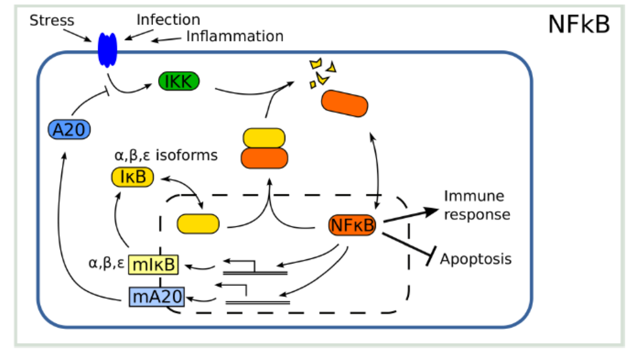
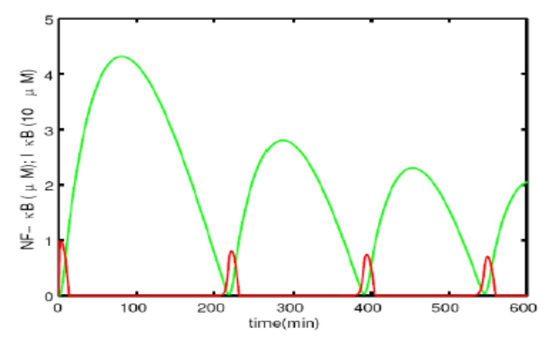
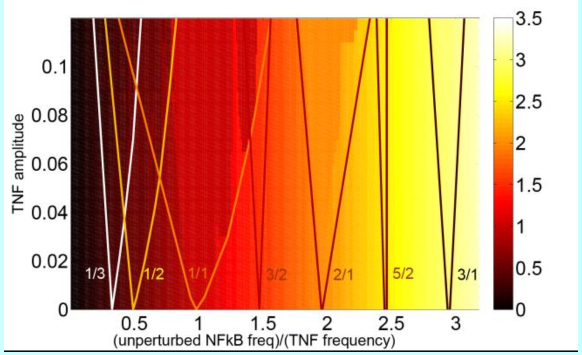
Coupled oscillators in Biology

KIPT, 8 January 2013
Mogens H. Jensen, Niels Bohr Institute







1. **Two oscillators couple:**

   One internal to one external:

   Arnold tongues !

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

3. NF-κB, p53, Wnt systems: Protein oscillations regulated by negative feed-back loops:

inflammation , apoptosis, segmentation.

4. An external (cytokine) oscillations coupled to internal oscillations: Oscillations synchronize →

Arnold tongues → Chaotic attractors

5. Pulsatile extracellular signalling:

A way to control cell dynamics ?

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

Occurrences of Arnold tongues ?

Collaborators:

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

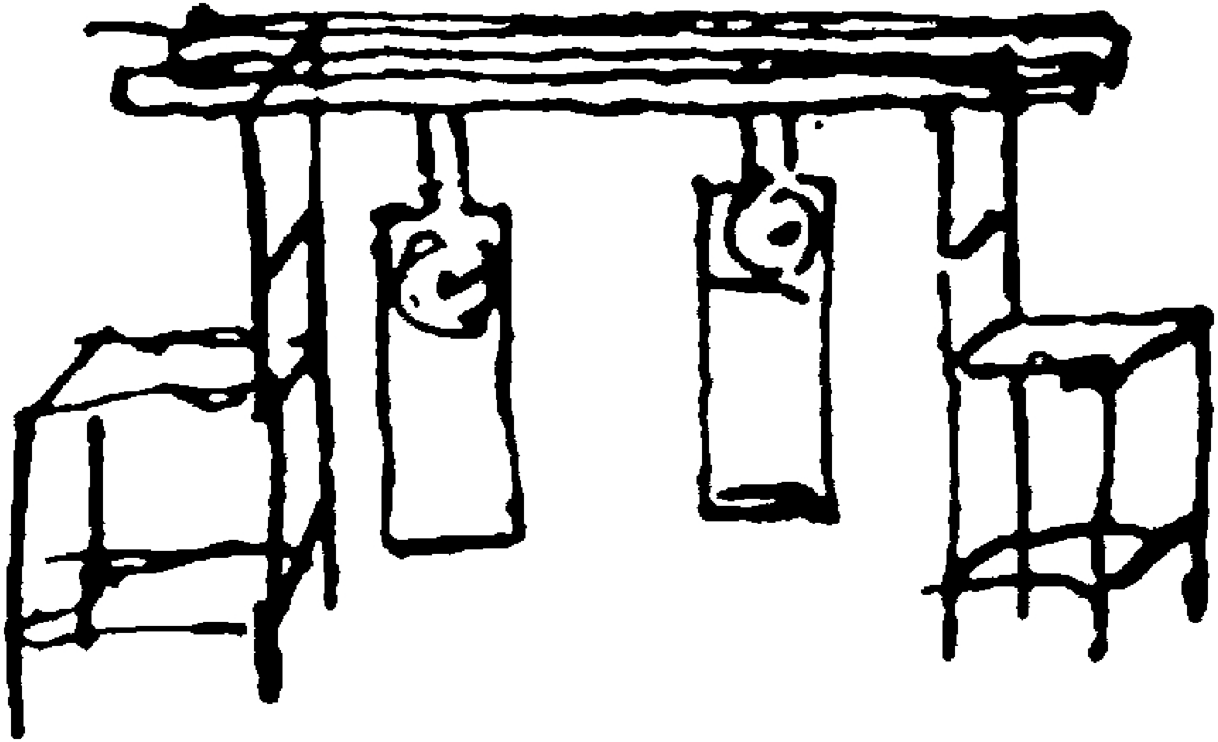
Leo Kadanoff and M.H. Jensen, "Global and Local: Synchronization and Emergence", Review (2012)

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", preprint (2013)

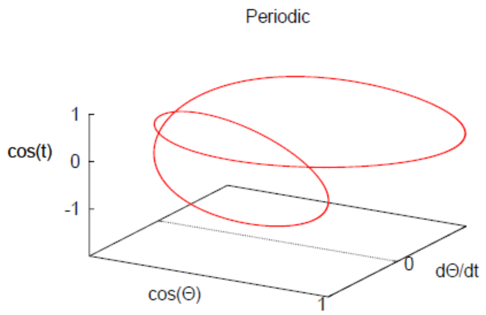
Oscillations: S. Pigolotti, L. Pederse, B. Mengel, A. Trusina, P. Jensen, P. Yde,
S. Chakraborty, S. Semsey, A. Hunziker, …….

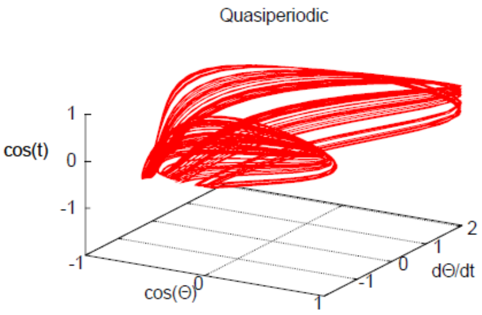
Synchronization of two oscillators

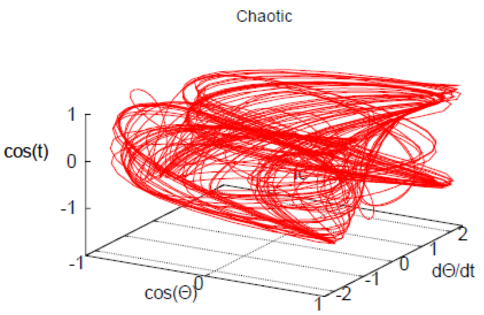


Huygens’ clocks 1665

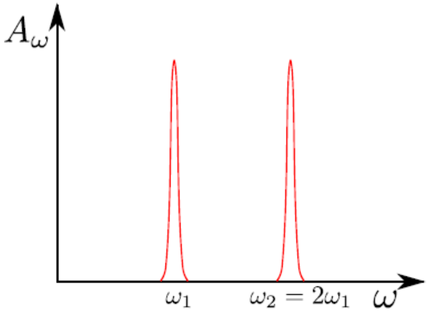
Three different non-linear dynamics



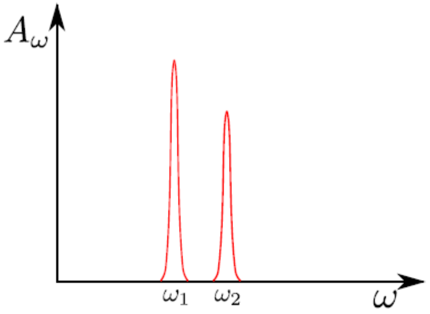




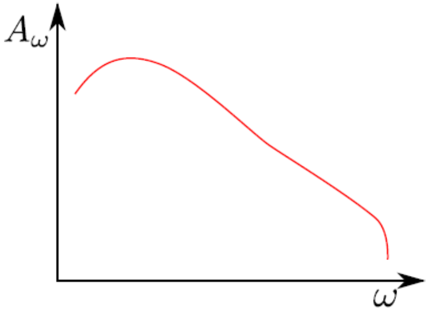
Periodic



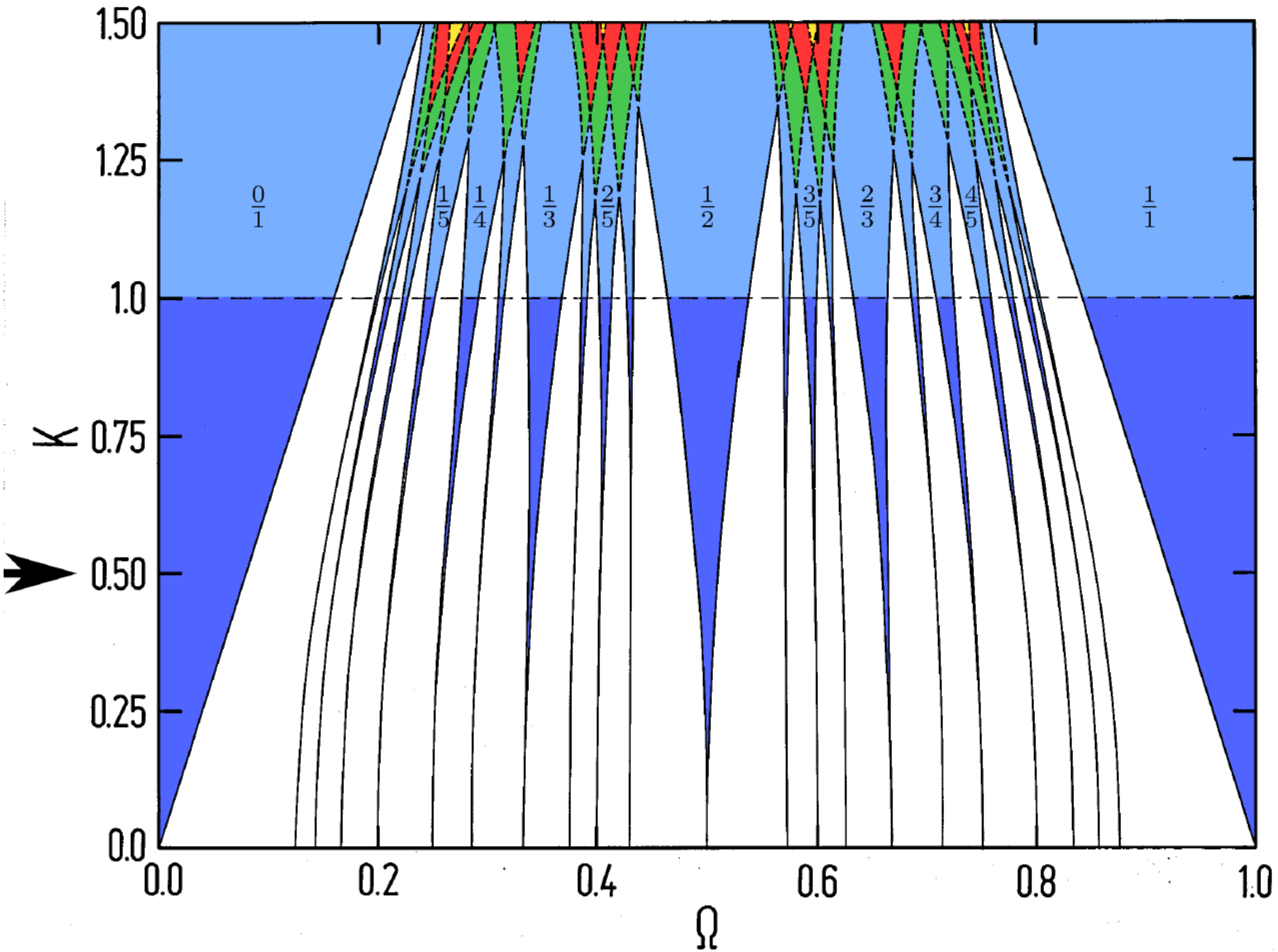
Quasiperiodic



Chaotic



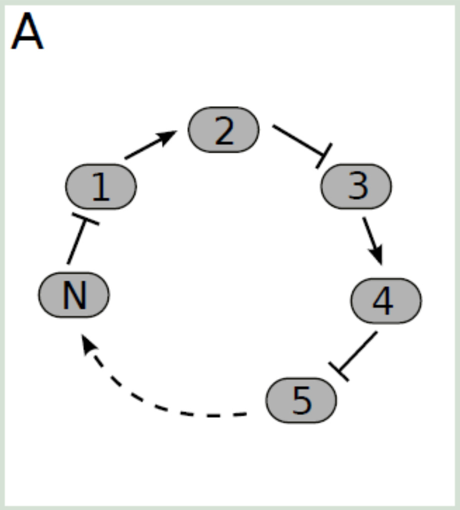
Two coupled oscillators: Arnold tongues

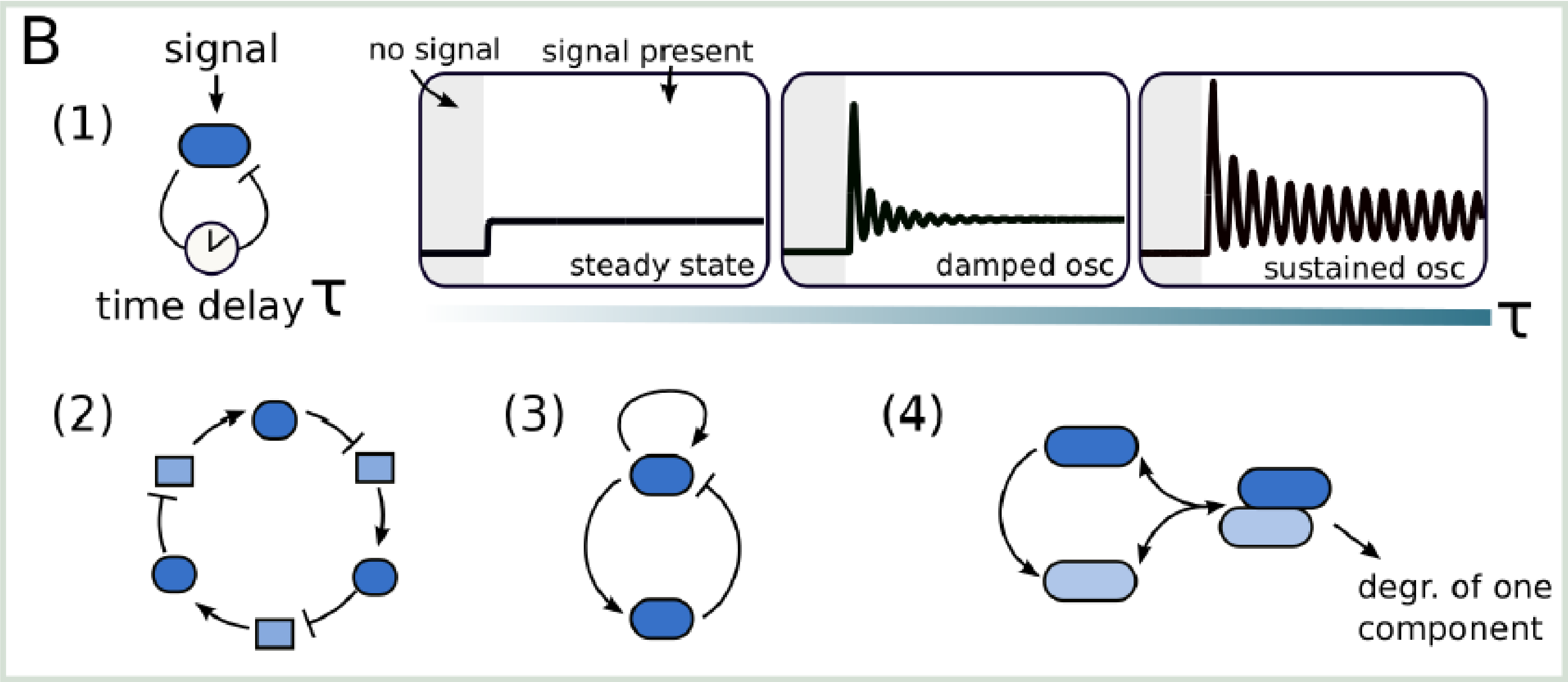


What about biology – many oscillators !

