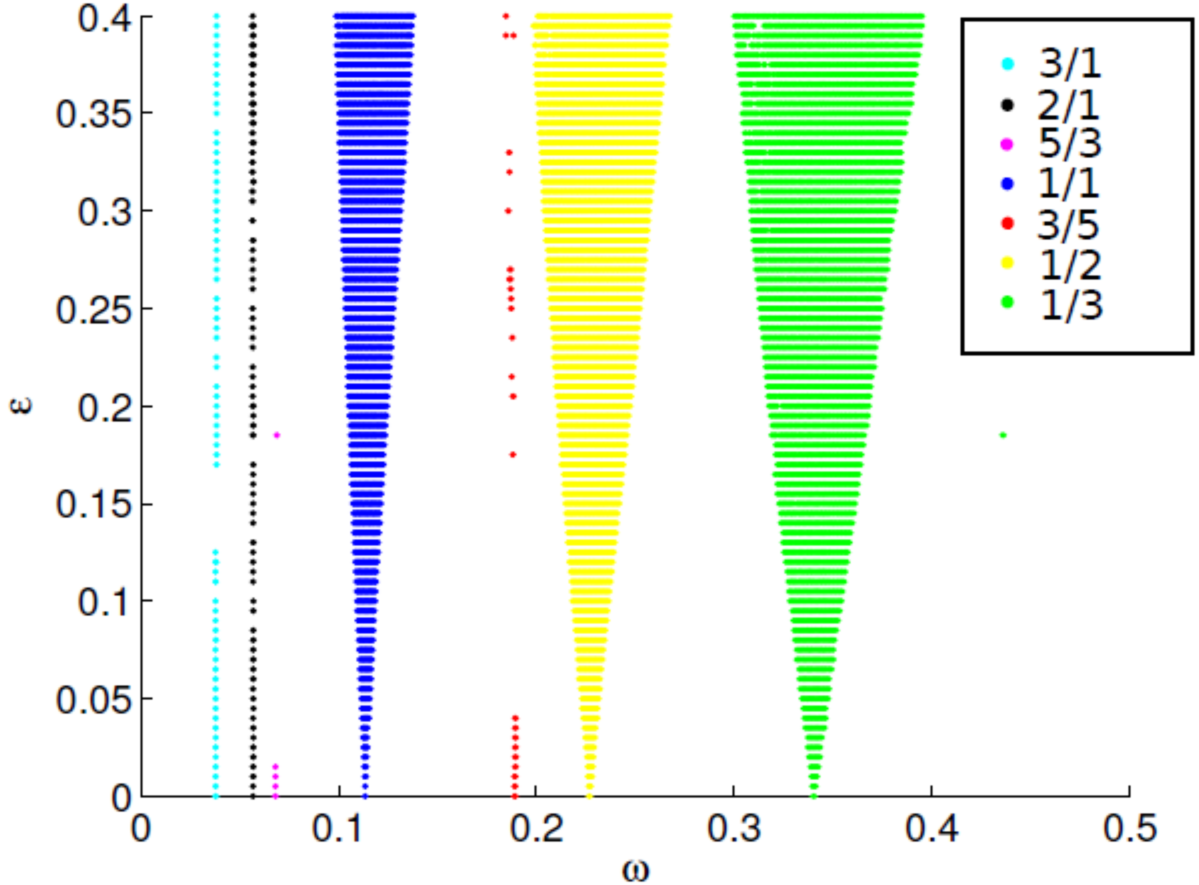
$$\frac{dA_m}{dt} = k_c B^2 - \beta A_m,$$

$$\frac{dA}{dt} = k_l A_m - (1 + \epsilon \cos(\omega t)) \cdot \alpha_{Wnt} \frac{A}{K_A + A} + \epsilon \cos(\omega t).$$

