Discrete time piecewise affine models of gene regulatory networks

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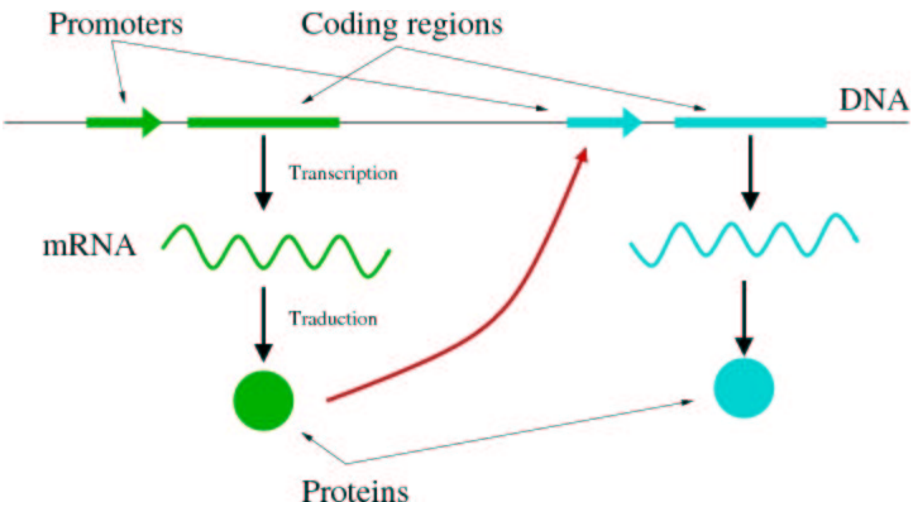
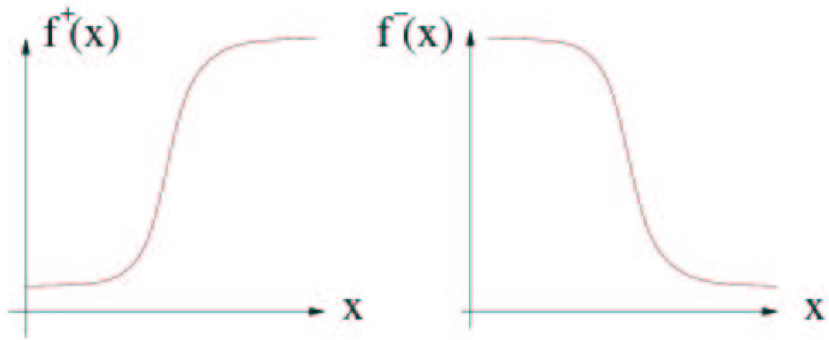
Principles and modelling of gene regulation



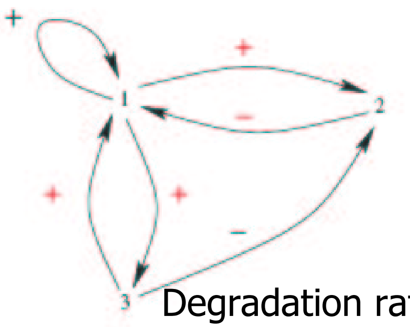
Dynamics:

- **Expression level** = x_i in [0,1]
- **Interaction:** [+ = Activation, - = Inhibition] + threshold

$$d_t x_B = -x_B + f^s(x_A) + \ldots$$



Gene regulatory networks

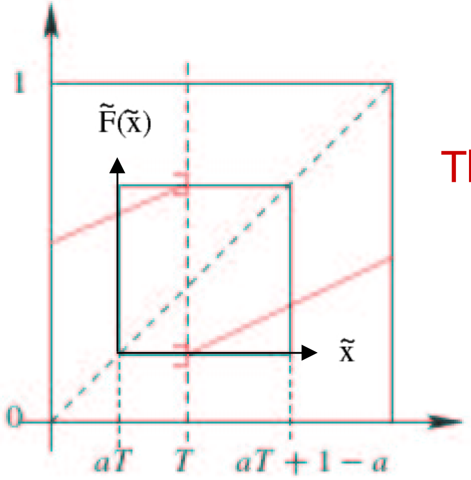


Weight [positive and normalized] Sign in {+,-} Threshold in [0,1]

$$x_i^{t+1} = a x_i^t + (1-a) \sum_{j \in I(i)} K_{ij} H(s_{ij}(x_j^t - T_{ij})), \quad i = 1, N$$