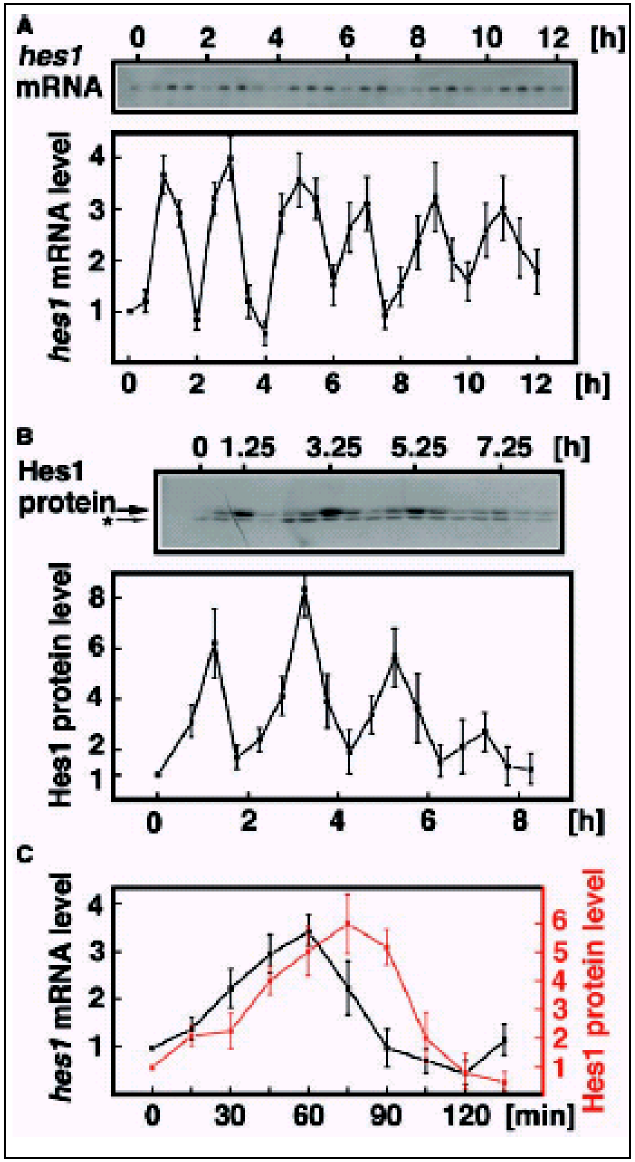
- Cell cycles
- Circadian clocks
- Calcium oscillators
- Embryos
- Pace maker cells
- Protein oscillations (DNA damage)
- Population dynamics

Basic oscillator: Negative Feed-Back loops:



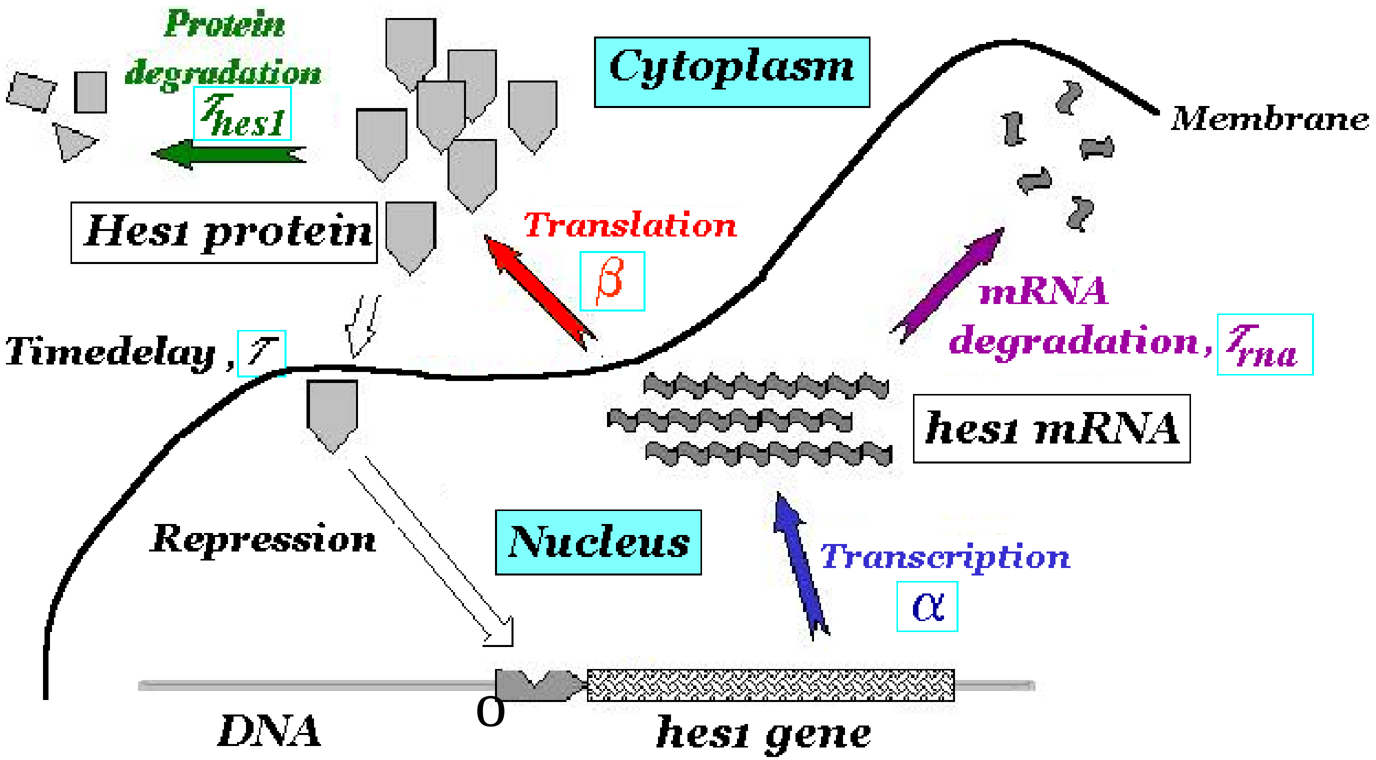


‘Typical’ Oscillating data: Hes1 - segmentation



(Hirata et al, 2002)

Simplest negative feed-back loop: Hes1



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

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

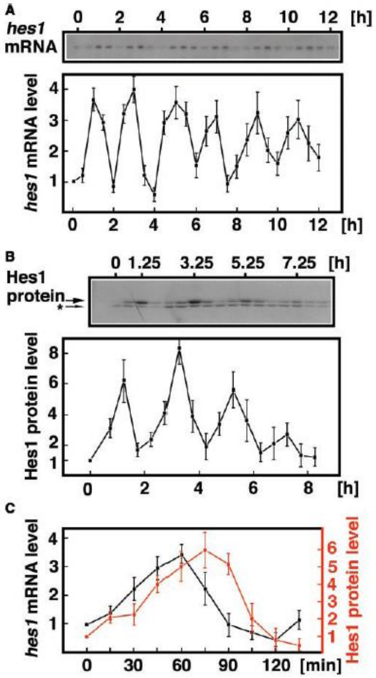
Jensen et al 2003

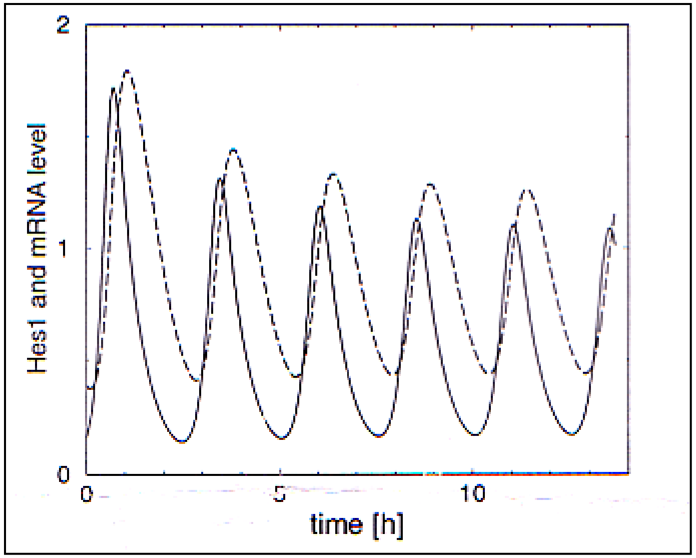
$$\frac{d[mRNA]}{dt} = \alpha \cdot \frac{K_M}{K_M + [Hes1(t-\tau)]^n} - \frac{[mRNA(t)]}{\tau_{rna}}$$

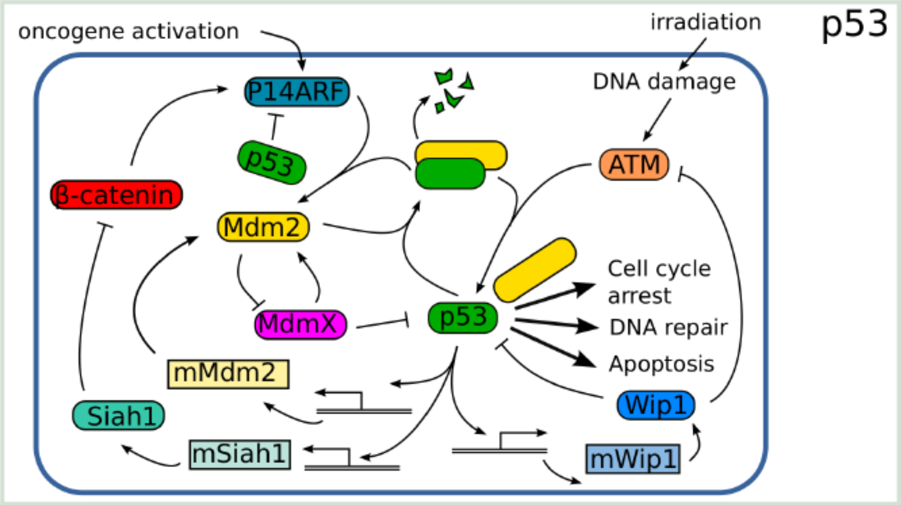
$$\frac{d[Hes1]}{dt} = \beta \cdot [mRNA(t)] - \frac{[Hes1(t)]}{\tau_{hes1}}$$

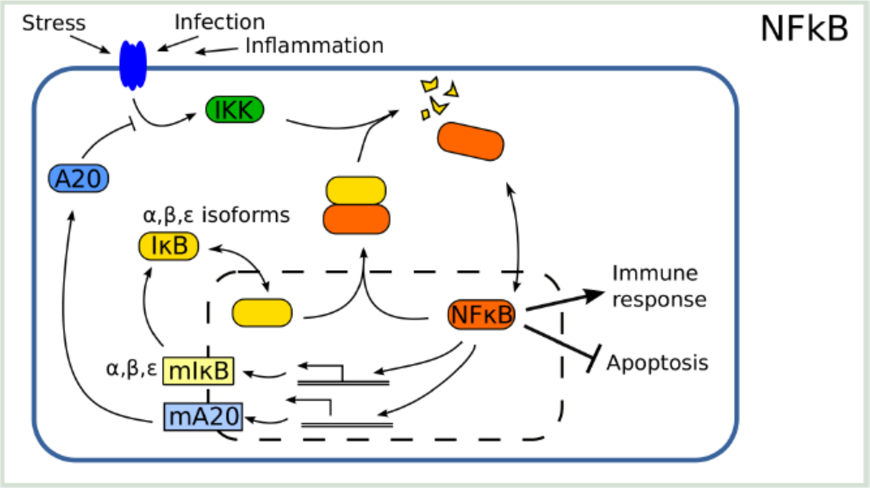
- Dashed curve [Hes1]
- Solid curve [mRNA]

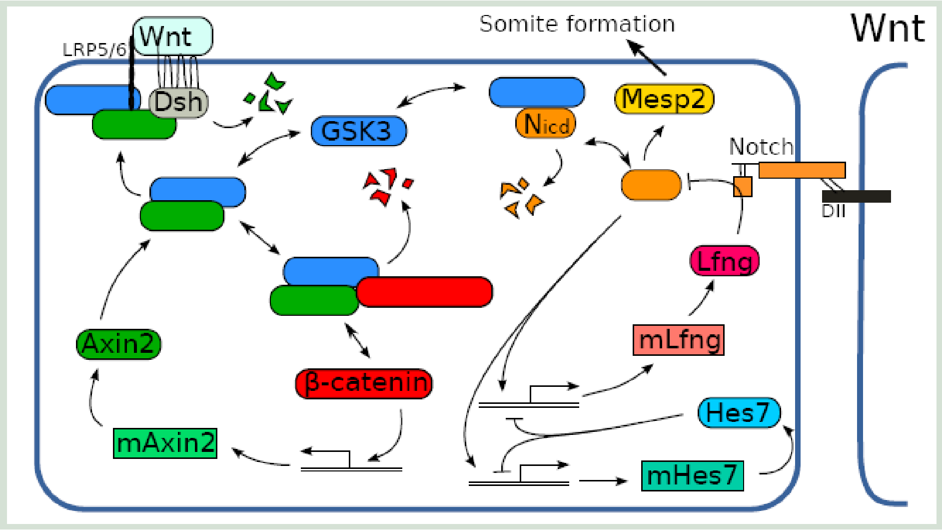
- τ_{rna} = 24.1 min
- τ_{hes1} = 22.3 min
- τ = 24 min
- $\alpha = 20\ [R]_0\ \text{min}^{-1}$
- $\beta = 1/20\ \text{min}^{-1}$
- $K_M = (0.1[R]_0)^n$
- n = 4

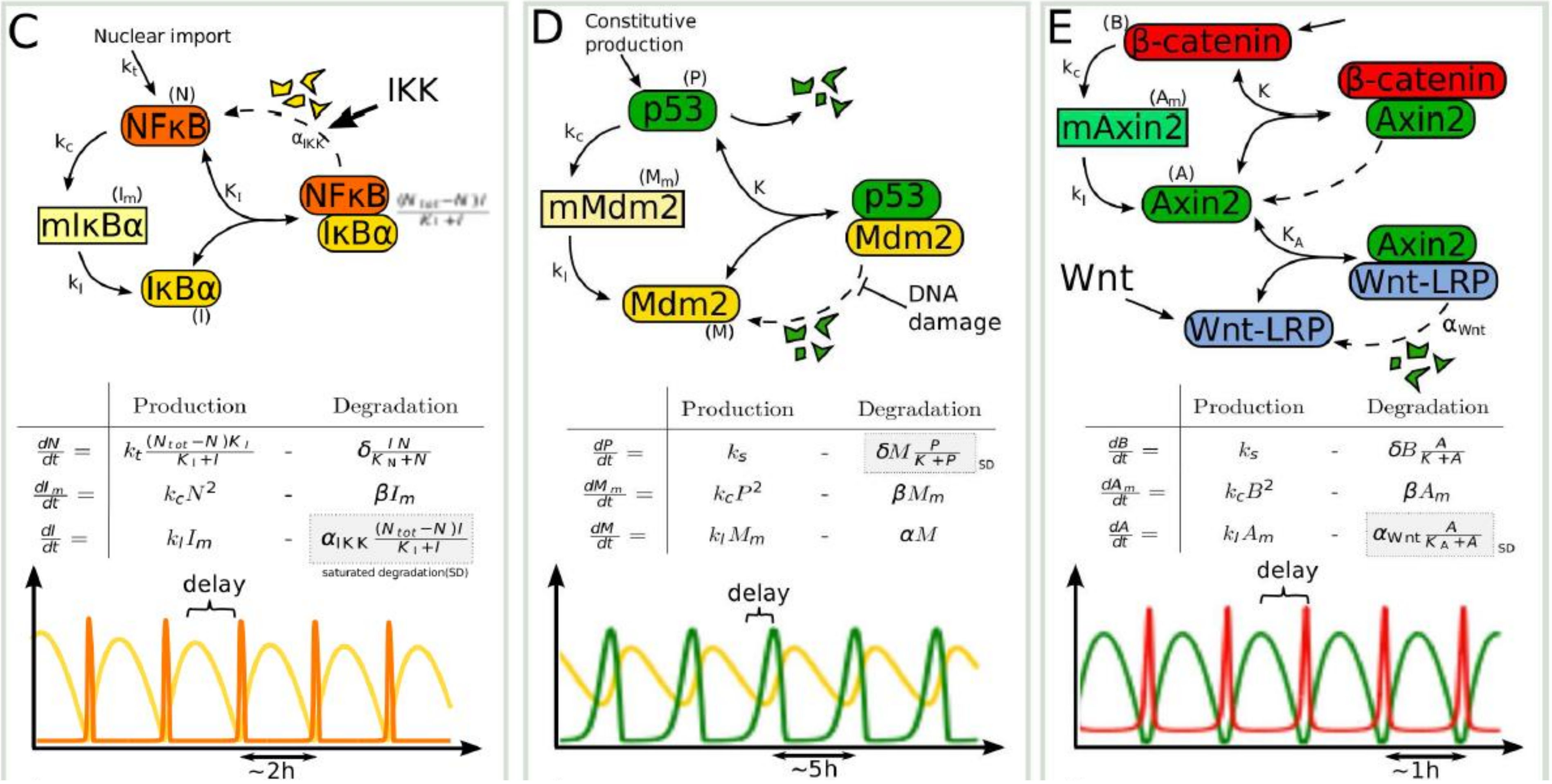





p53
oncogene activation
irradiation
DNA damage
P14ARF
p53
ATM
β-catenin
Mdm2
MdmX
p53
Cell cycle arrest
DNA repair
Apoptosis
mMdm2
Siah1
Wip1
mSiah1
mWip1


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



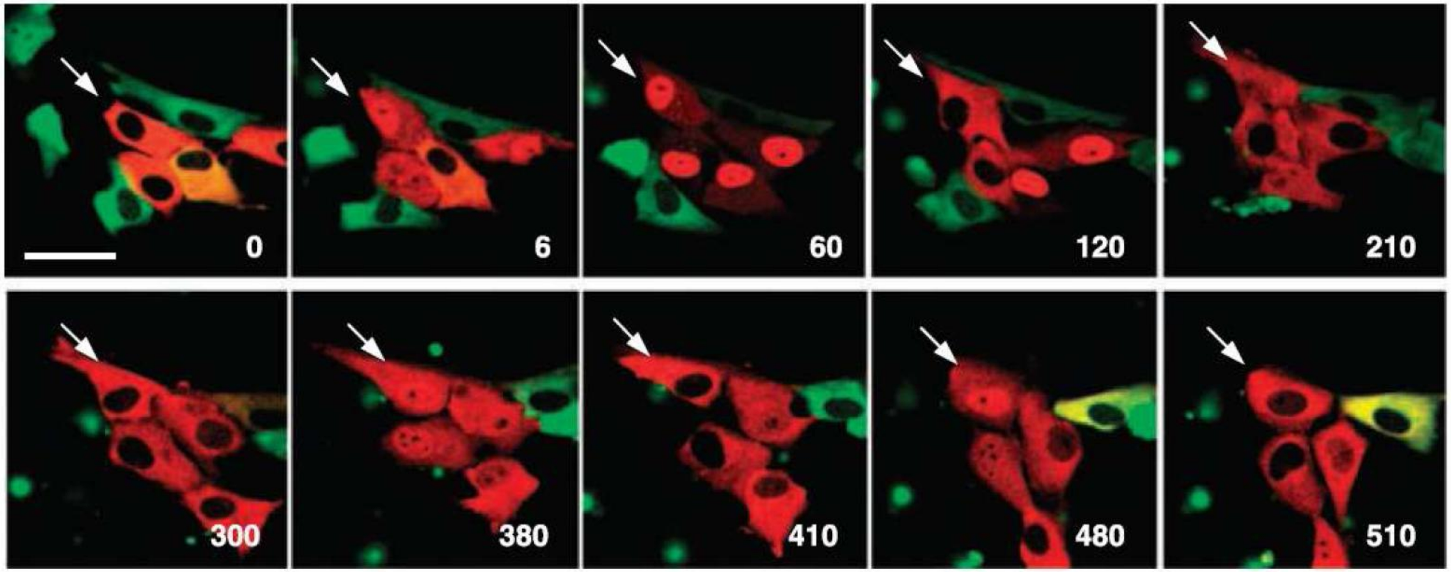
	Production		Degradation
$\frac{dN}{dt} =$	$k_t \frac{(N_{tot}-N)K_I}{K_I+I}$	-	$\delta \frac{IN}{K_N+N}$
$\frac{dI_m}{dt} =$	$k_c N^2$	-	βI_m
$\frac{dI}{dt} =$	$k_l I_m$	-	$\alpha_{IKK} \frac{(N_{tot}-N)I}{K_I+I}$

saturated degradation(SD)

	Production		Degradation
$\frac{dP}{dt} =$	k_s	-	$\delta M \frac{P}{K+P}$ SD
$\frac{dM_m}{dt} =$	$k_c P^2$	-	βM_m
$\frac{dM}{dt} =$	$k_l M_m$	-	αM

	Production		Degradation
$\frac{dB}{dt} =$	k_s	-	$\delta B \frac{A}{K+A}$
$\frac{dA_m}{dt} =$	$k_c B^2$	-	βA_m
$\frac{dA}{dt} =$	$k_l A_m$	-	$\alpha_{Wnt} \frac{A}{K_A+A}$ SD

‘Direct’ observations of oscillations in nucleus



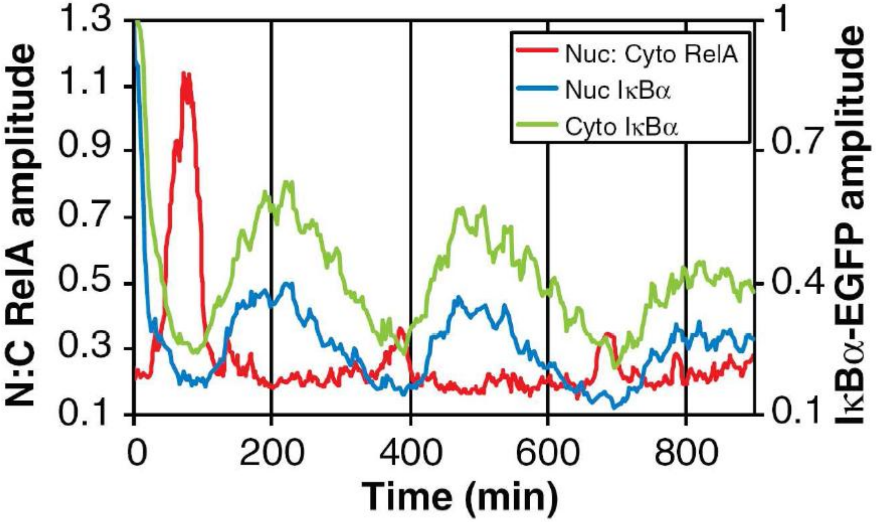
Oscillations in the nuclear localization of an NF-κB transcription factor in human cells

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.