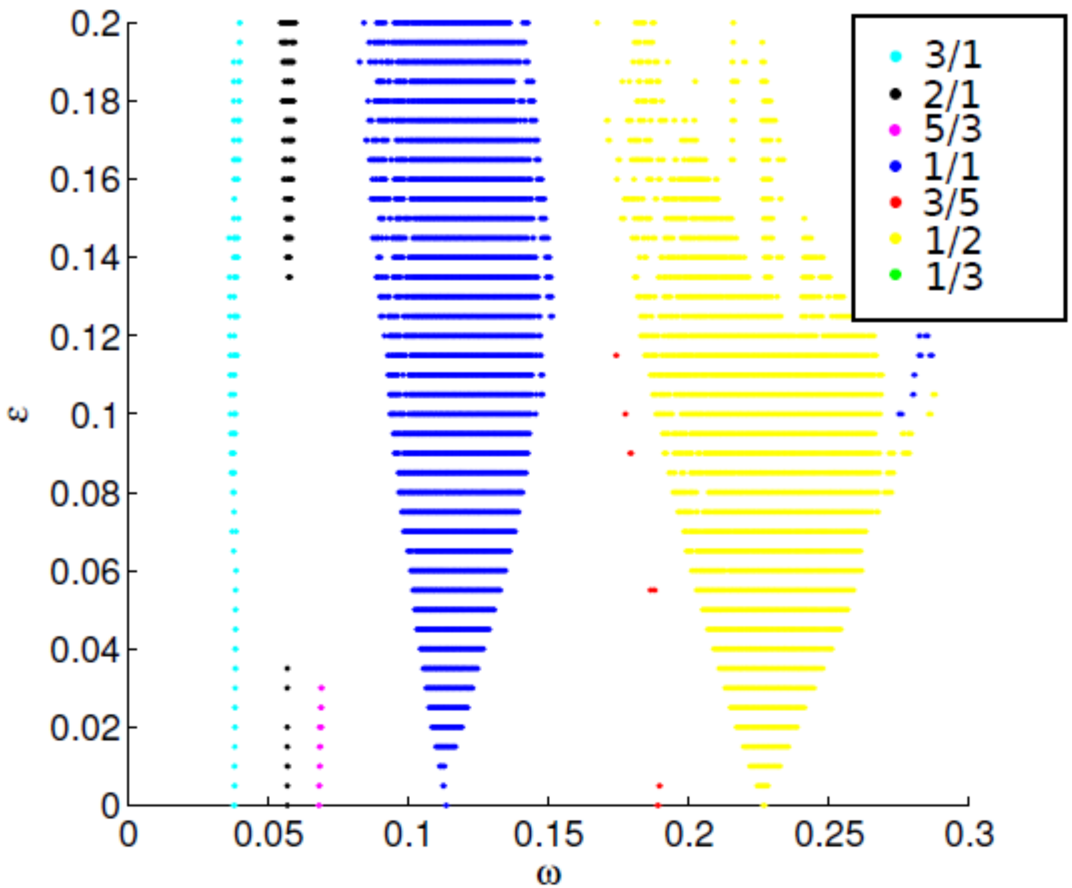
1) Additive
2) Multiplicative (biologically realistic)

(Jonas Juul, prelininary results)