Degradation rate a in [0,1) Set of genes with action over i Heaviside function

Self-inhibitor $F(x) = ax + (1-a)H(T-x)$

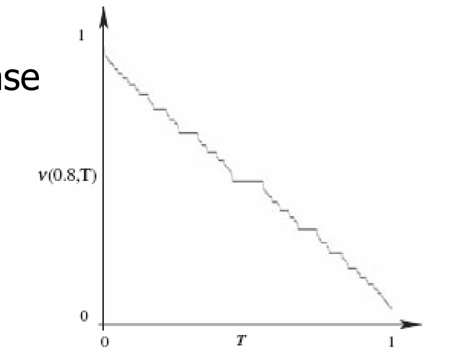


$\phi : \mathbb{R} \to [0,1]$ *is 1-periodic*

rotation number $\nu \in [0,1)$

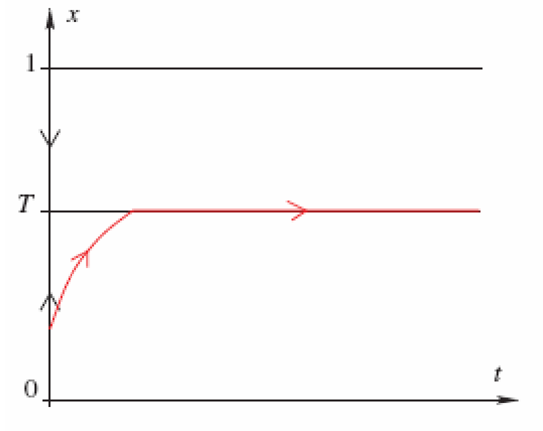
Thm: $\lim_{t\to+\infty} \left(\tilde{F}^t(\tilde{x}) - \phi(\nu t + \alpha) \right) = 0$ for all $\tilde{x} \in (0,1]$

$T \mapsto \nu(a,T)$ = decreasing Devil's staircase

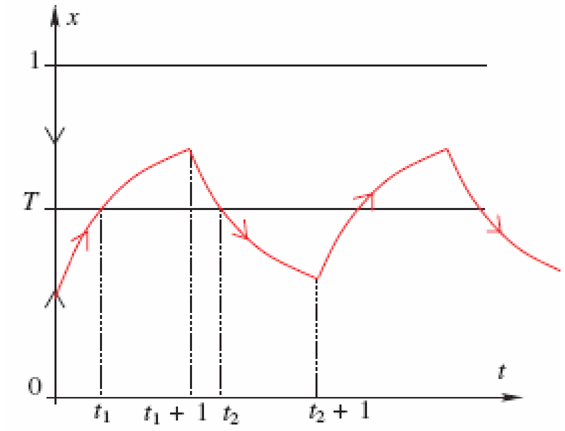


Biological relevance: Permanent oscillations with frequency mode-locking

Origin of oscillations: Delays

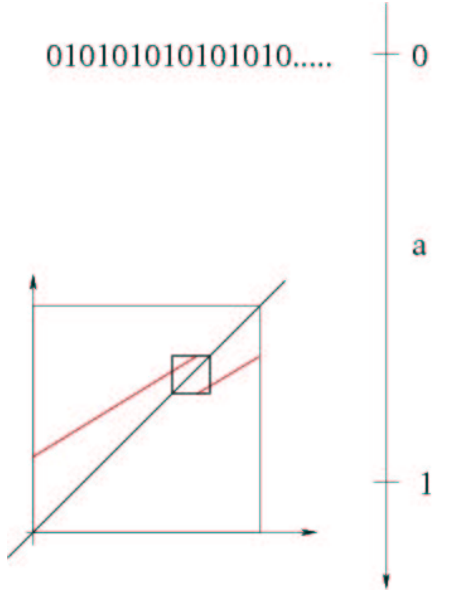


$$\frac{dx}{dt} = -x(t) + H(T - x(t))$$

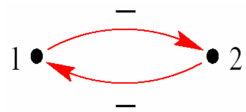


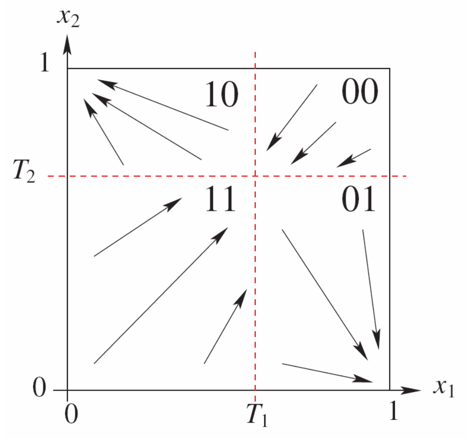
$$\frac{dx}{dt} = -x(t) + H(T - x(t-1))$$