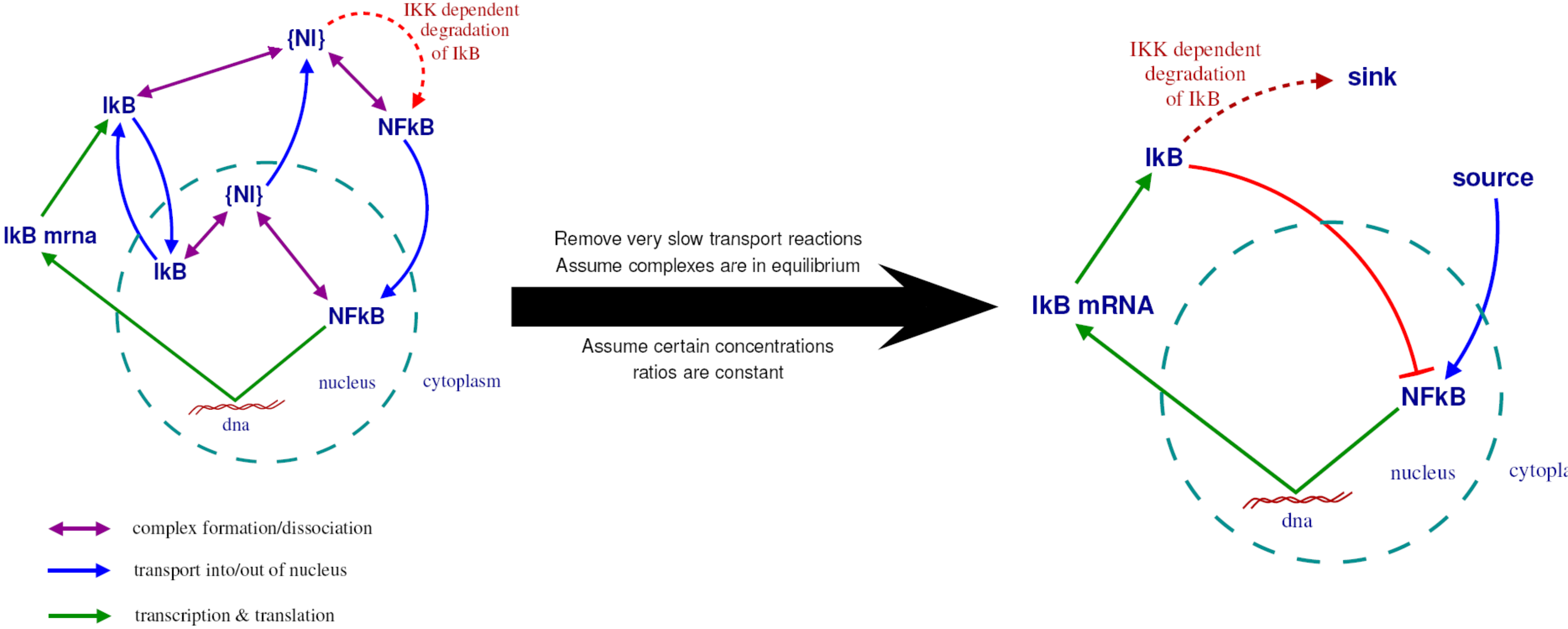
How does the network produce oscillations?

Why does the cell need the oscillations?

Reduction of the NF-κB system

7-variable model

3-variable model

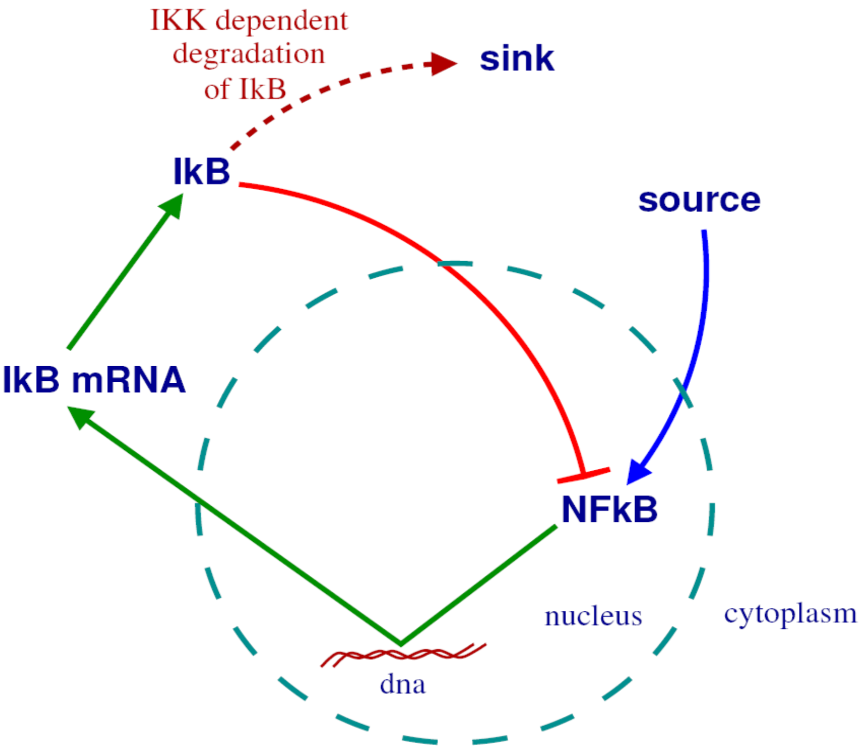


Remove very slow transport reactions
Assume complexes are in equilibrium

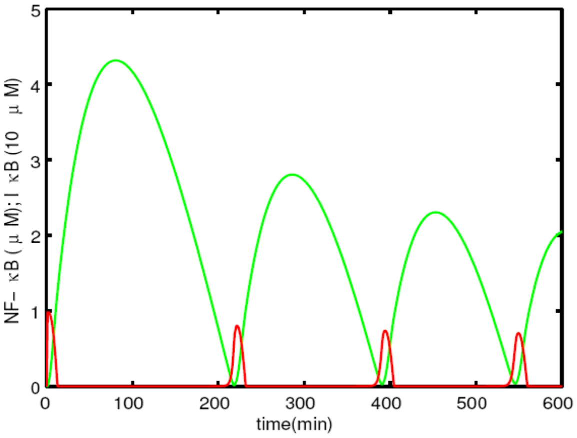
Assume certain concentrations
ratios are constant

complex formation/dissociation
transport into/out of nucleus
transcription & translation

Simple Model for Protein Oscillations



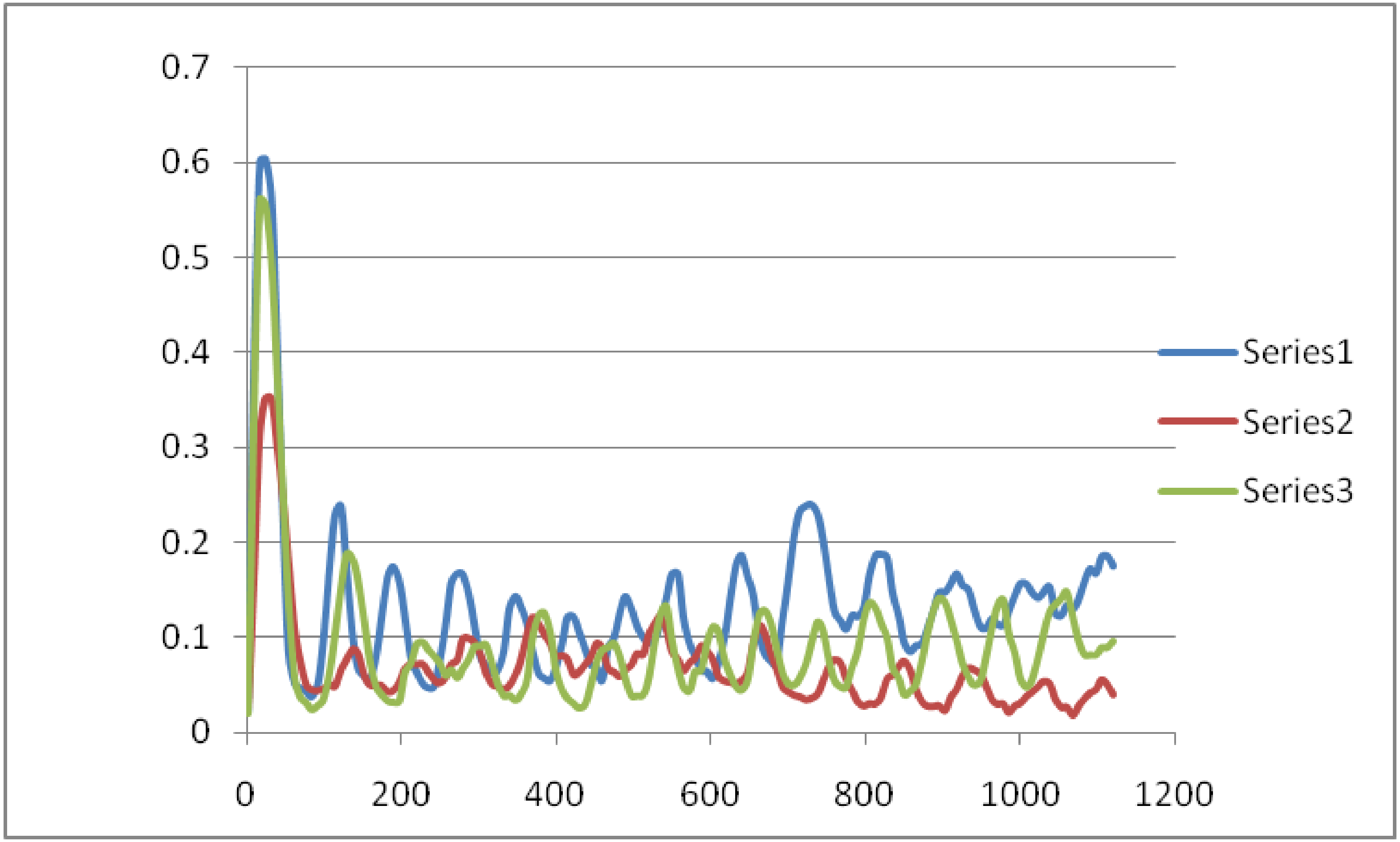
$$
\begin{aligned}
\frac{dN_n}{dt} &= A\frac{(1-N_n)}{\epsilon+I} - B\frac{I\,N_n}{\delta+N_n},\\
\frac{dI_m}{dt} &= N_n^2 - I_m,\\
\frac{dI}{dt} &= I_m - C\frac{(1-N_n)I}{\epsilon+I}.
\end{aligned}
$$



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

$$\delta = 0.029,\ \epsilon = 2\times10^{-5}$$

Oscillations of protein densities in a single cell



(M. Covert, Stanford, unpublished)

Response to irradiation in single cells

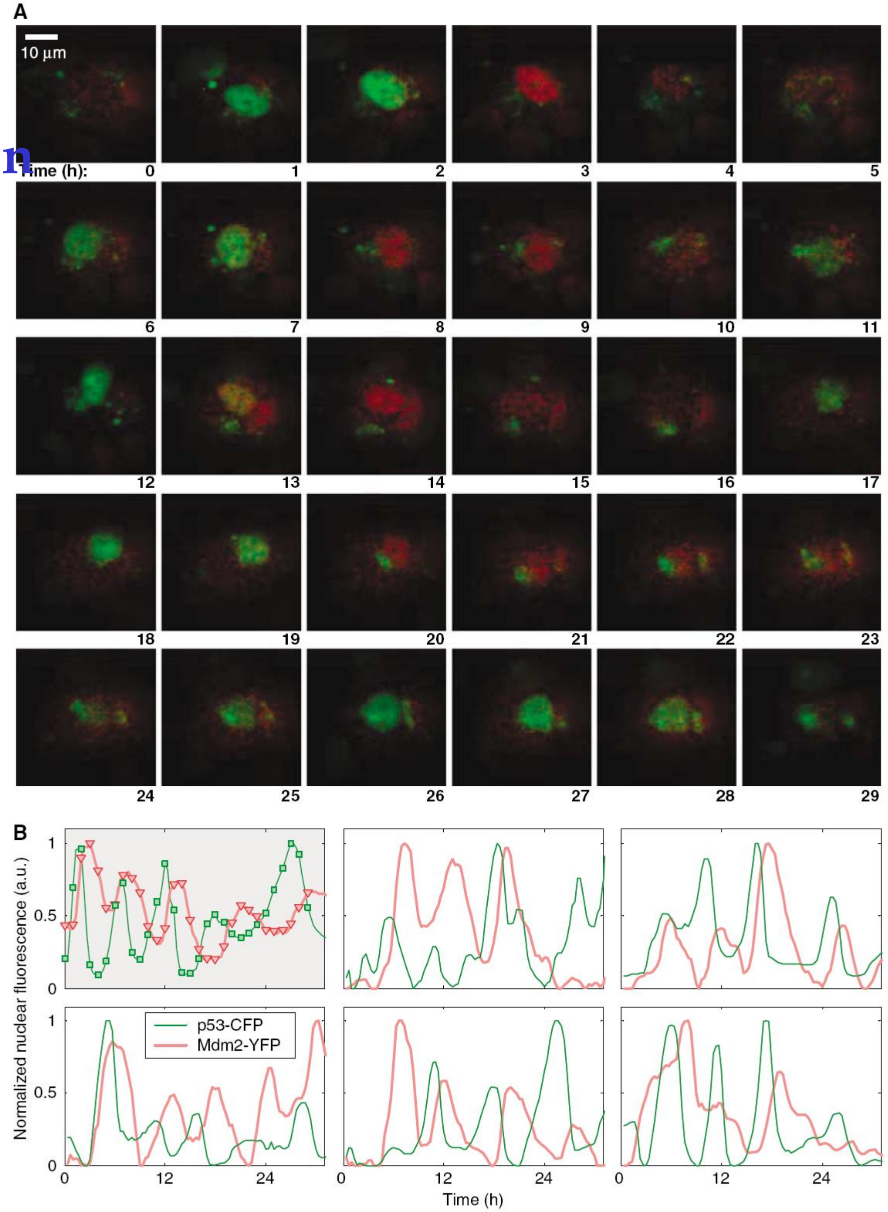
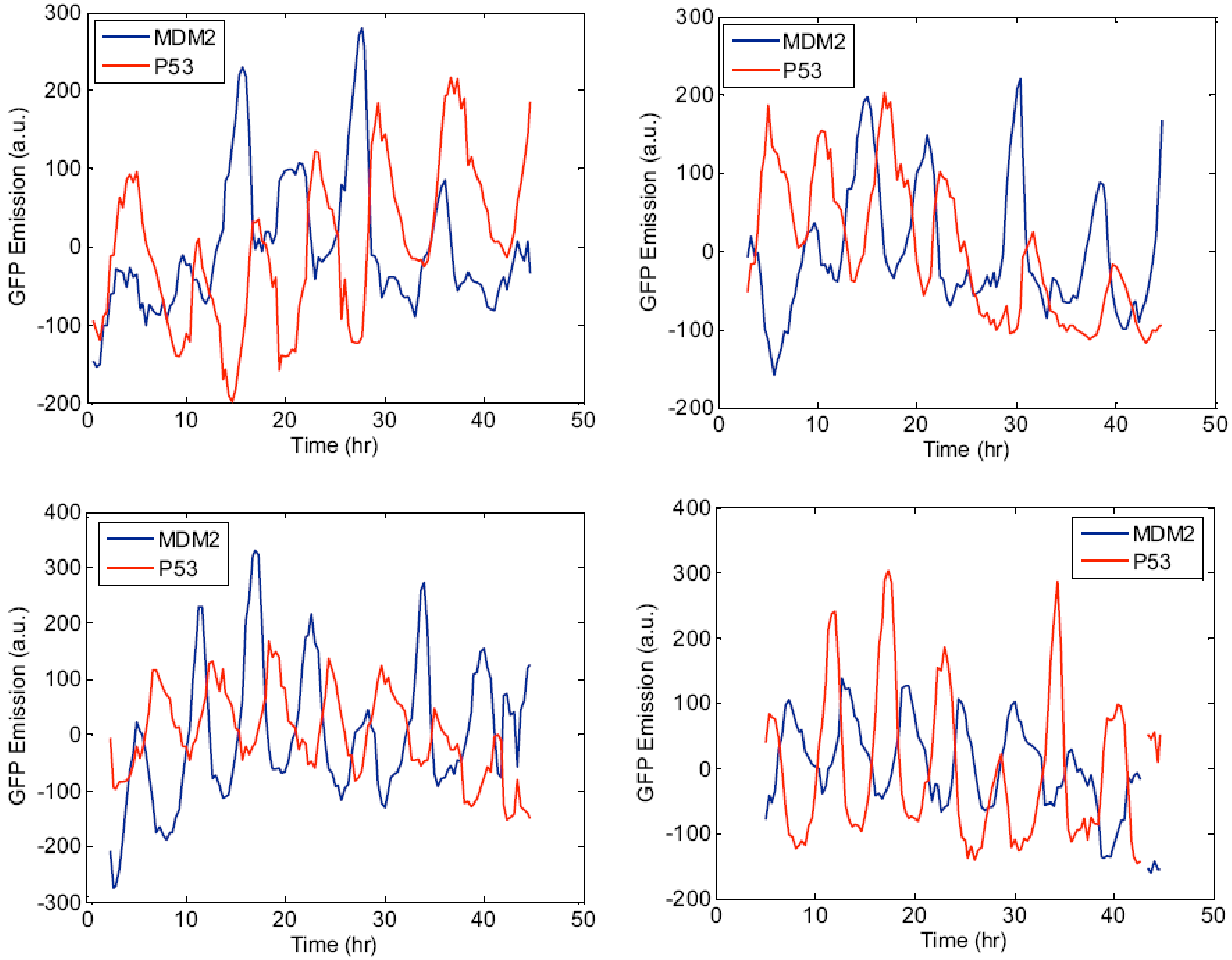


Figure 1 Prolonged oscillations in the nuclear levels of fluorescently tagged p53 and Mdm2 in individual MCF7, U280, cells following gamma irradiation. (**A**) Time-lapse fluorescence images of one cell over 29 h after 5 Gy of gamma irradiation. Nuclear p53-CFP and Mdm2-YFP are imaged in green and red, respectively. Time is indicated in hours. (**B**) Normalized nuclear fluorescence levels of p53-CFP (green) and Mdm2-YFP (red) following gamma irradiation. Top left: the cell shown in panel A. Other panels: five cells from one field of view, after exposure to 2.5 Gy gamma irradiation.

