

Discrete-time piecewise-affine models of genetic regulatory networks: single cell and population dynamics

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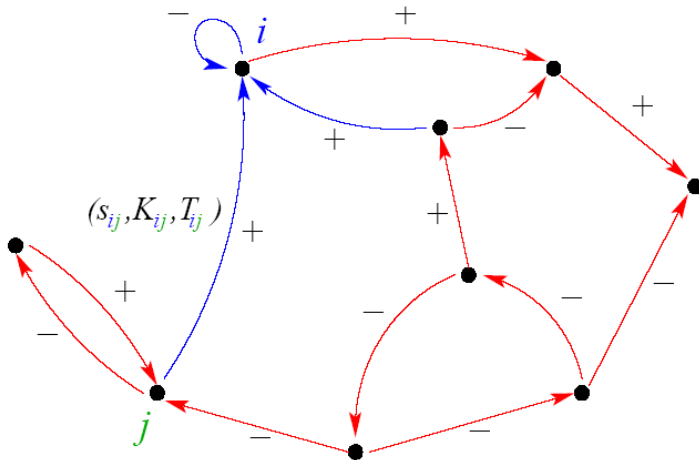
In collaboration with:

- R. Lima, B. Fernandez: *Centre de Physique Théorique (CPT, Marseille)*
- R. Coutinho: *Universidade Técnica de Lisboa (IST, Portugal)*
- E. Ugalde: *Universidad Autónoma de San Luis Potosí (UASLP, Mexico)*
- M. Bonnet, P. Ferrier, S. Jaeger, S. Spicuglia: *Centre d'Immunologie de Marseille Luminy (CIML)*

References:

- *Discrete time piecewise affine models of genetic regulatory networks*, Coutinho *et al.*, J. Math. Bio., in press.
- *Dynamical complexity of discrete-time regulatory networks*, Lima *et al.*, Nonlinearity, **19**, 2006.
- *Regulations and time scales in the control of the TCR β allelic exclusion*, in preparation.

G.R.N. & Discrete-time piecewise-affine models



Gene i	\leftrightarrow	Node i
Gene density	\leftrightarrow	Variable $x_i^t \in \mathbb{R}$
Action of gene j over gene i	\leftrightarrow	Arrow $j \rightarrow i$
Action characteristics	\leftrightarrow	$\left\{ \begin{array}{l} \text{Sign } s_{ij} \in \{-1, +1\} \\ \text{Threshold } T_{ij} \in [0, 1] \\ \text{Intensity } K_{ij} > 0 \end{array} \right.$

At each node i of the network, the dynamics on gene densities $x_i^t \mapsto x_i^{t+1}$ is given by:

$$x_i^{t+1} = ax_i^t + \sum_{j \rightarrow i} K_{ij} H(s_{ij}(x_j^t - T_{ij}))$$

Two time-scales, and Discrete time dynamics

 \Rightarrow Delays

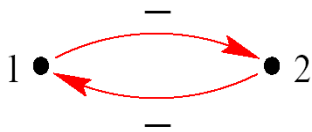
with:

- $a \in [0, 1)$ is constant: extinction rate
- H the Heaviside function:

$$H(x) = 1 \text{ if } x \geq 0 \text{ and } H(x) = 0 \text{ if } x < 0$$

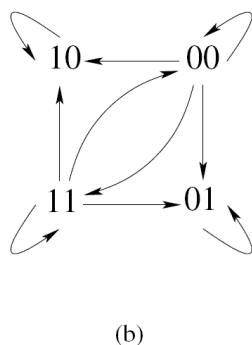
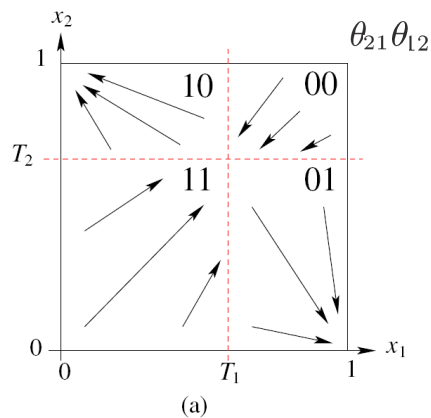
} \rightarrow Piecewise (affine) contracting dynamical system

two-node positive circuit:

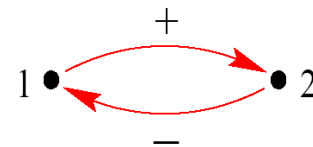


$$x_1^{t+1} = ax_1^t + (1-a)\theta_{12}^t, \quad \theta_{12}^t = H(T_{12} - x_2^t)$$

$$x_2^{t+1} = ax_2^t + (1-a)\theta_{21}^t, \quad \theta_{21}^t = H(T_{21} - x_1^t)$$

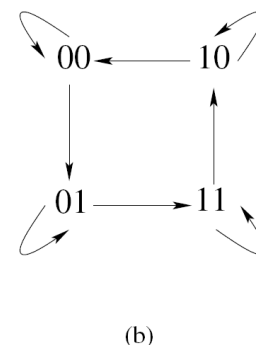
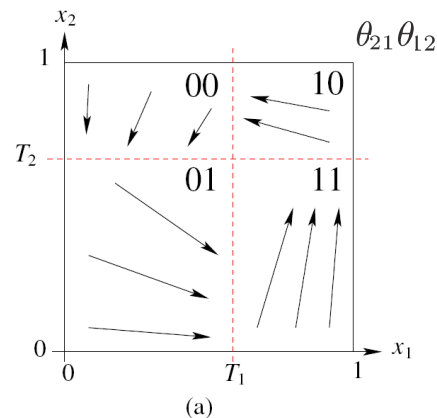


two-node negative circuit:



$$x_1^{t+1} = ax_1^t + (1-a)\theta_{12}^t, \quad \theta_{12}^t = H(T_{12} - x_2^t)$$

$$x_2^{t+1} = ax_2^t + (1-a)\theta_{21}^t, \quad \theta_{21}^t = H(x_1^t - T_{21})$$



Given a symbolic sequence $\mathcal{S} \rightarrow$ Is it the code \mathcal{C} of at least one orbit?

Main tool of dynamics analysis: Symbolic Dynamics

- **Coding:** Orbit $\{x_i^t\}_{i \in \llbracket 1, n \rrbracket, t \in \mathbb{N}} \rightarrow$ Symbolic sequence $\{\theta_{ij}^t\}_{t \in \mathbb{N}}$ where $\theta_{ij}^t = H(s_{ij}(x_j^t - T_{ij})) \in \{0, 1\}$, the code of the orbit.
- **Conversly:** Given a symbolic sequence $\mathcal{S} \rightarrow$ Is it the code \mathcal{C} of at least one orbit?
- **Admissibility:** Yes iff \mathcal{S} satisfies an Admissibility Condition (A.C.).
 - This A.C. ensures that the sequence of states computed with \mathcal{S} provides a sequence \mathcal{S}' s.t. $\mathcal{S} = \mathcal{S}' \Rightarrow \mathcal{S} = \mathcal{C}$.

- | |
|---|
| Symbolic sequence $\{\theta_{ij}^t\}_{t \in \mathbb{Z}}$ satisfying an Admissibility Condition (A.C.) |
|---|

 \Rightarrow

Orbit $\{x_i^t\} \in$ Attractor
$x_i^t = \sum_{q=0}^{+\infty} a^q \sum_{j \rightarrow i} K_{ij} \theta_{ij}^{t-q-1}$