« a = delay parameter »



Two mutually inhibiting interactions [Positive circuit]





$$\begin{cases} x_1^{t+1} = a x_1^t + (1-a) H(T_2 - x_2^t) \\ x_2^{t+1} = a x_2^t + (1-a) H(T_1 - x_1^t) \end{cases}$$

- either the orbit visits only 00 and 11
- or it converges either to (0,1) [when in 10] or to (1,0) [when in 01]

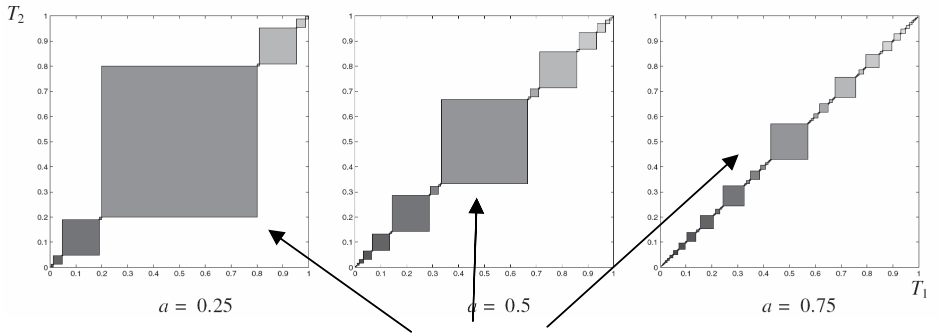
Existence of orbit visiting only 00 and 11 ?

Yes, depending on parameters

Asymptotically, we have $x^t = x_1^t = x_2^t$ and $x^{t+1} = ax^t + (1-a)H(T_1 - x^t) = ax^t + (1-a)H(T_2 - x^t)$

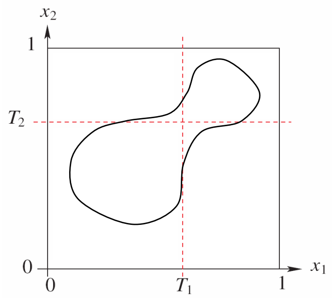
[Self-inhibitor: x^t attracted by a unique (quasi)-periodic orbit with rotation number ν **]**

Existence domains of (quasi-)periodic orbits



ν = 1/2

Origin of permanent oscillations

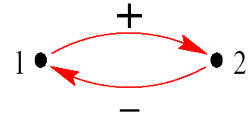


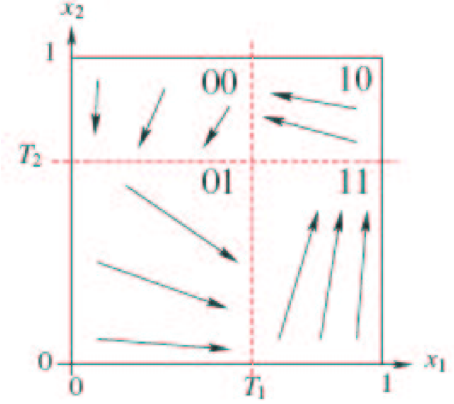
(possible) trajectory in a system of coupled differential equations with **delays**

Negative circuit of two genes

$$x_i^t = (1-a)\sum_{k=0}^{\infty} a^k \theta_{3-i}^{t-k-1} \text{ for all } t \in \mathbb{Z},\ i = 1, 2.$$