Often time series
are very noisy !
→ Then what ?

N. Geva-Zatorsky, *Mol. Sys. Biol.*2:2006.0033 (2006)

p53 oscillations: Apoptosis

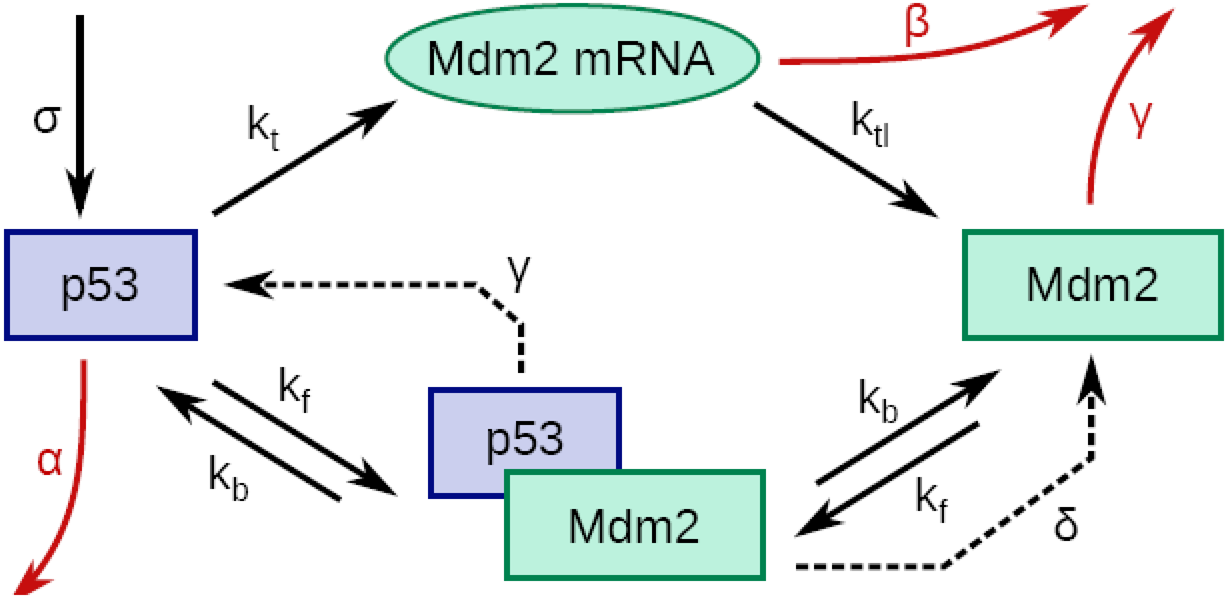


Lahav, Alon, Geva-Zatorsky, Levine,..

What happens during oscillations:

Hypothesis:

- Cell-cycle stops
- Tries to repair DNA. If repaired → Fine !
- If DNA not repaired → Apoptosis !
- If DNA not repaired, and no apoptosis: Cancer



$$\frac{dp}{dt} = \sigma - \alpha p - k_f p m + k_b c + \gamma c$$

$$\frac{dm_m}{dt} = k_t p^2 - \beta m_m$$

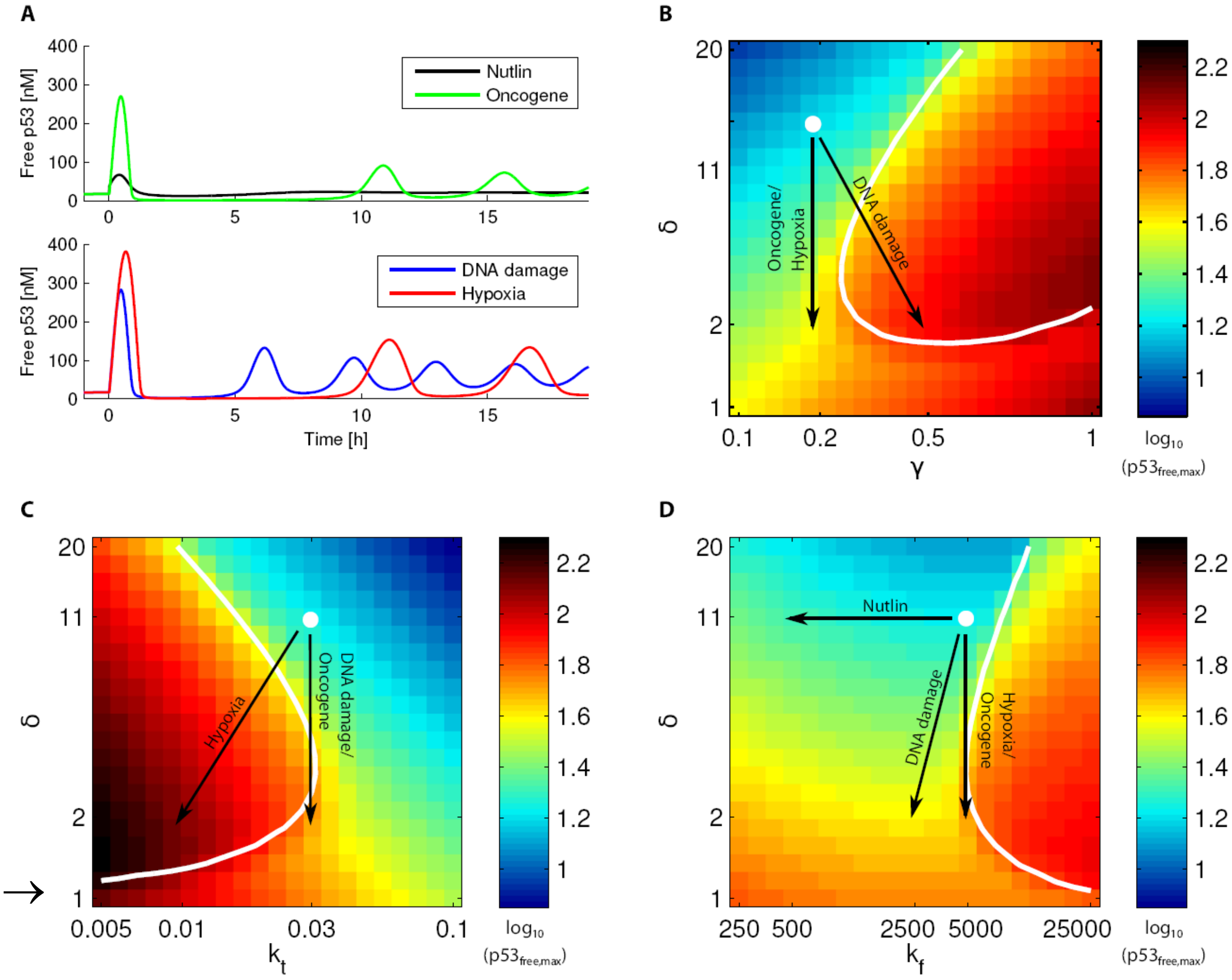
$$\frac{dm}{dt} = k_{tl} m_m - k_f p m + k_b c + \delta c - \gamma m$$

$$\frac{dc}{dt} = k_f p m - k_b c - \delta c - \gamma c$$

Mdm2 regulates both activity and stability

tions: nuclear-p53, p; Mdm2, m; Mdm2 mRNA, m_m; and the p53-Mdm2 complex, c. The tempo-

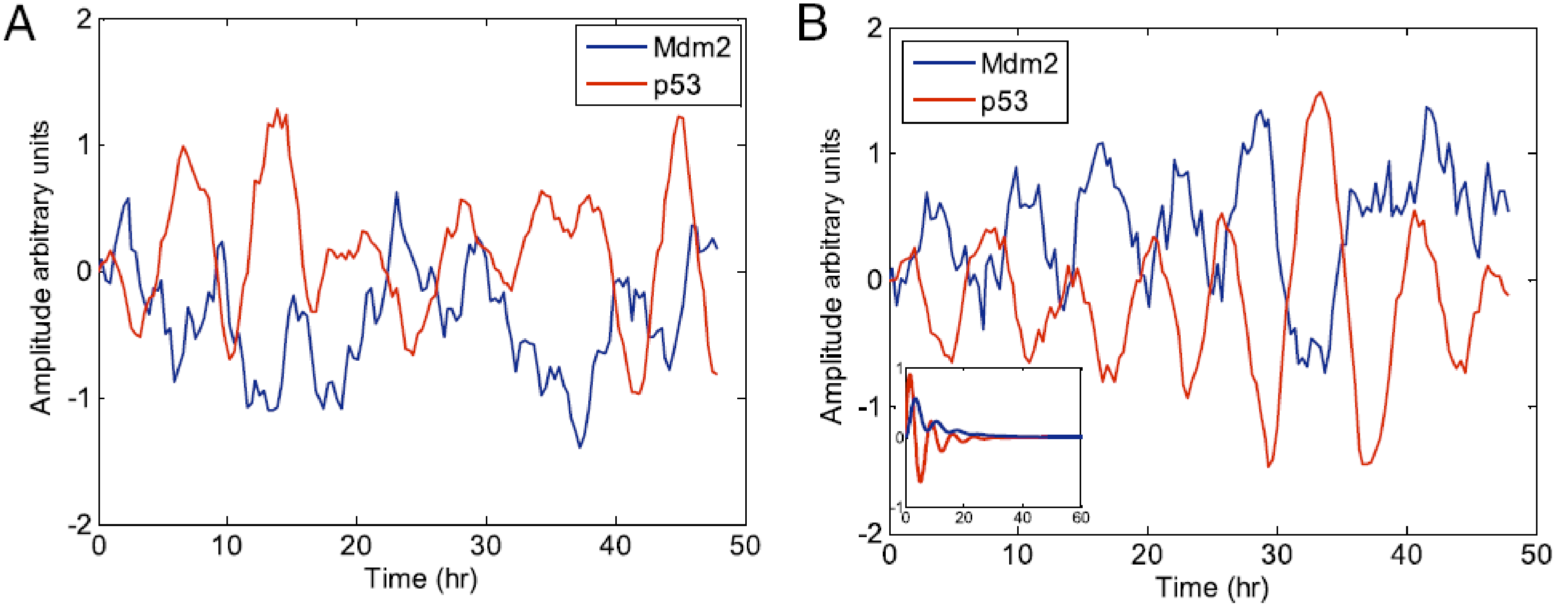
Stress variations in parameters



Spikyness →

p53 concentrations (peak)

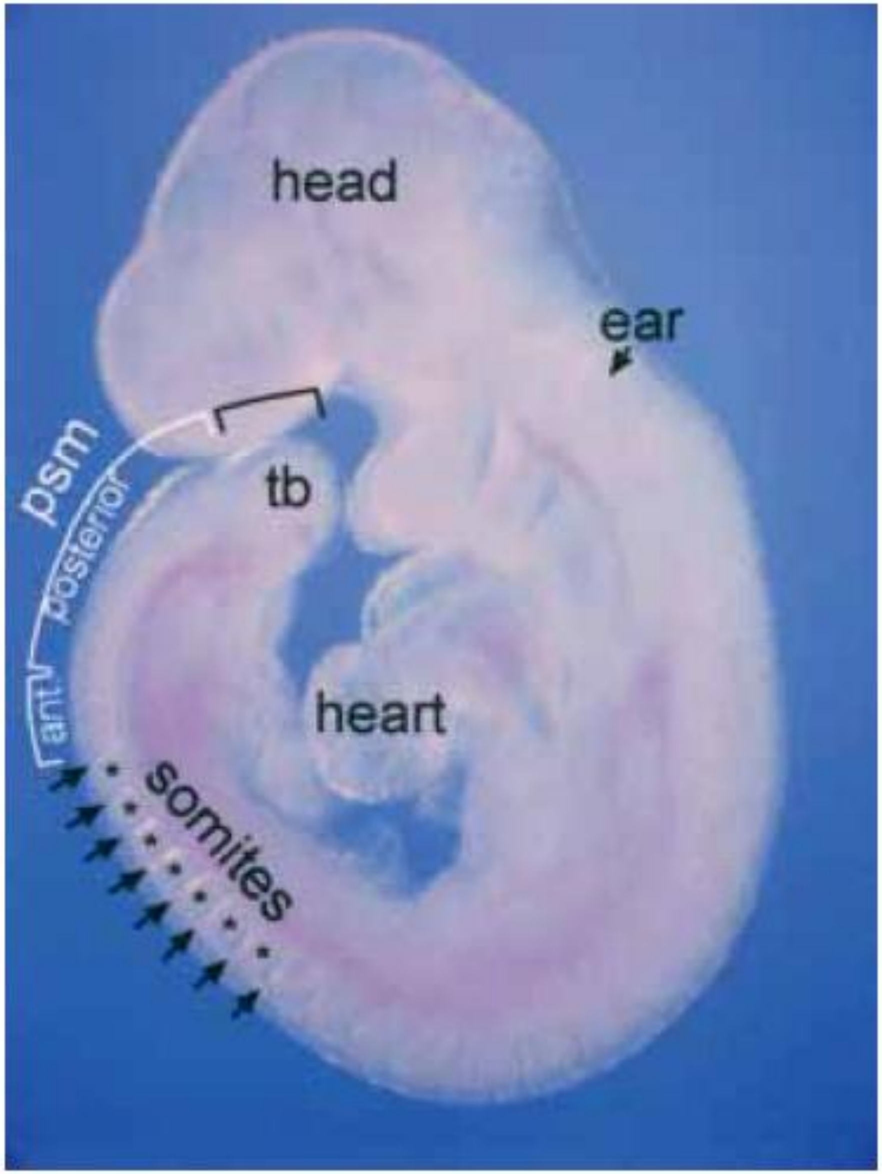
Stochastic simulations of linear noise induced model

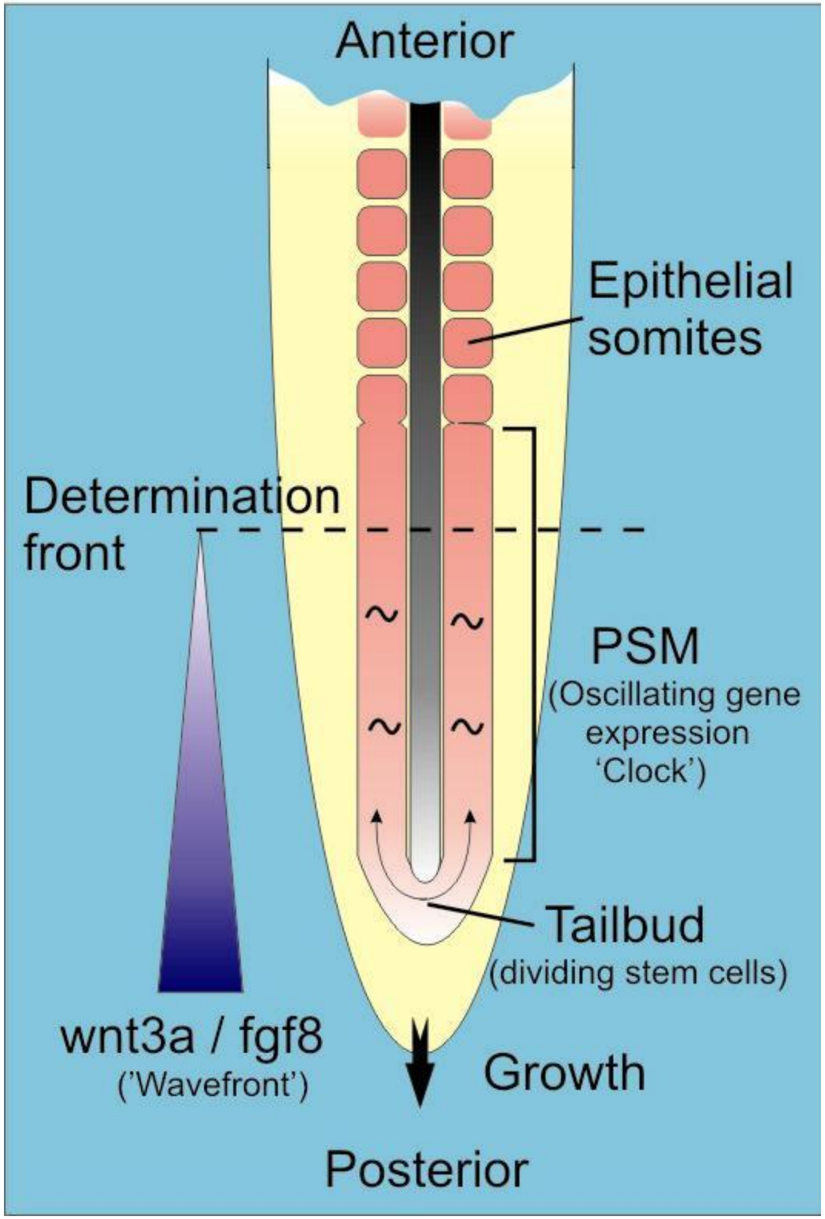


$$\frac{dx}{dt} = a_{xy}y - a_{xx}x + N_1$$
$$\frac{dy}{dt} = a_{yx}x - a_{yy}y + N_2$$

A_xy = -0.8 ; A_yx = 0.8

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


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

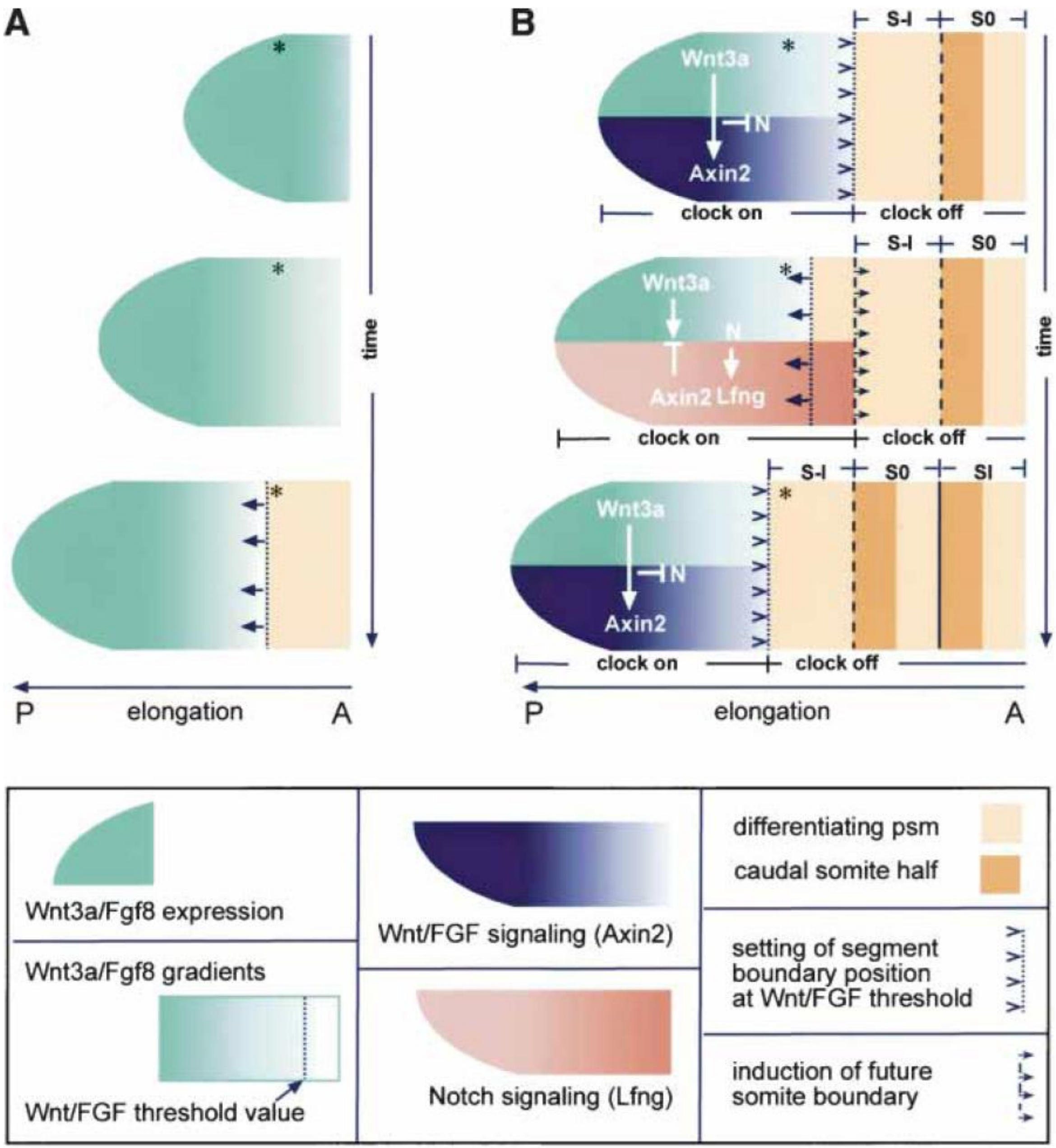
PSM cells have locally syncronized oscillating expression patterns with periods matching somite formation (90 min in chick) – **Clock**