Additive Variation



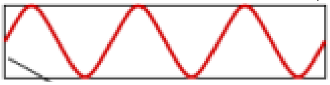
Multiplicative Variation

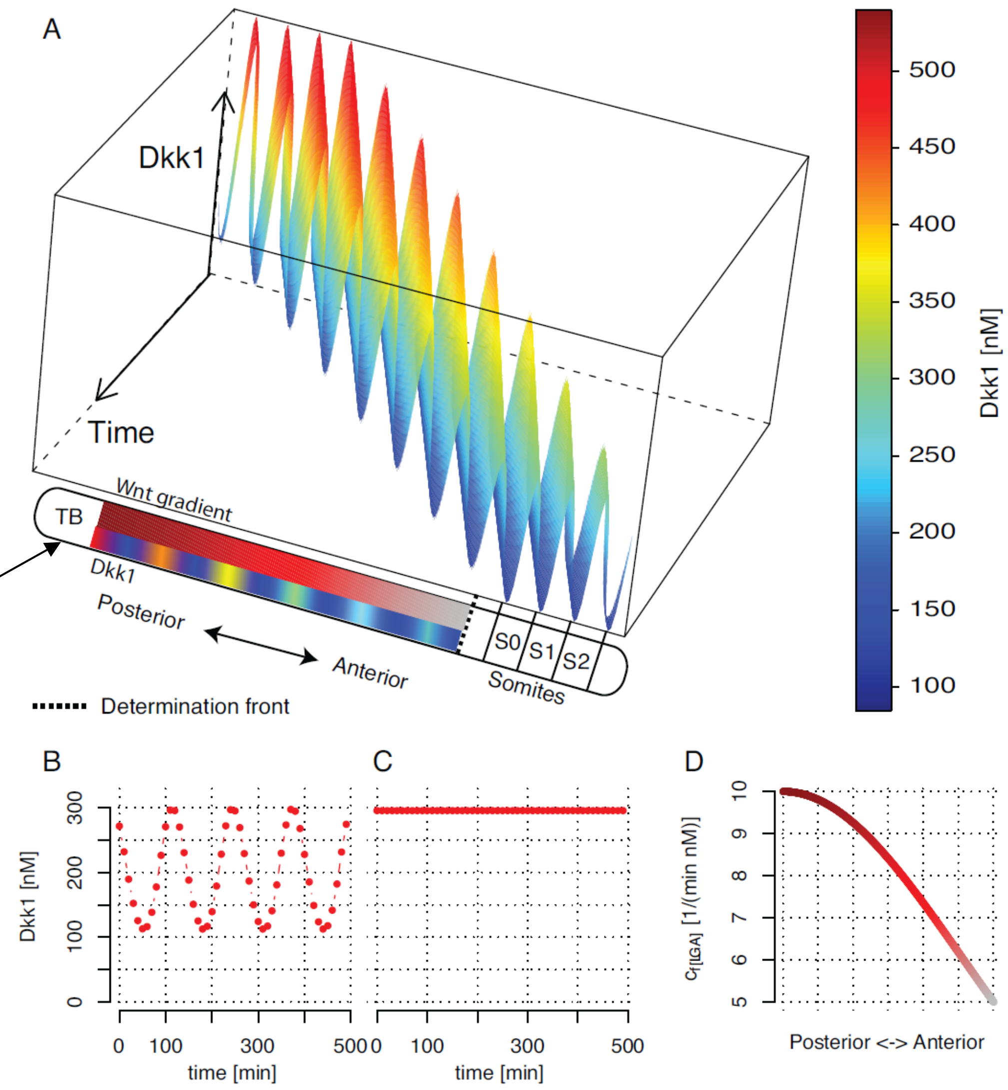


Question: Could the presence of Arnold tongues change periodicity and structure of somites !?

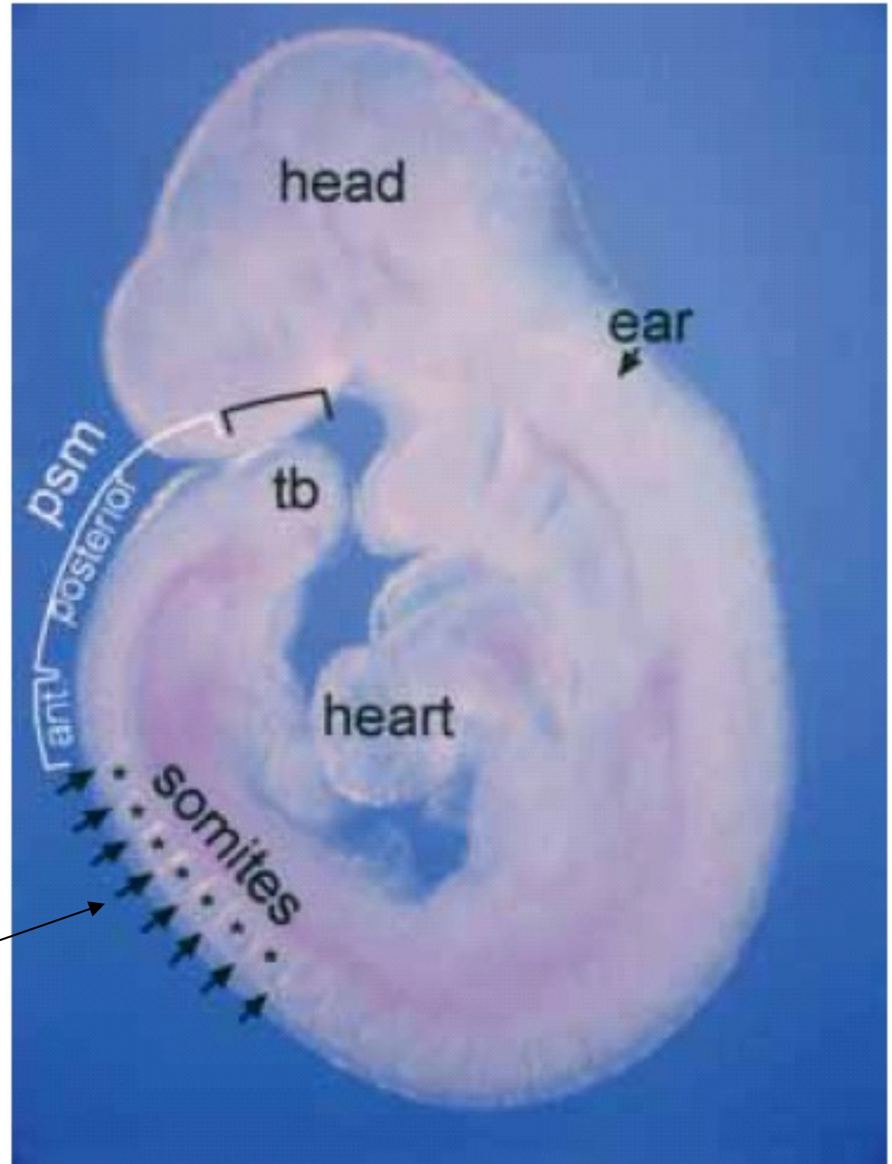
Spatial gradient of Wnt:

External Wnt
oscillation

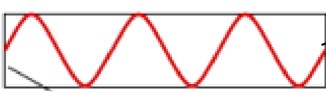




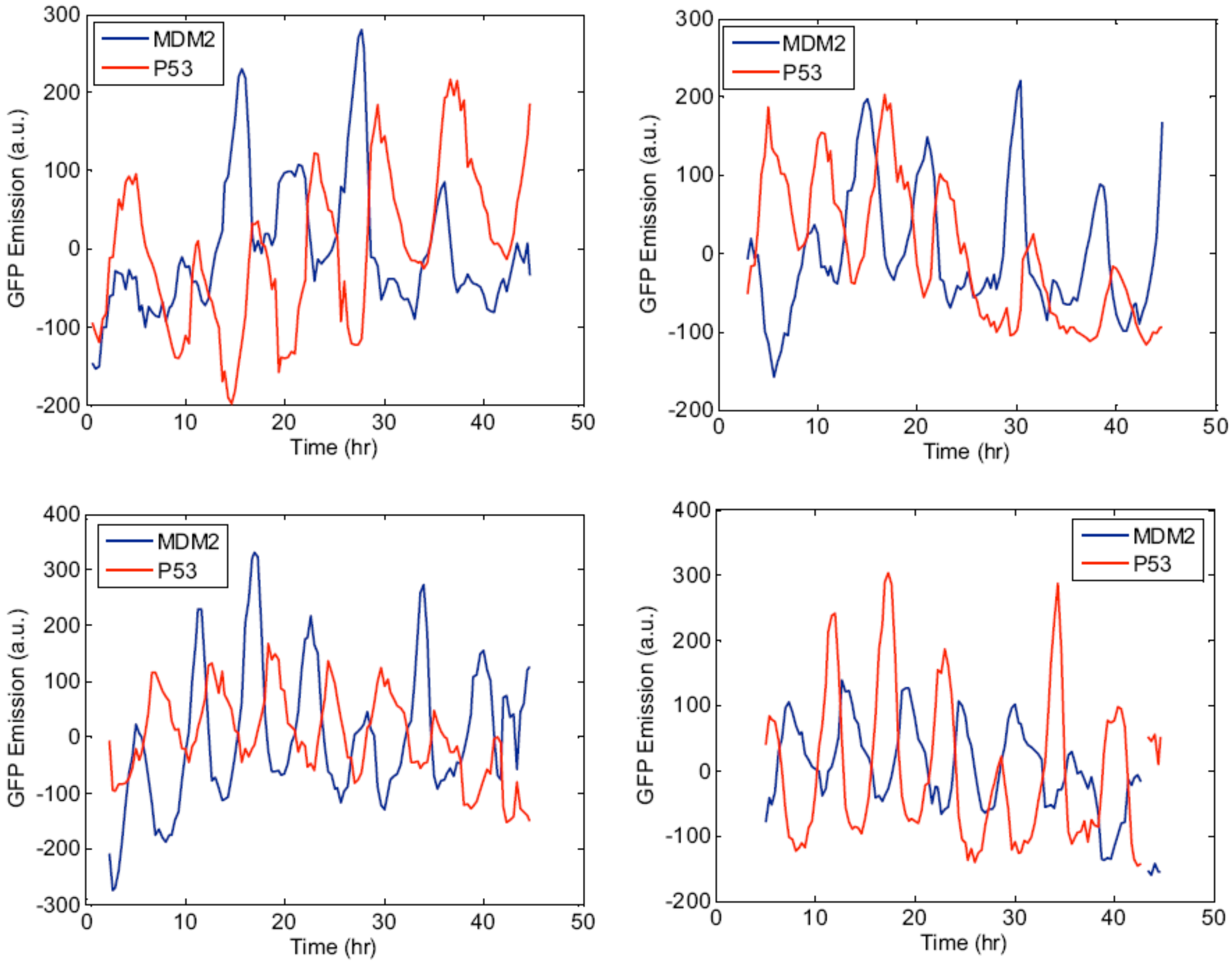
A ‘new’ periodic structure of somites in embryos ?