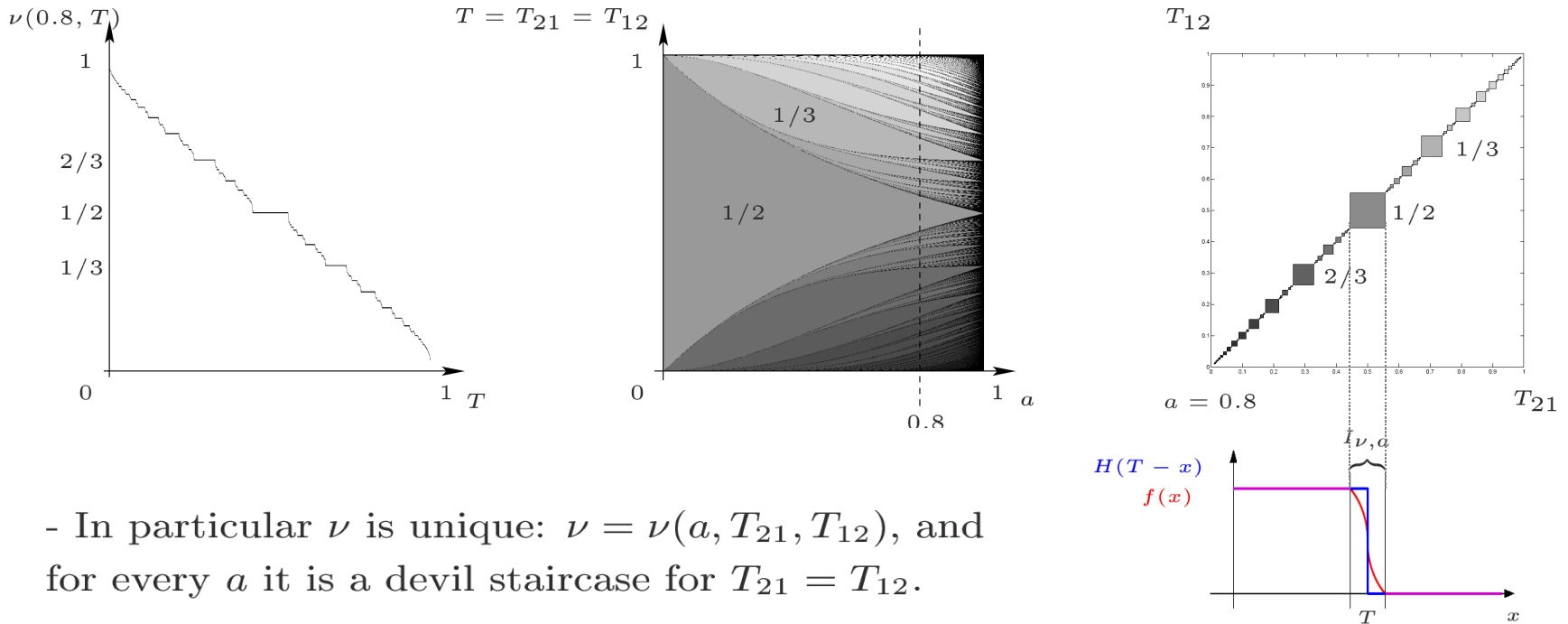
[Consequence of piecewise contracting dynamical system!]

- Verifying these conditions explicitly gives the bounds of the parameter domains (a, T, K) in which $\mathcal{S} \equiv \mathcal{C}$.
- **Strategy:** Attractor description = Description of admissible sequences!

two-node positive circuit:

- (Quasi-)periodic orbits: $x_1^t = x_2^t = \phi(\nu t + \alpha) \forall t \in \mathbb{Z}$, with $\alpha \in \mathbb{R}$, $\phi(x + 1) = \phi(x)$

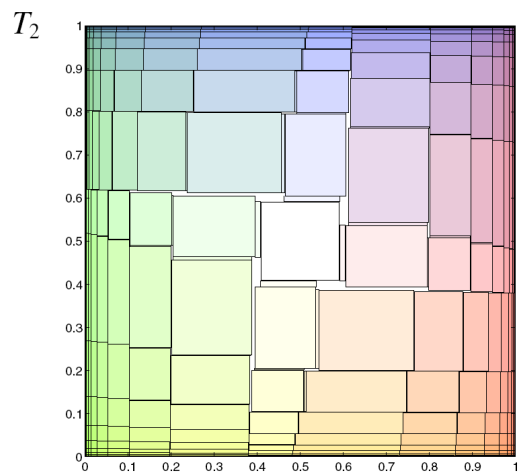
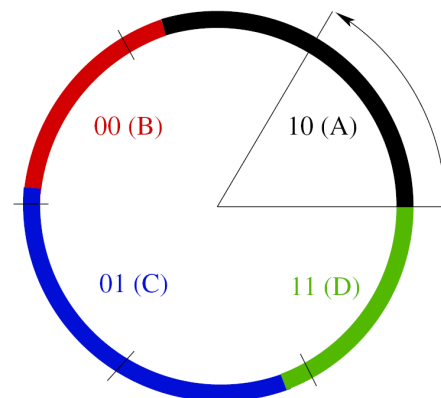
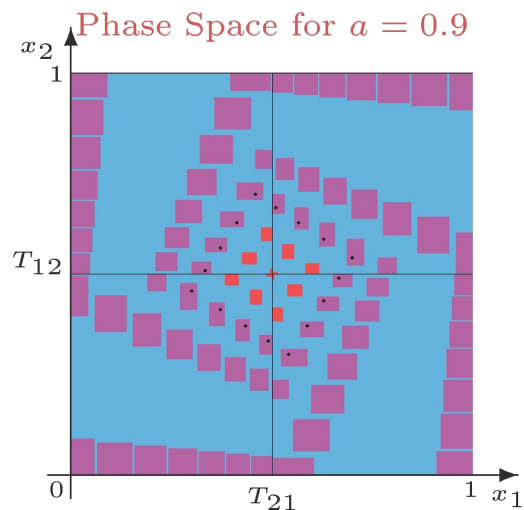
i.e characterized by a rotation number $\nu \in (0, 1)$, exist iff $(T_{21}, T_{12}) \in I_{\nu, a}^2$, where $I_{\nu, a}$ are explicitly known!