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

Clock determines susceptibility to **wavefront**, which ensures groupwise

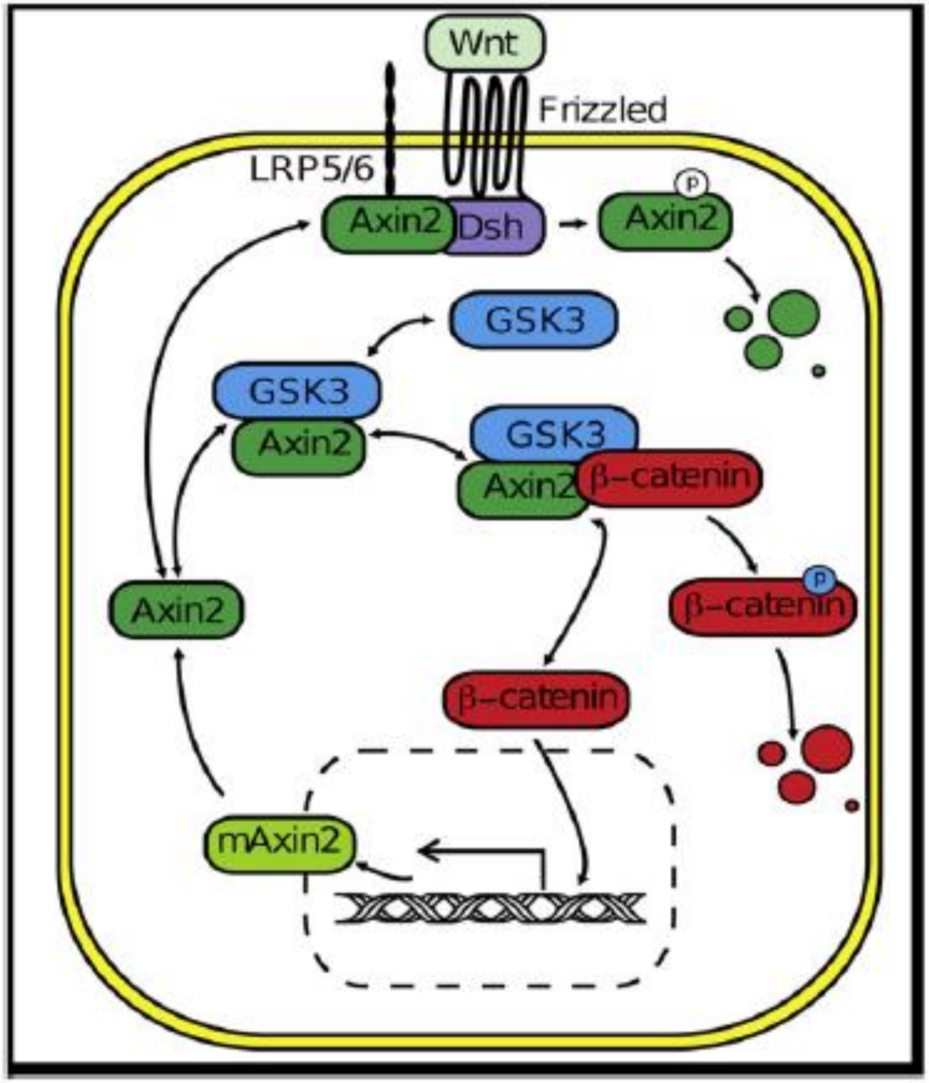
incorporation into somites

Wnt gradient and Clock are coupled



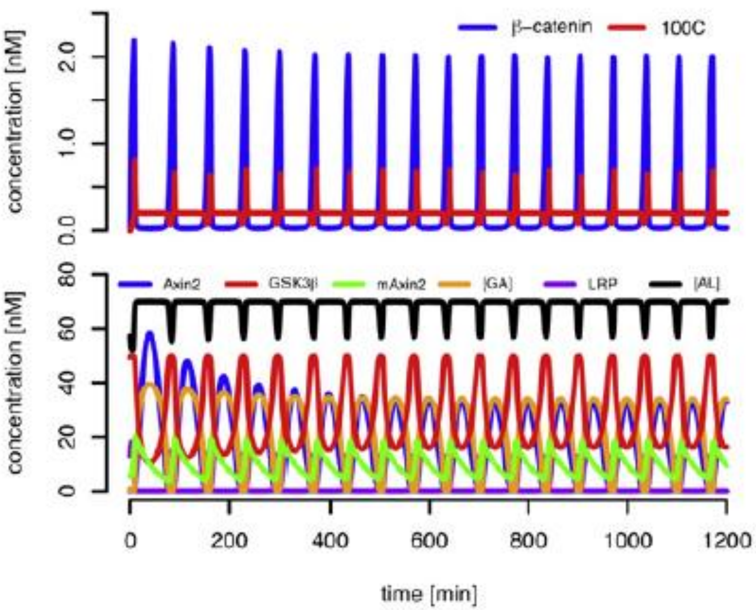
Aulehla and Herrmann

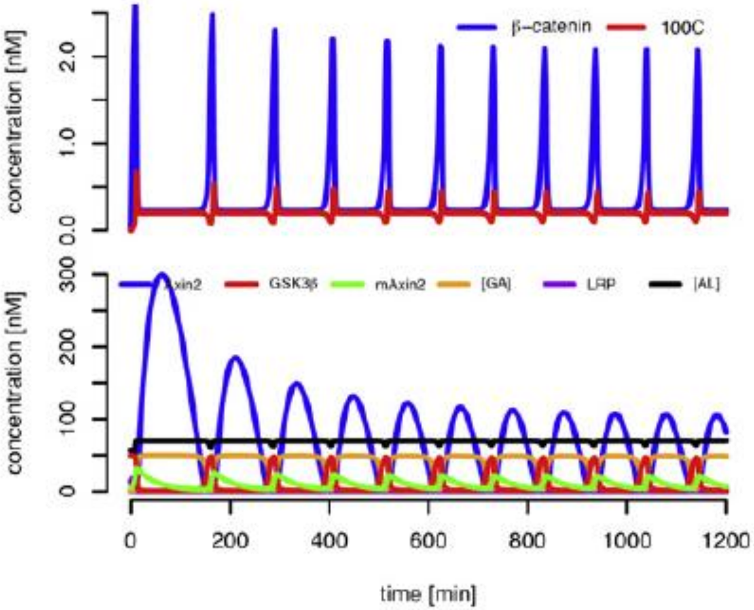
The Wnt systems

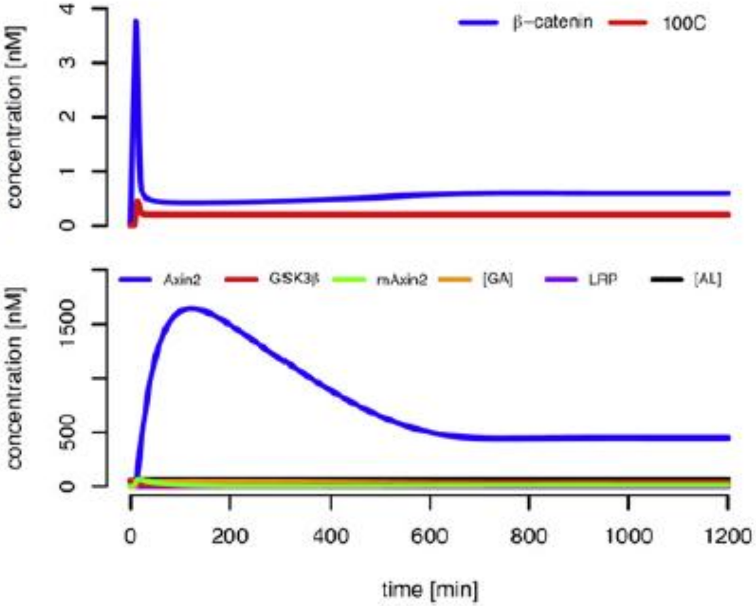


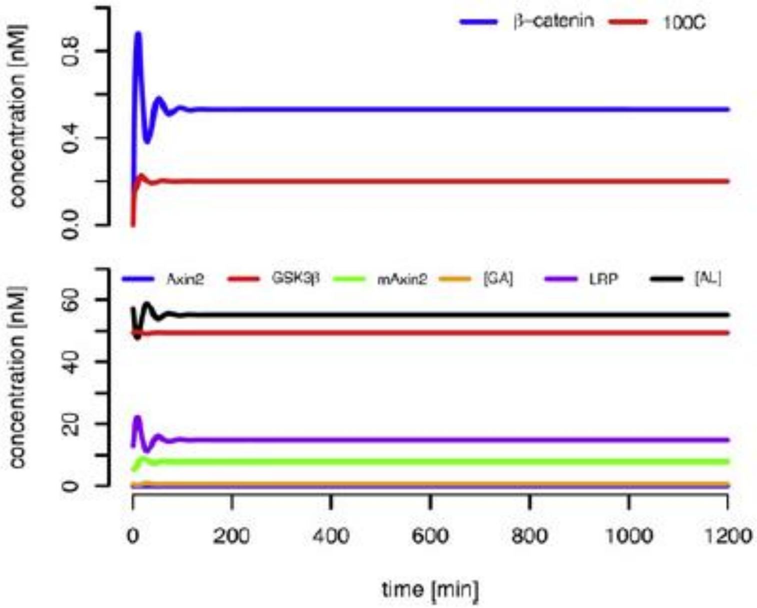
Goldbeter,
Pourquie

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]
concentration [nM]
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]
concentration [nM]
0
100
200
300
0
200
400
600
800
1000
1200
time [min]


β−catenin
100C
concentration [nM]
0
1
2
3
4
Axin2
GSK3β
mAxin2
[GA]
LRP
[AL]
concentration [nM]
0
500
1500
0
200
400
600
800
1000
1200
time [min]


β−catenin
100C
concentration [nM]
0.0
0.4
0.8
Axin2
GSK3β
mAxin2
[GA]
LRP
[AL]
concentration [nM]
0
20
40
60
0
200
400
600
800
1000
1200
time [min]

Externally ‘forced’ NF-κB system

External modulation of TNF cytokine signal

→ Transformed into IKK signal (C)

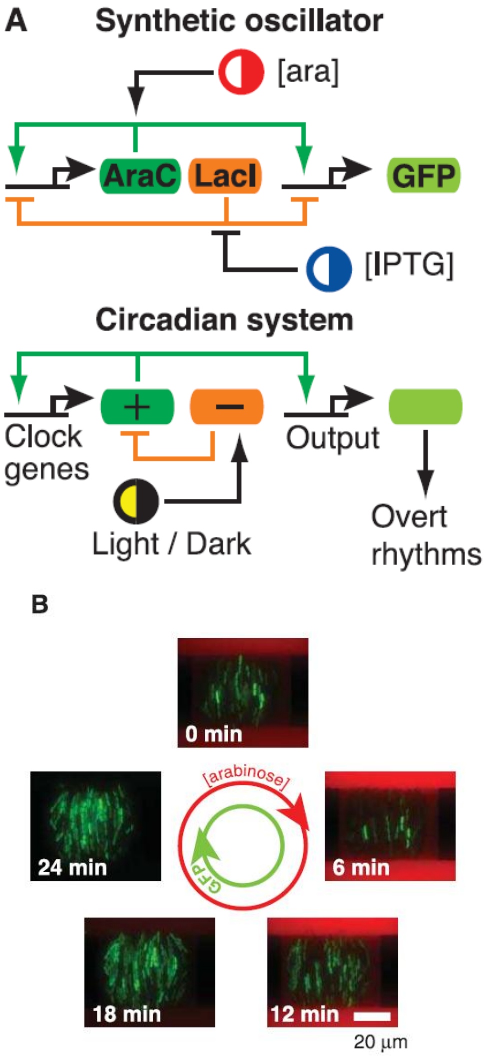
Arnold tongues:

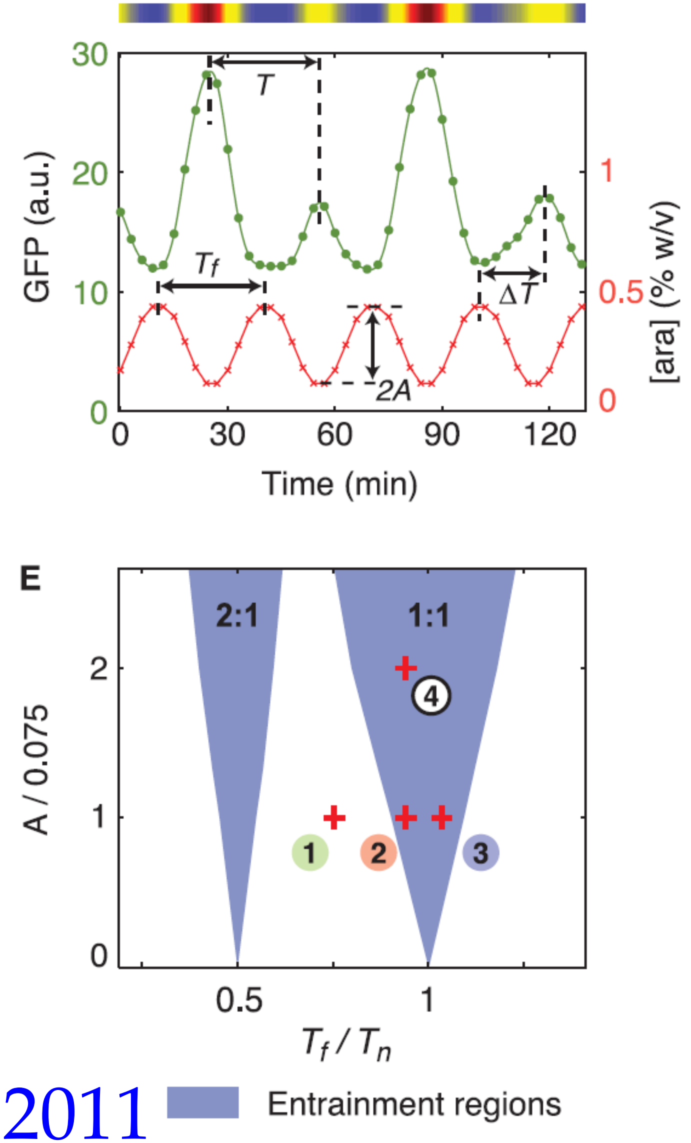
Can synchronize the dynamics of a single cell:

Maybe a way to control DNA damage/DNA repair

(S. Krishna, MHJ)