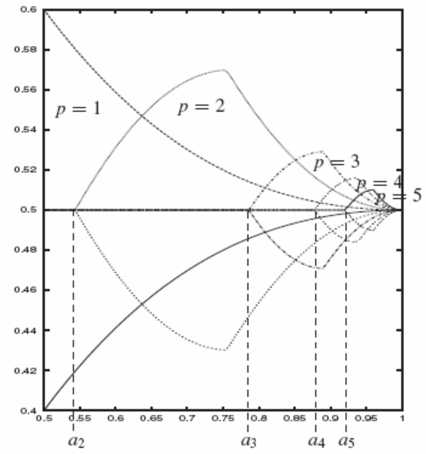
Symbolic dynamics

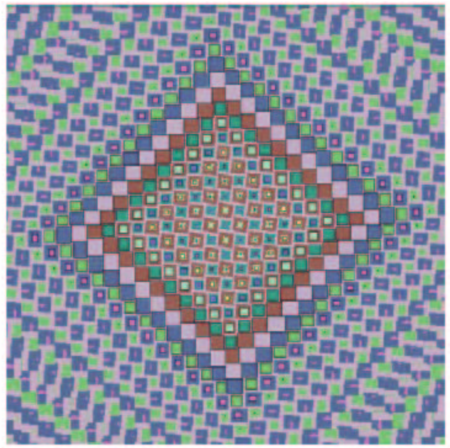




1/Balanced orbits

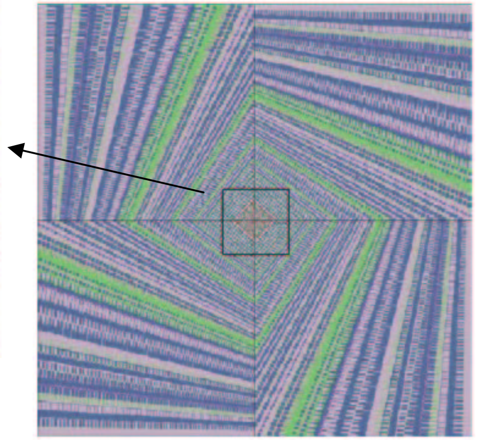
$\theta^t = (00^p\ 01^p\ 11^p\ 10^p)^\infty$ exists iff (T_1, T_2) in $[T_p(a), 1-T_p(a)]^2$



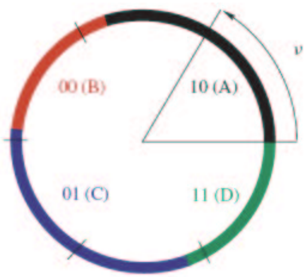


T_1 = T_2 =1/2

Ex: a = 0.99 > a_14



2/ Regular orbits

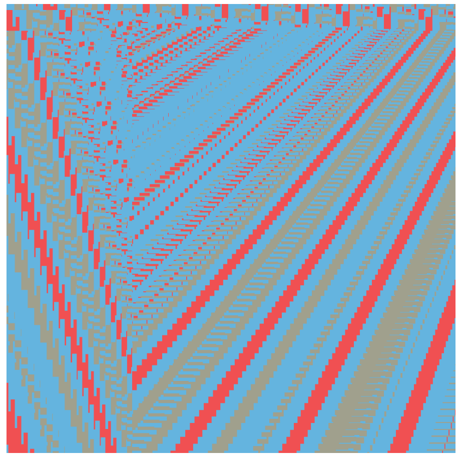


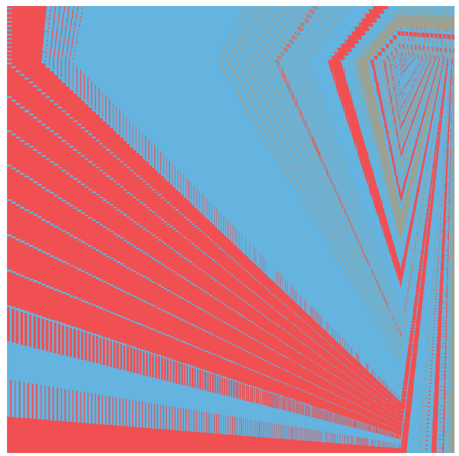
$\rightarrow \theta^t$

Parameters: (A,B,C,D,ν)

Analysis of a family of regular orbits:
(A,B,C,D,ν) such that
-1 point/lap in 10 and 00
- p points/lap in 01
- ρ points/lap in 11