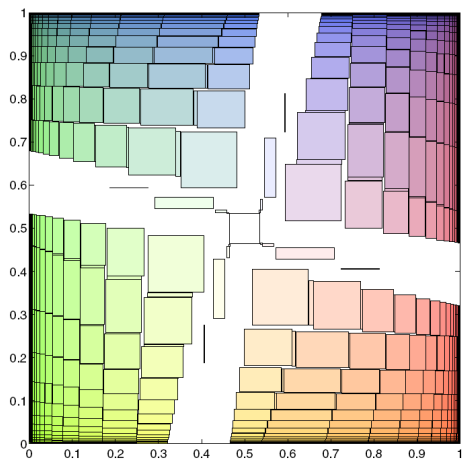
- In particular ν is unique: $\nu = \nu(a, T_{21}, T_{12})$, and for every a it is a devil staircase for $T_{21} = T_{12}$.

- There exists a non-zero Lebesgue measure set of **initial conditions** in phase space such that the dynamics of every point in this set is asymptotically conjugate to a rigid rotation on the circle.

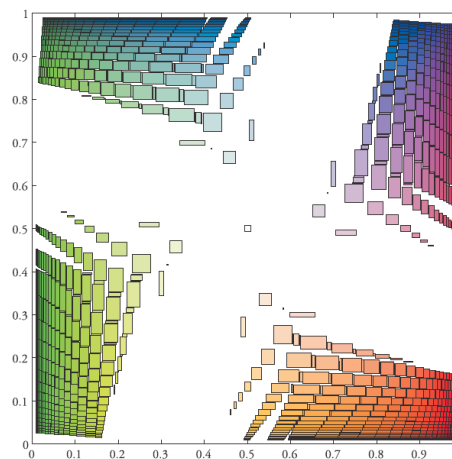
two-node negative circuit:



$a = 0.52$



$a = 0.68$



$a = 0.842$

What for bigger networks?

Dynamical complexity: $C(t) = \#\mathcal{P}^t$

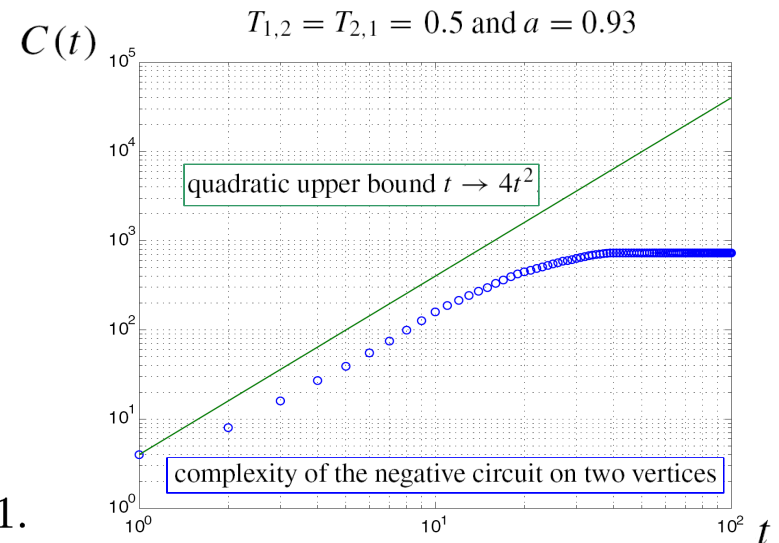
$$h_{\text{top}} \leq \limsup_{t \rightarrow \infty} \frac{1}{t} \log C(t)$$

Given the regulatory network with d nodes, there exists $a_0 \in [0, 1]$ such that for each contraction rate $a \in [0, a_0]$:

$$C(t) \leq 1 + c(1 + c^d t^d) \text{ with } c := \#\mathcal{P}^0 - 1.$$

More results on piecewise contracting dynamics:

- *Discrete time piecewise affine models of genetic regulatory networks*, accepted at J. Math. Bio.
- *Dynamical complexity of discrete time regulatory networks*, Nonlinearity, **19**, 2006.