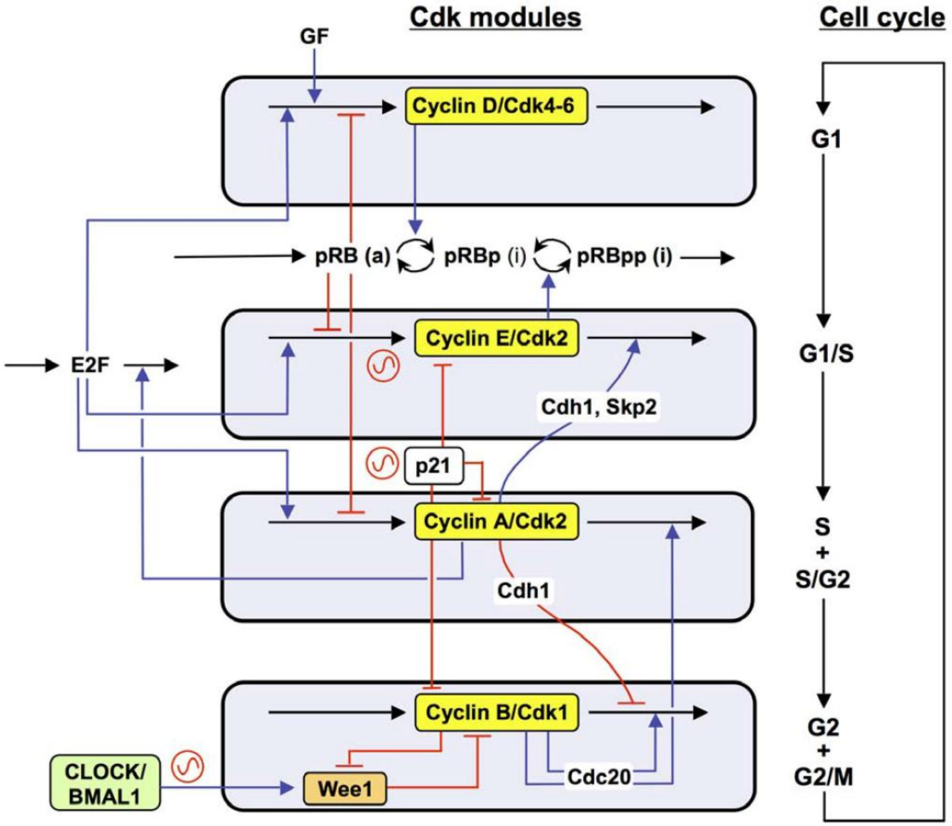
Populations of genetic oscillators





Jeff Hasty et al, Science 2011

Cell cycle and circadian clock



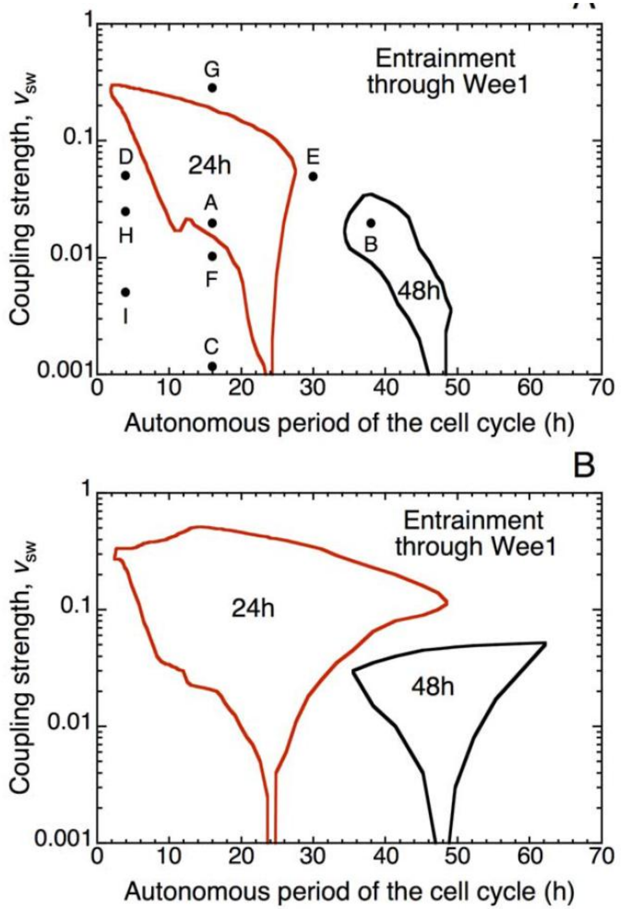
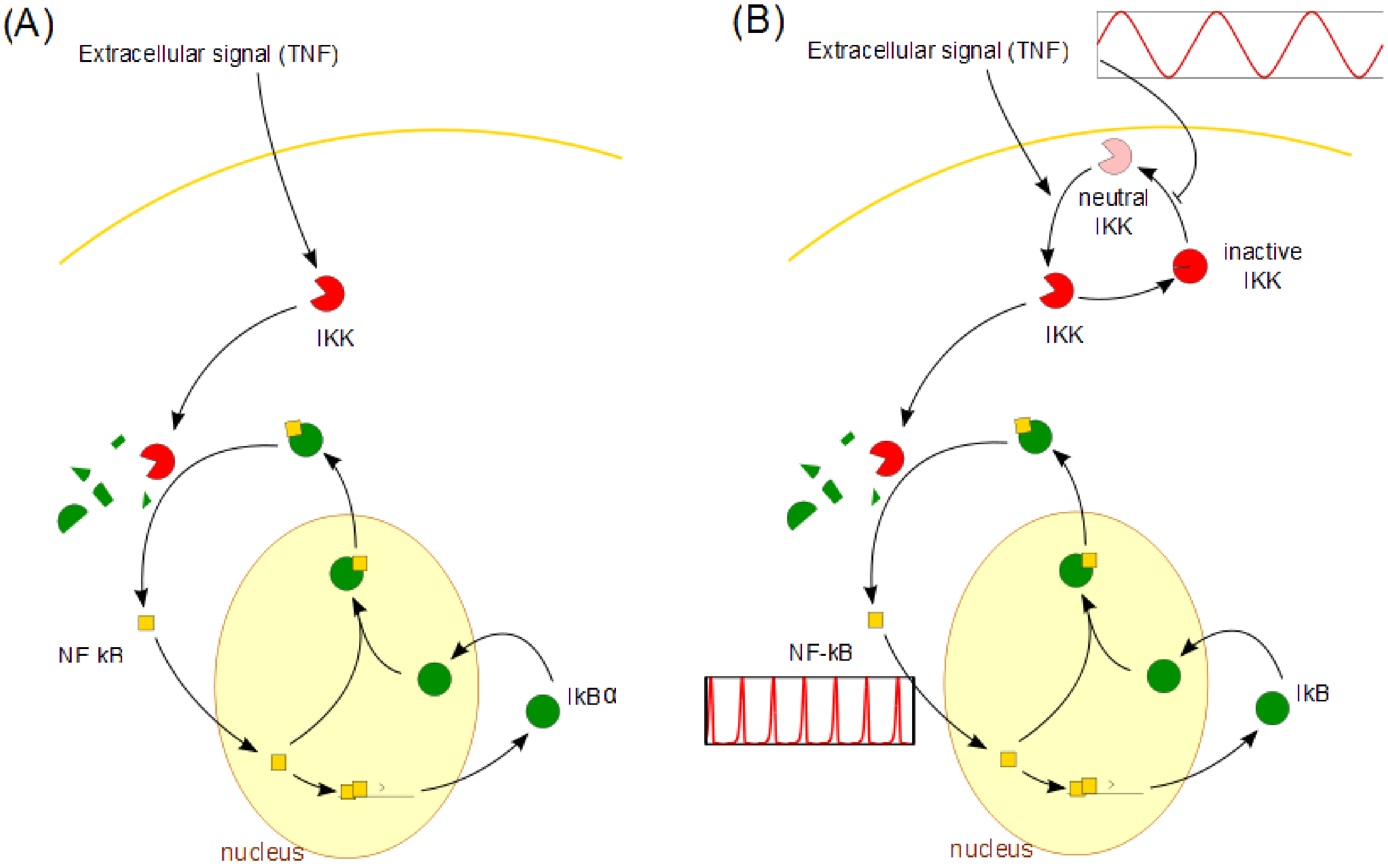


Figure 4. Domains of entrainment of the cell cycle by the circadian clock via circadian control of the kinase Wee1. The

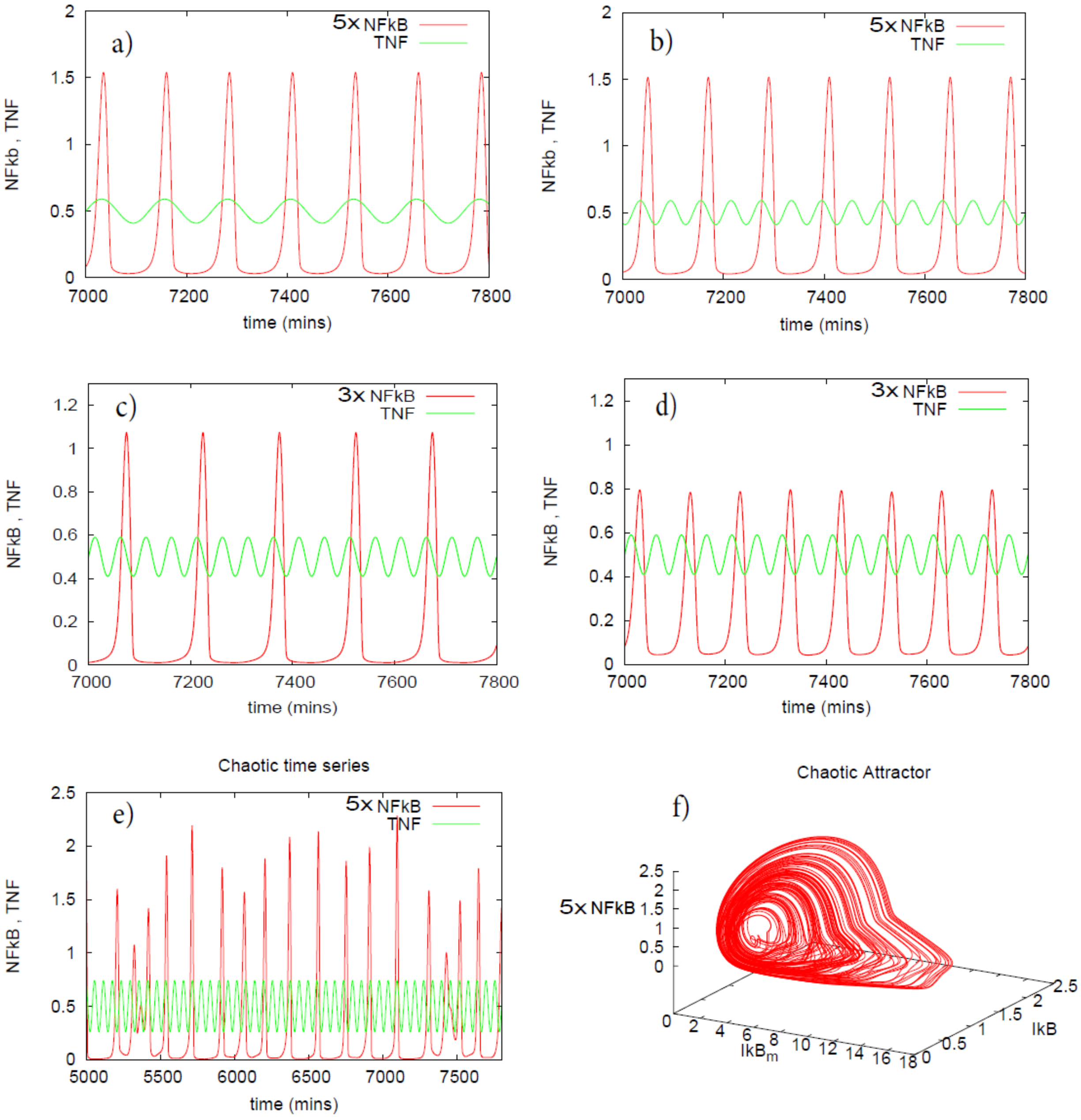
Gerard and Goldbeter, May, 2012

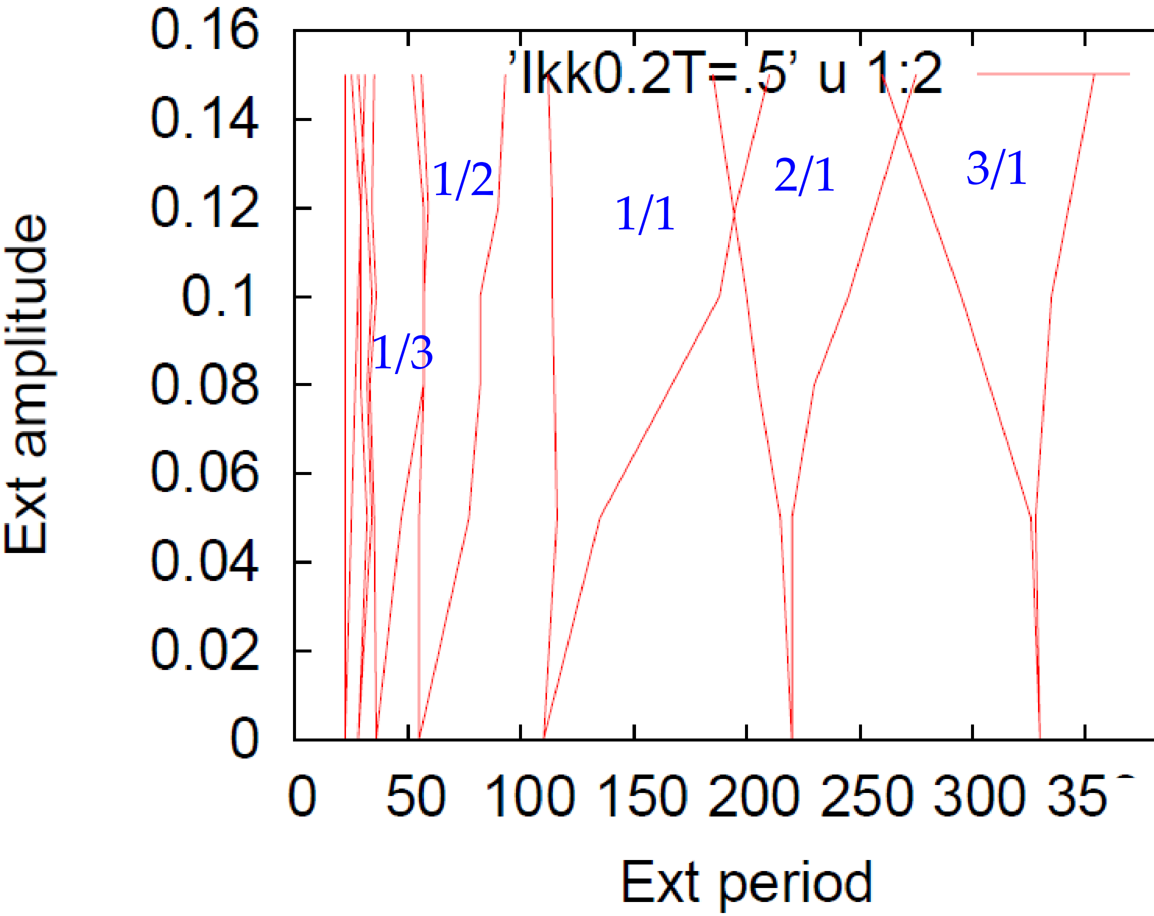
Externally ‘forced’ NF-κB system



(S. Krishna, MHJ)

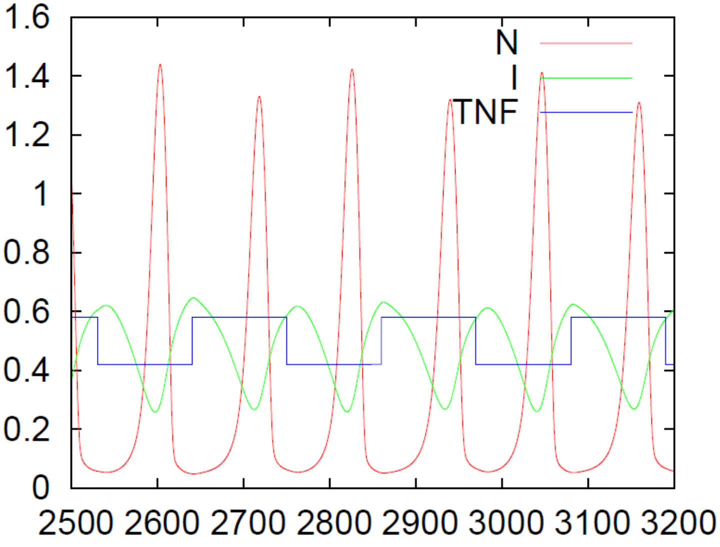
Sinusoidal TNF stimulus



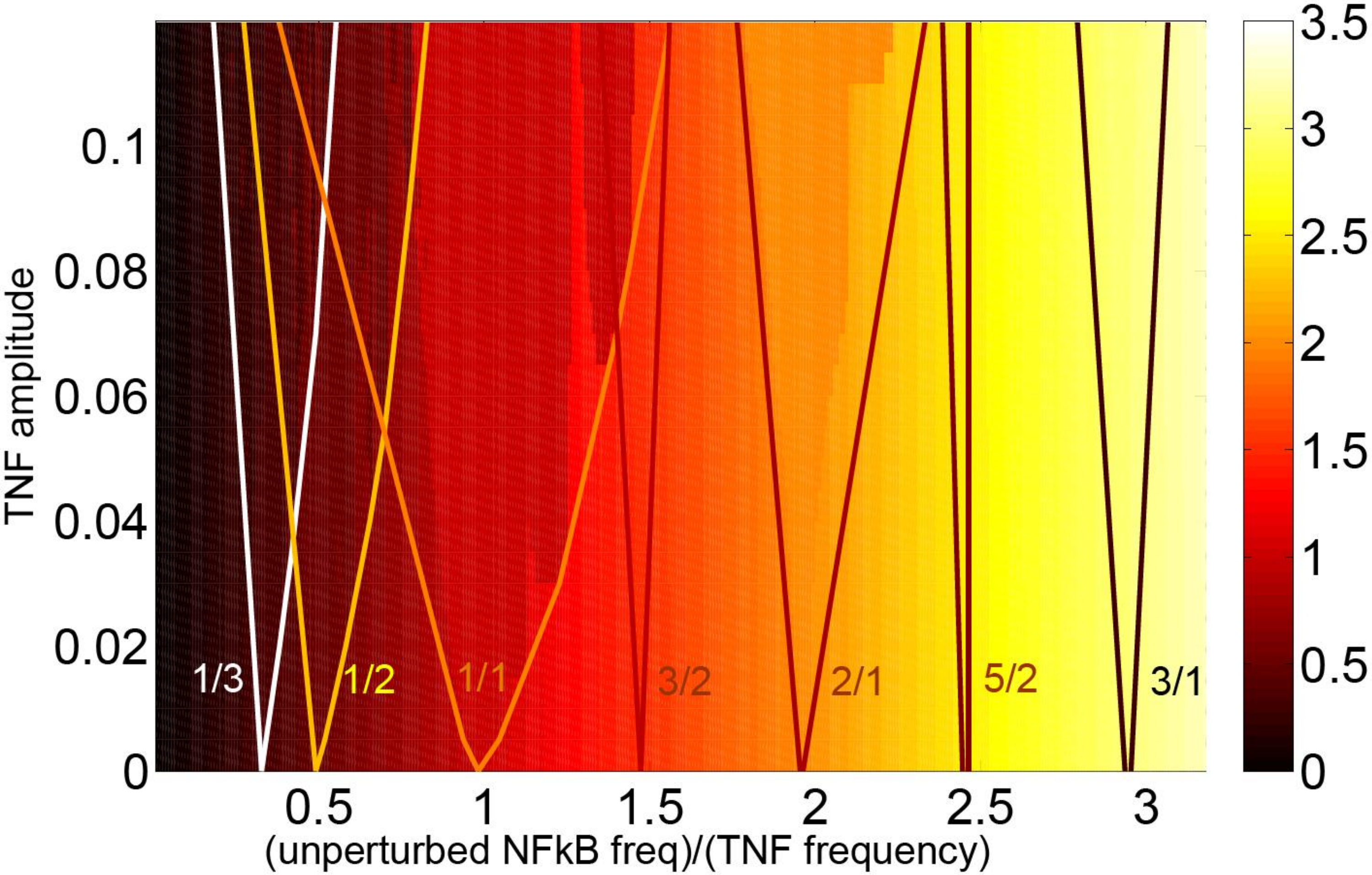


Square external TNF wave

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

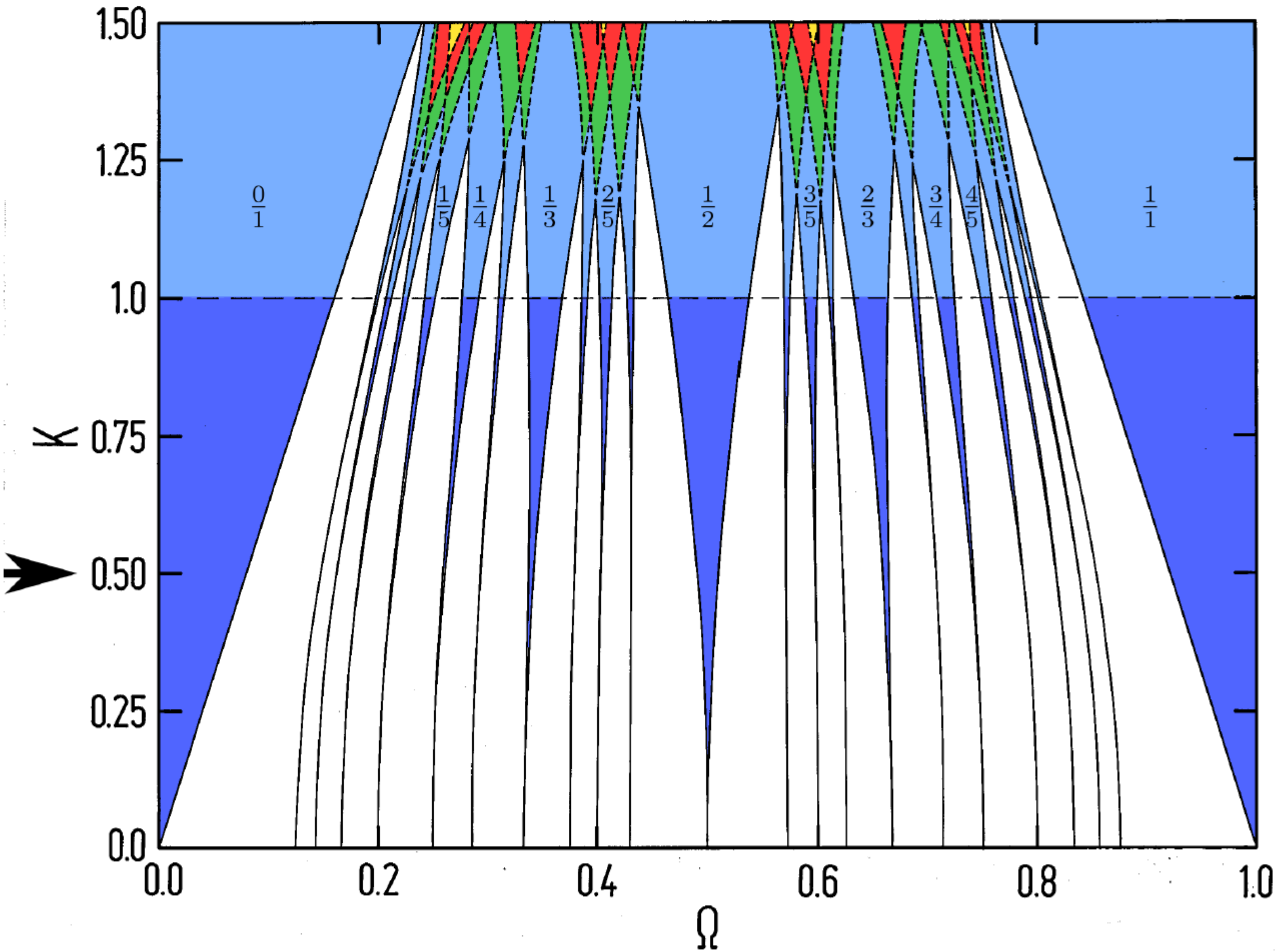


Arnold tongues for NF-kB/TNF system



External sine wave

Two coupled oscillators: Arnold tongues



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)