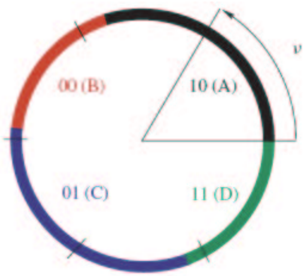
Ex2: T_1 = T_2 = 0.88





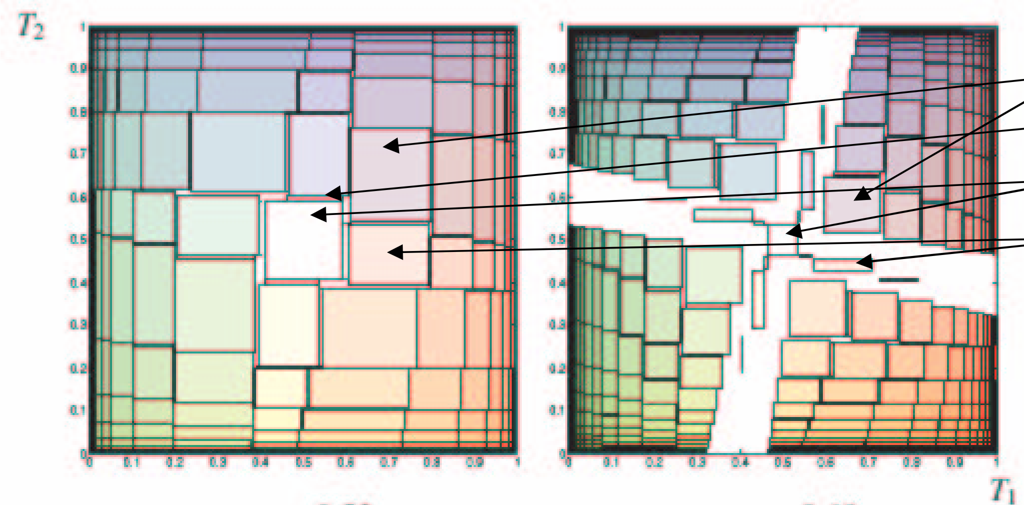
Existence and uniqueness of regular orbits

with (A,B,C,D,ν) s.t. 1 pt/lap in 10 and 00, p pts/lap in 01, ρ pts/lap in 11



a_c ~ 0.544

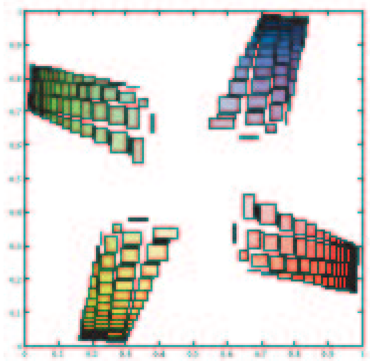
Theorem 4.1. (Families of regular orbits and their parameter dependence. Simple case) *The (p, ρ)-regular orbit exists iff (T_1, T_2) belongs to a unique rectangle $I_1(a, p, \rho) \times I_2(a, p, \rho)$ which exists for every $p \geqslant 1$ and $\rho \geqslant 1$ provided that $a \in (0, a_c]$.*



$a = 0.52$ $a = 0.68$

(p,ρ) =
(2,2)
(1,3/2)
(1,1)
(2,1)

Proposition: **When a>a_c, existence for p>p(a) and ρ>ρ(a,p).**



$n_A = 2$ and $n_C = 2, 6$

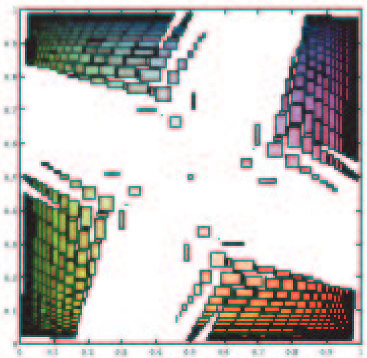
Ex: a = 0.842

Regular orbits with n_A pt/lap in 10, n_B pt/lap in 00, n_C pt/lap in 01, ρ pts/lap in 11

Theorem 4.3. (Families of regular orbits and their parameter dependence. General case) *Let $n_A \geqslant 1$ and $n_C \geqslant 1$ be arbitrary integers.*

The (n_A, n_B, n_C, ρ)-regular orbit can exist – upon a suitable choice of the parameters (a, T_1, T_2) – for any ρ in an interval of the form (ρ_c, ∞) only if $n_B = 1$.

The $(n_A, 1, n_C, \rho)$-regular orbit exists iff (T_1, T_2) belongs to a unique rectangle $I_1(a, n_A, n_C, \rho) \times I_2(a, n_A, n_C, \rho)$ which exists provided that $a \in [\underline{a}_{n_A,n_C}, \overline{a}_{n_A,n_C}]$ and that ρ is larger than a critical value (say $\rho \geqslant \rho_{a,n_A,n_C}$). The numbers $\underline{a}_{n_A,n_C}$ and $\overline{a}_{n_A,n_C}$ are known explicitly.



$n_A = 1$ and $n_C = 1, 20$

Open problems: Other regular orbits, non regular orbits, complete description (a < ½)