External Wnt oscillation

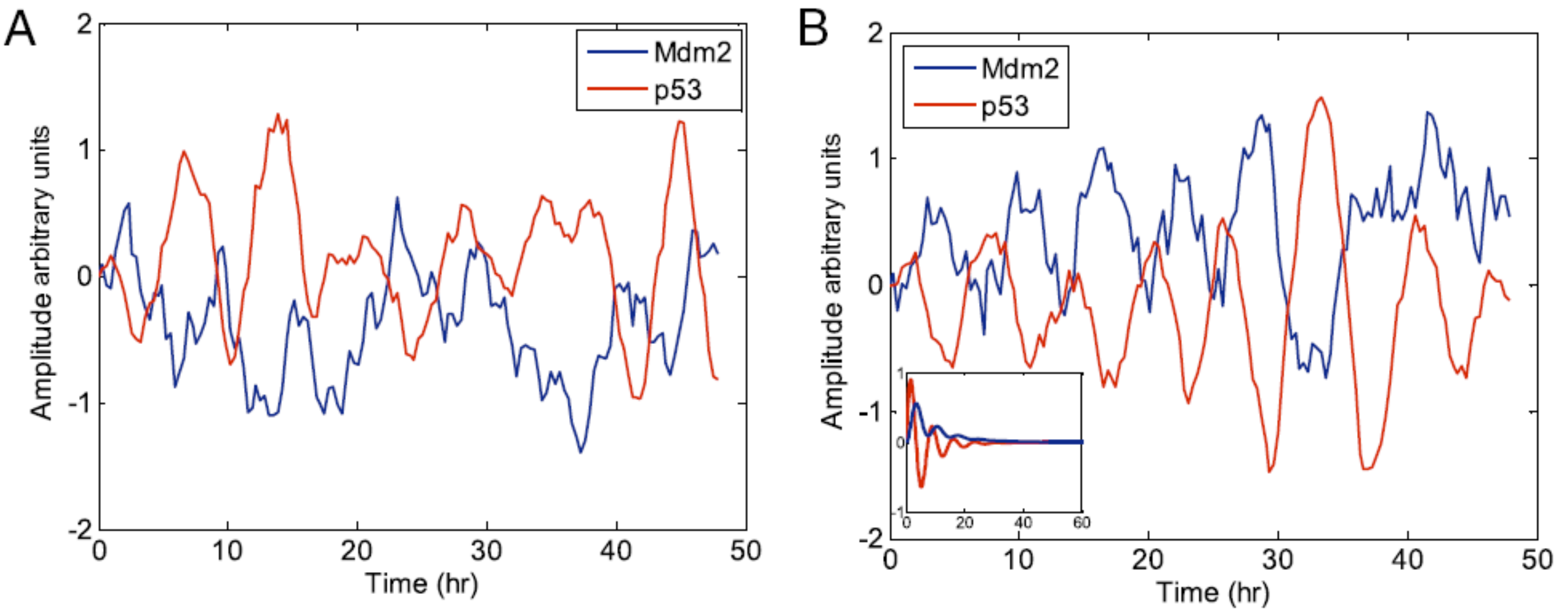


p53 oscillations: Apoptosis



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

Stochastic simulations of linear noise induced model



$$\frac{dx}{dt} = a_{xy}y - a_{xx}x + N_1$$
$$\frac{dy}{dt} = a_{yx}x - a_{yy}y + N_2$$

A_xy = -0.8 ; A_yx = 0.8

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

Linear system: Stable with complex eigenvalues

Noise can induce oscillations !

By applying external oscillation and see if one observed Arnold tongues or not:

Distinguish between linear and non-linear system

(Uri Alon, Namiko Mitarai, MHJ)