Consider the following two-dimensional equation with noise:

$$\dot{\vec{x}} = \vec{F}(\vec{x}) + \sigma^2 \vec{\Gamma}, \tag{1}$$

with

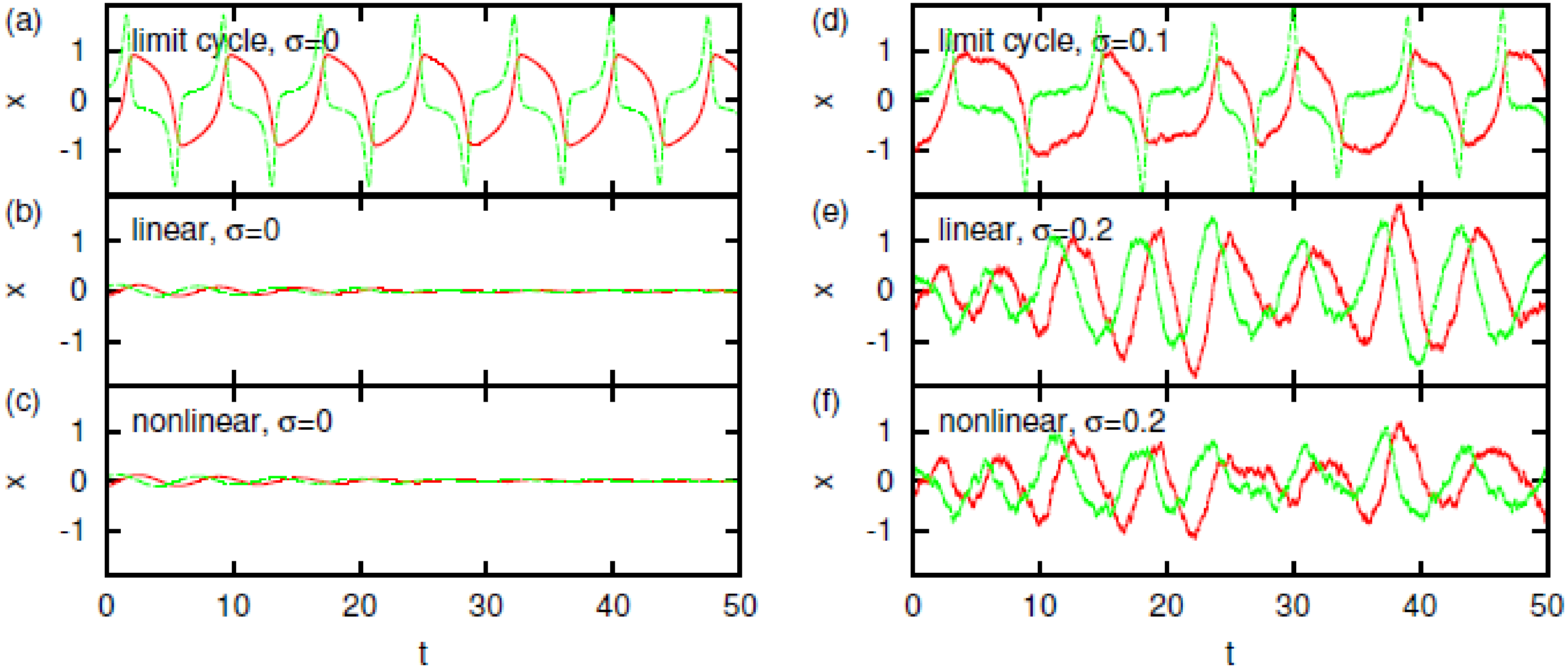
$$\vec{x} = \begin{pmatrix} x_1(t) \\ x_2(t) \end{pmatrix}, \quad \vec{\Gamma} = \begin{pmatrix} \Gamma_1(t) \\ \Gamma_2(t) \end{pmatrix}, \tag{2}$$

$$\vec{F}(\vec{x}) = \begin{pmatrix} x_2(t) \\ -(Bx_1(t)^2 - d)x_2(t) - x_1(x) \end{pmatrix}. \tag{3}$$

Here, d, σ, and B are parameters, and $\Gamma_i(t)$ are uncorrelated, statistically independent Gaussian white noise, satisfying

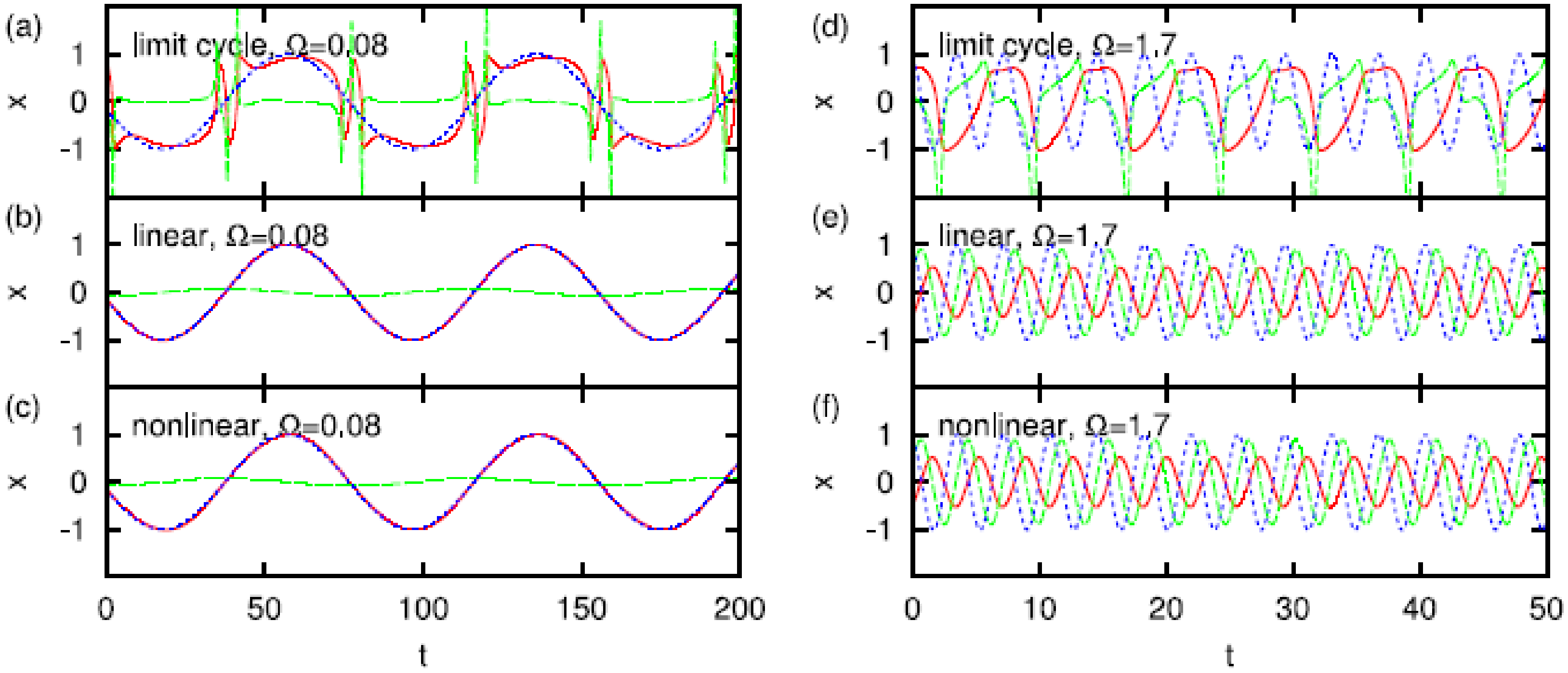
$$\langle \Gamma_j(t) \rangle = 0, \quad \langle \Gamma_j(t) \Gamma_k(t') \rangle = \delta_{j,k} \delta(t - t'). \tag{4}$$

Noise induced oscillations for a linear system !



With external additive oscillation

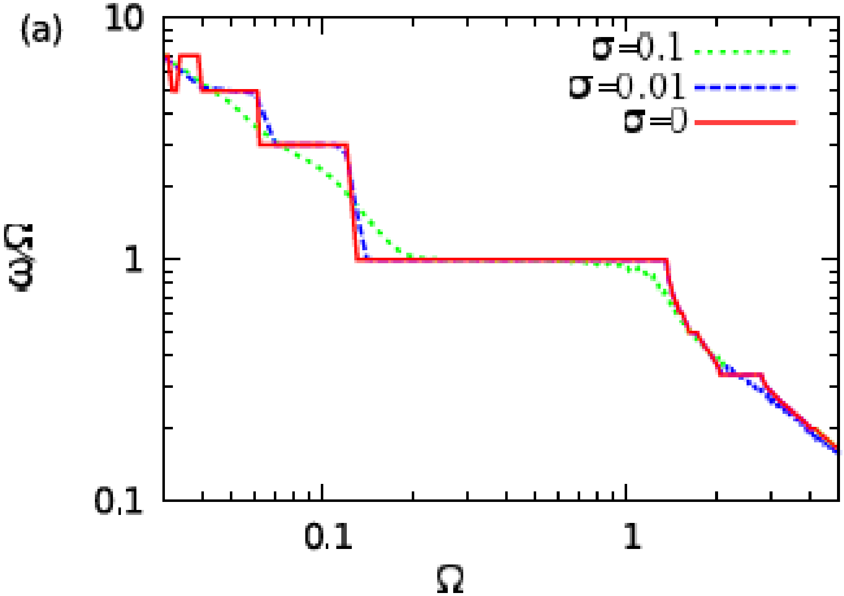
$$\dot{\boldsymbol{x}} = \boldsymbol{F}(\boldsymbol{x}) + \sigma^2\boldsymbol{\Gamma} + \boldsymbol{A}(t)$$



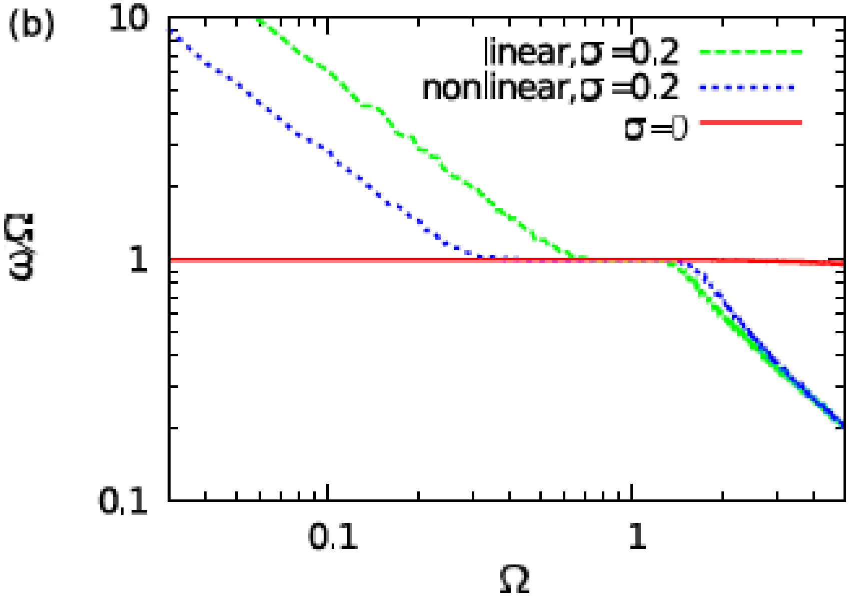
Full model: limit cycle

Linear, stable fixed point: ‘slaved´ oscillation

Mode-locking under noise and additive forcing

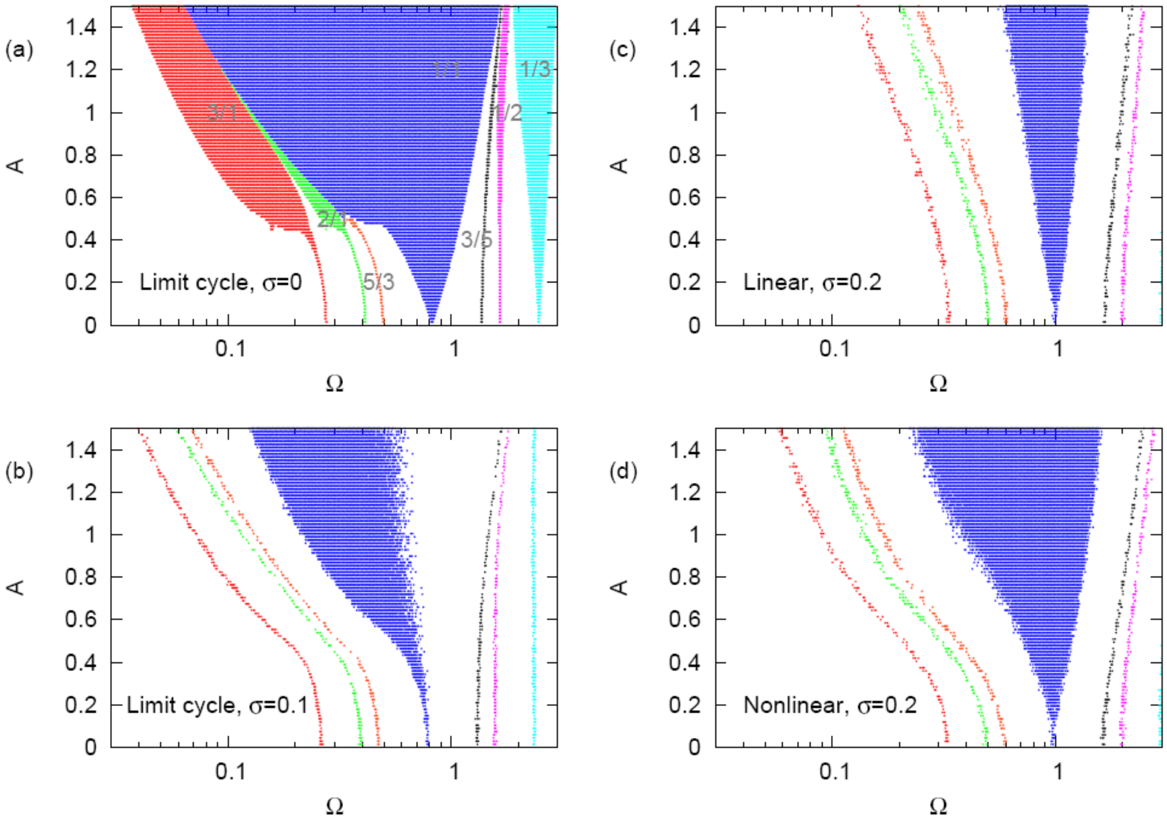


Full, non-linear model



Linear, stable fixed point

Arnold tongues with additive forcing

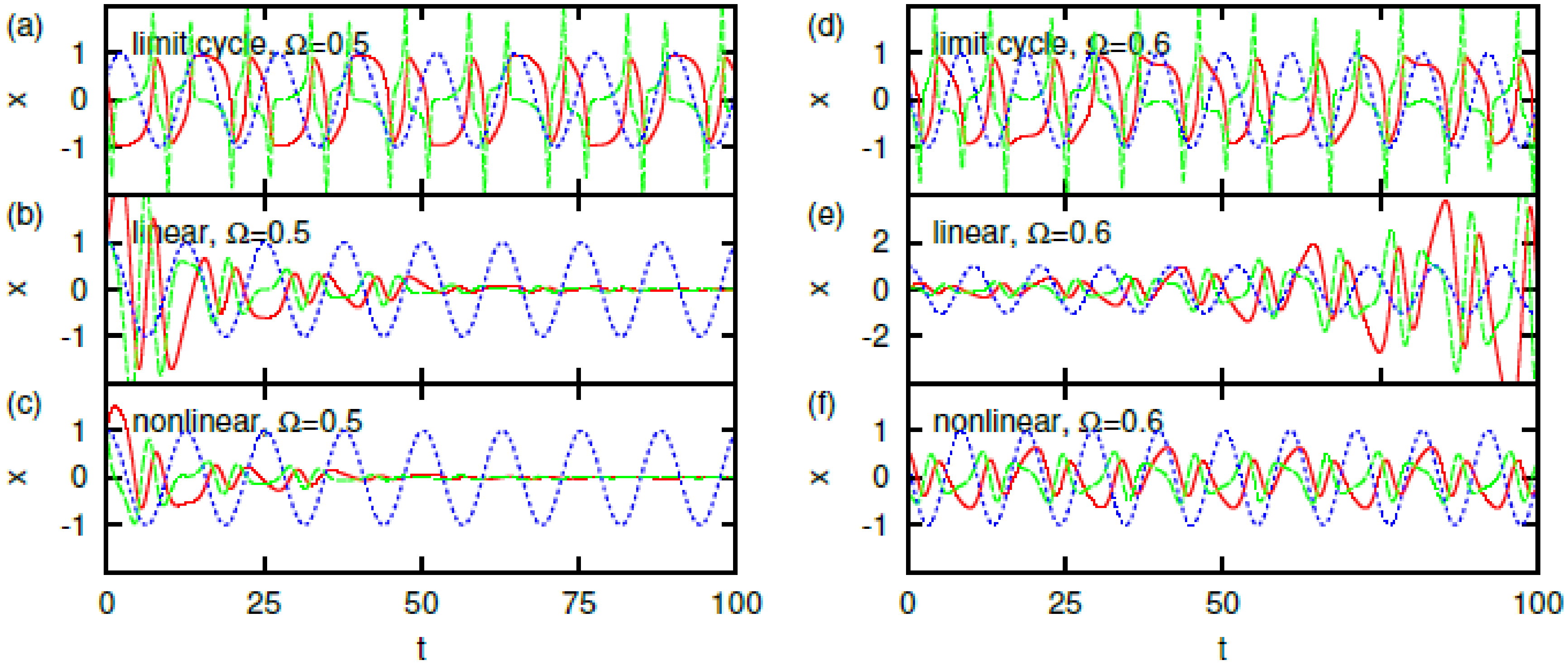


Conclusion: Arnold tongues → Non-linear system

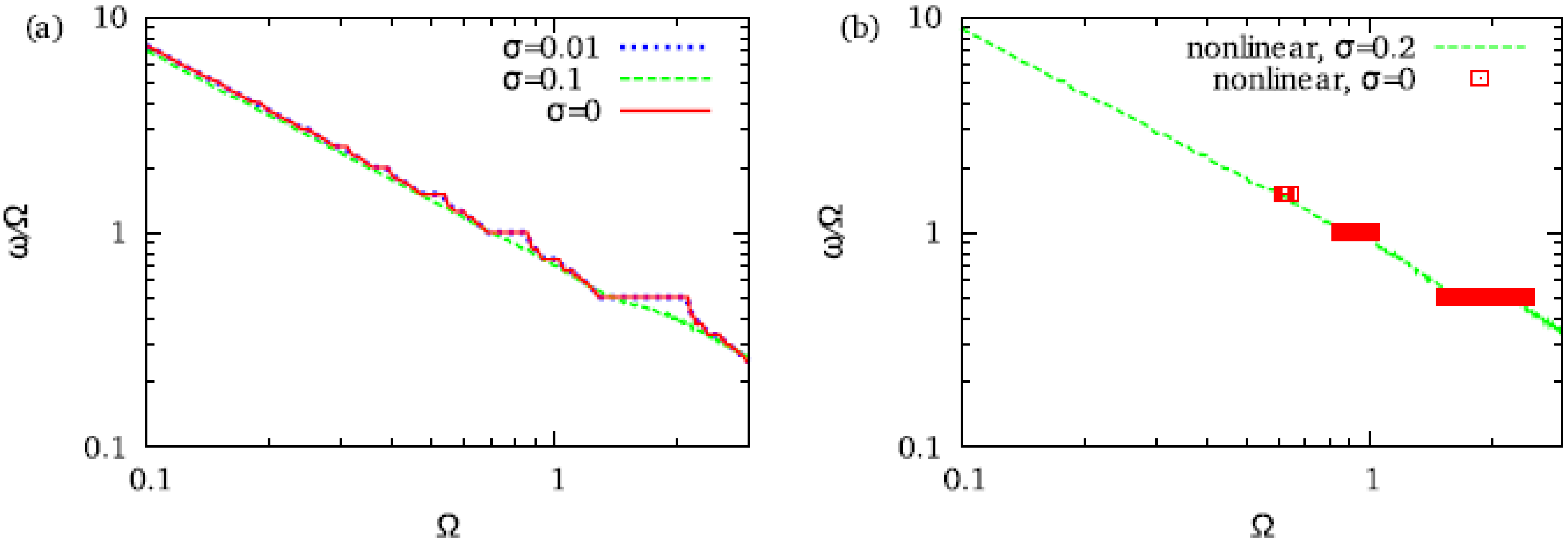
Only 1:1 tongue (slaved) → Linear system

Multiplicative forcing

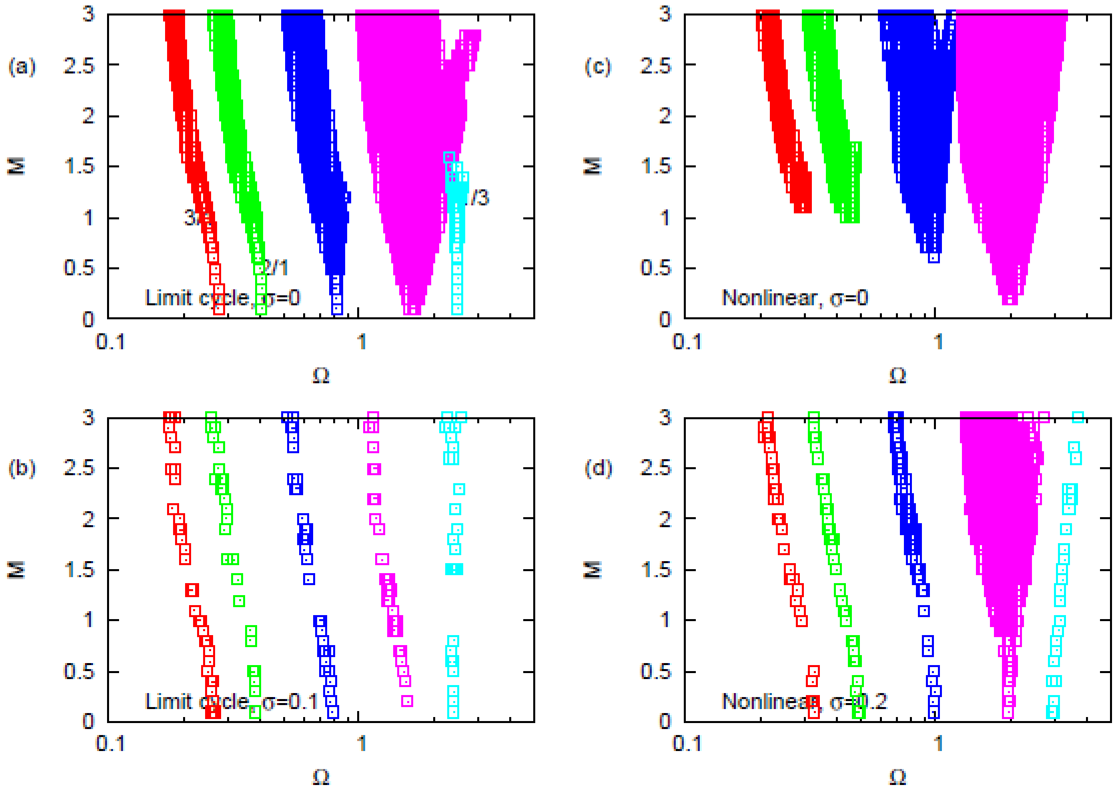
$$\dot{\boldsymbol{x}} = \boldsymbol{F}(\boldsymbol{x}) + \sigma^2\boldsymbol{\Gamma} + \mathbf{M}(t)\boldsymbol{x}$$



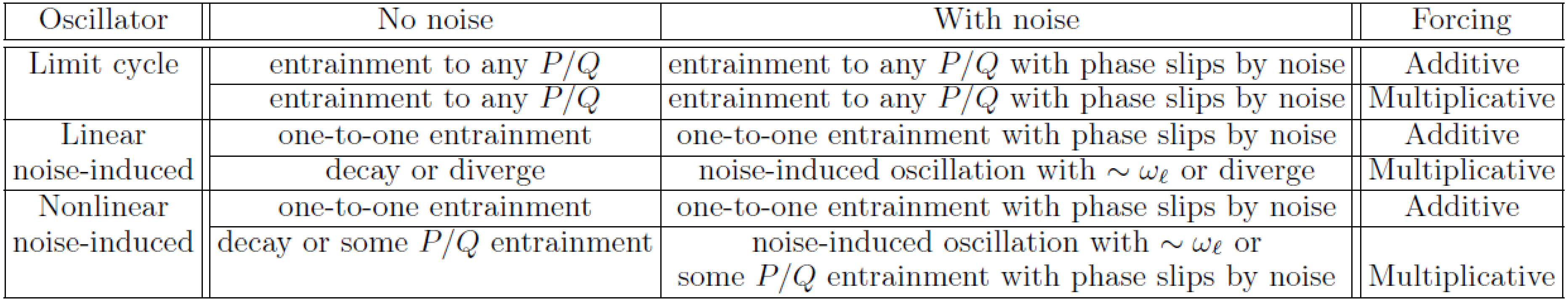
Mode-locking under noise and multiplicative forcing



Arnold tongues with multiplicative forcing

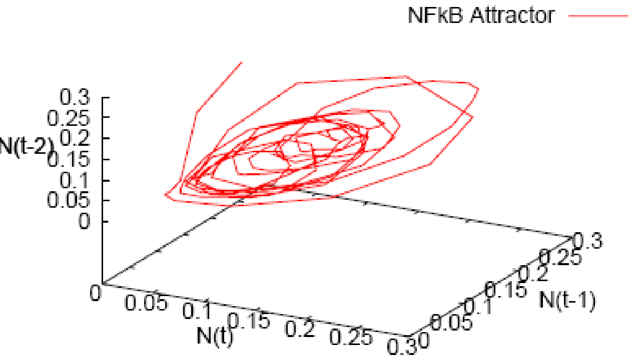


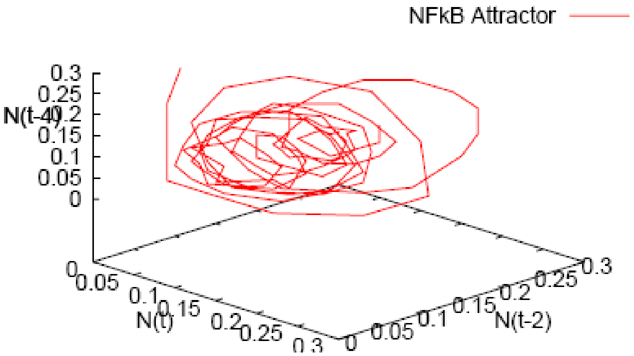
Summary of results: Additive and multiplicative forcing

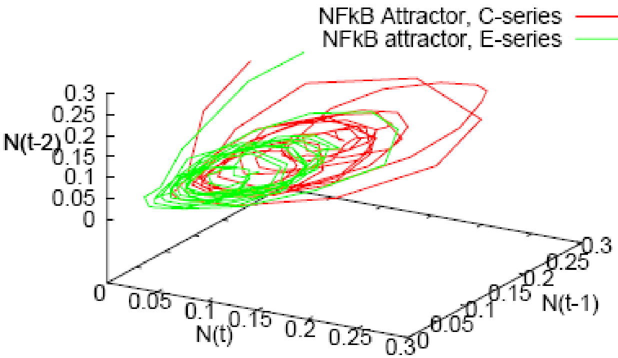


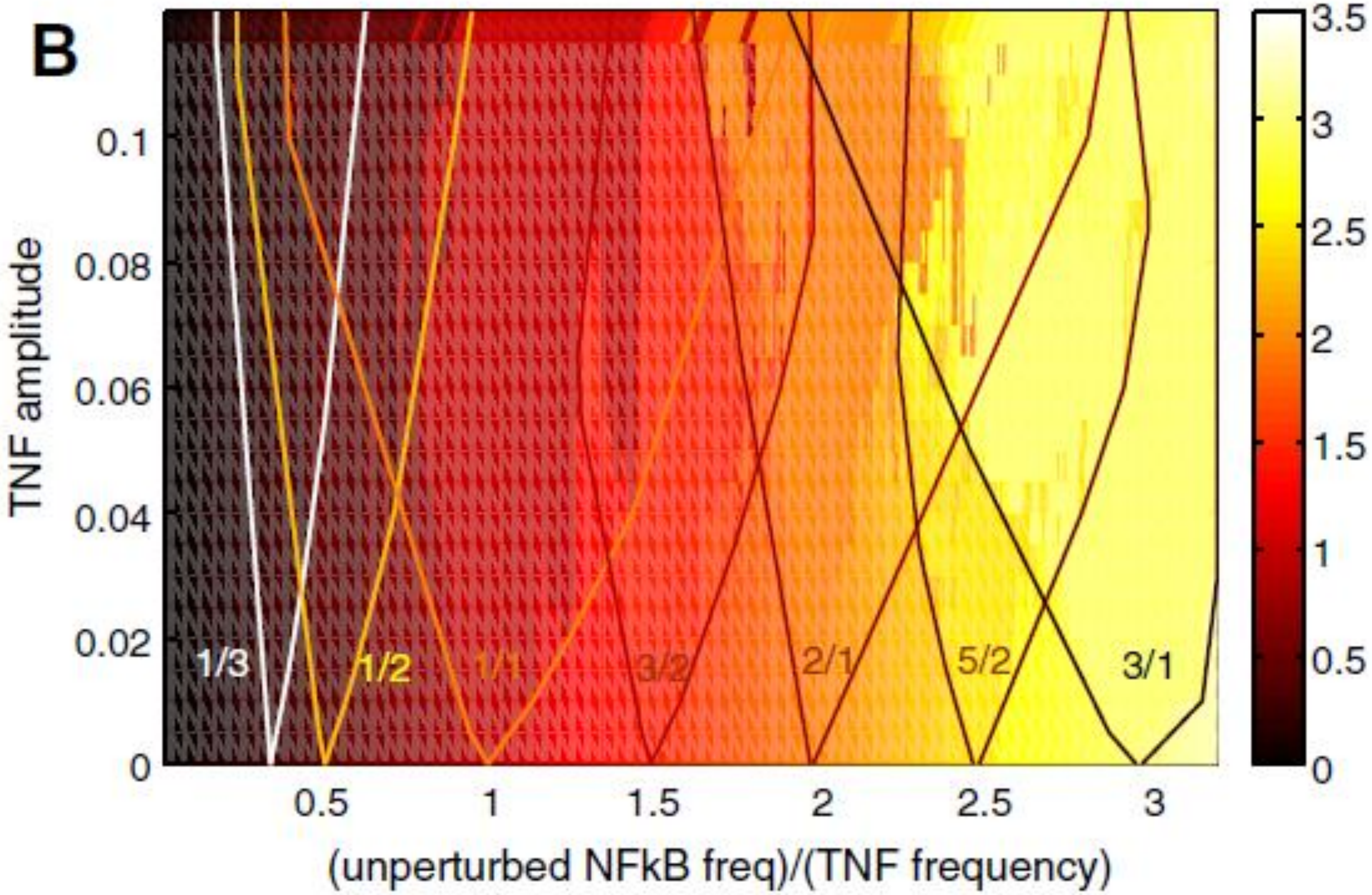
Oscillator	No noise	With noise	Forcing
Limit cycle	entrainment to any P/Q	entrainment to any P/Q with phase slips by noise	Additive
	entrainment to any P/Q	entrainment to any P/Q with phase slips by noise	Multiplicative
Linear noise-induced	one-to-one entrainment	one-to-one entrainment with phase slips by noise	Additive
	decay or diverge	noise-induced oscillation with $\sim \omega_\ell$ or diverge	Multiplicative
Nonlinear noise-induced	one-to-one entrainment	one-to-one entrainment with phase slips by noise	Additive
	decay or some P/Q entrainment	noise-induced oscillation with $\sim \omega_\ell$ or some P/Q entrainment with phase slips by noise	Multiplicative

Embedded attractors:
Chaos ??



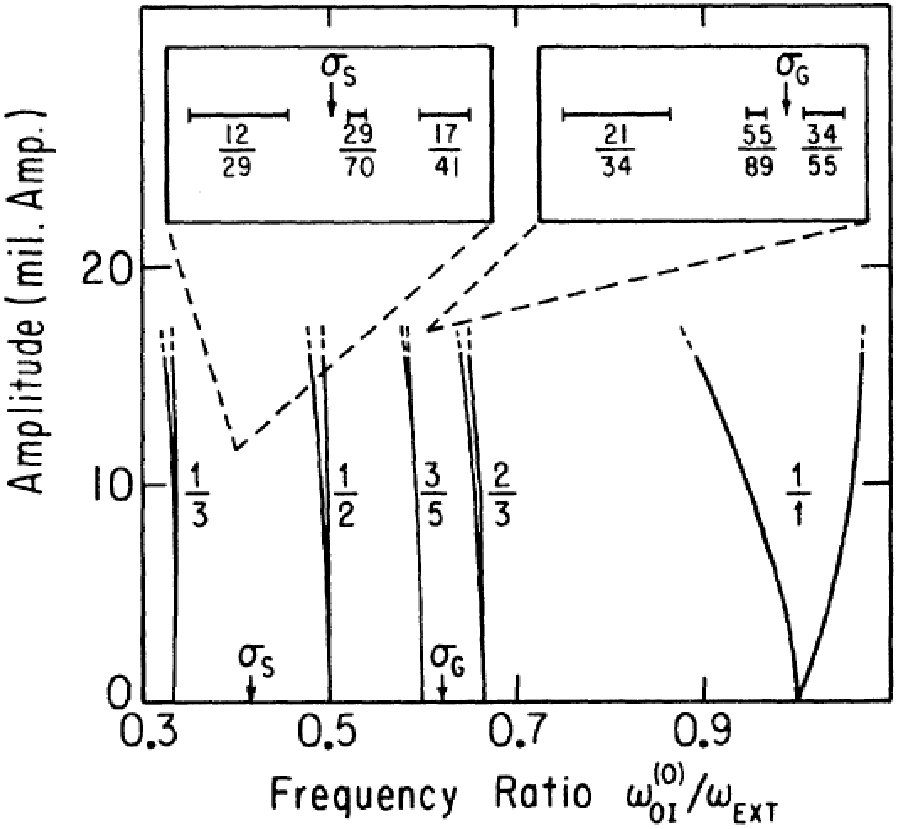




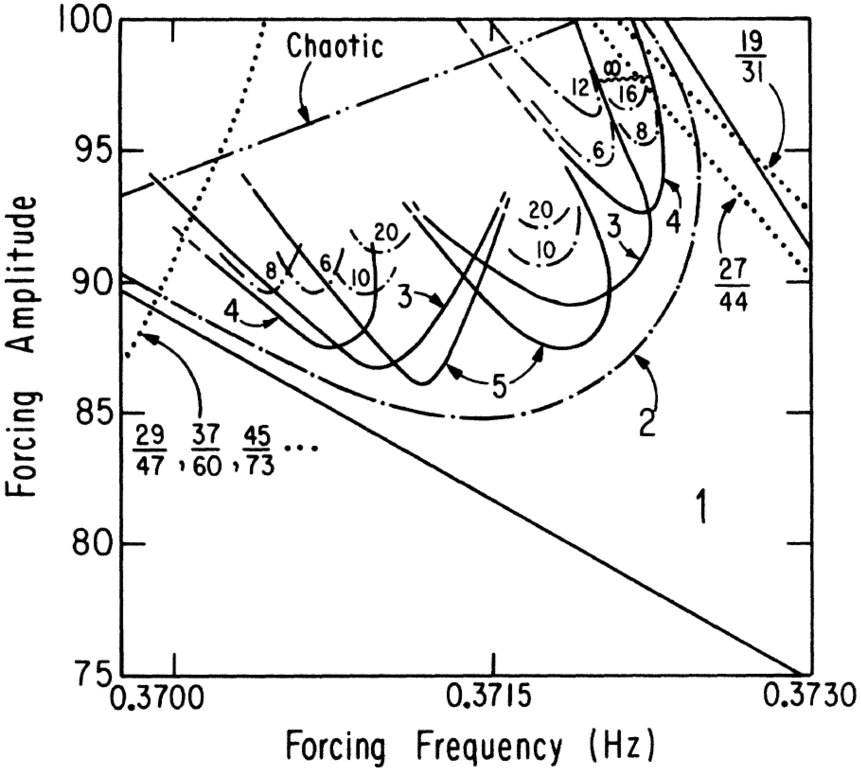


External square wave

Chicago basement convection !



Stavans, Heslot, Libchaber



Glazier, Jensen, Libchaber, Stavans

Electronic system, Gwinn, Westervelt, Harvard