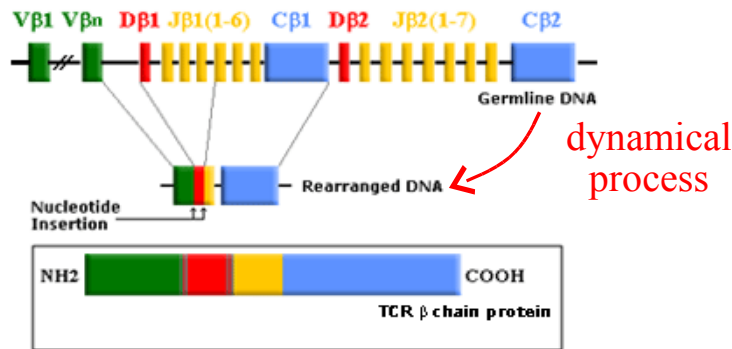


We consider a wider class of piecewise affine models, not limited to piecewise contractions.

We also consider locally expanding dynamics, as in the following modelisation.

The biology of the TCR β VDJ - recombinations

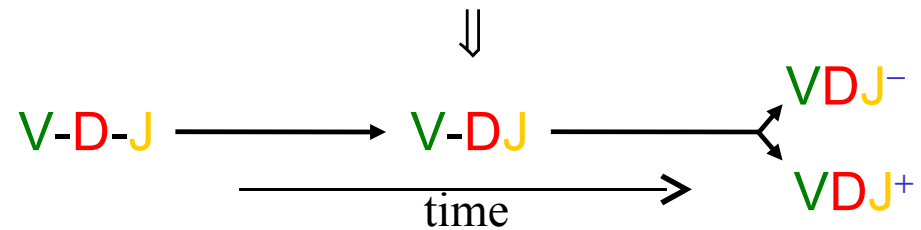
TCR β locus:



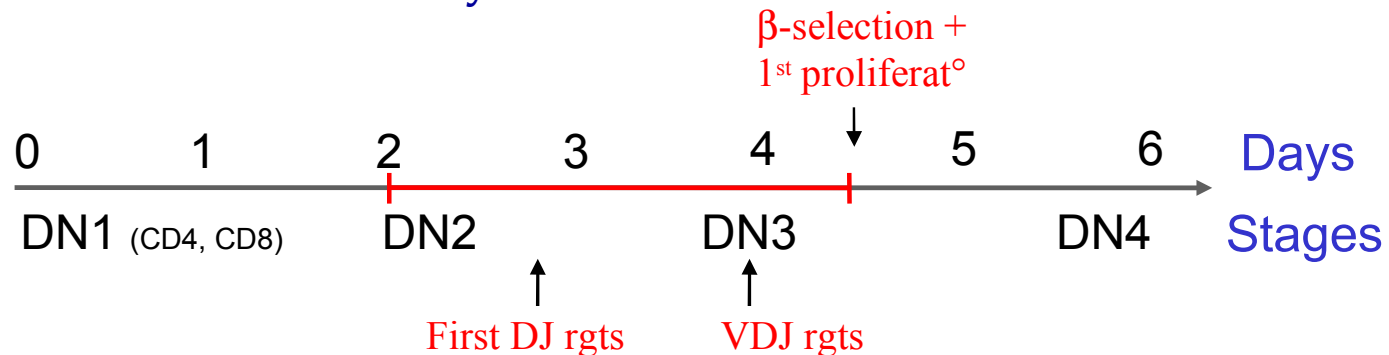
Human TCR beta chain gene rearrangement and expression

VDJ recombinations:

RAG proteins + Recombination Signal Sequences
 \Rightarrow DNA double-strand breaks
 + chromatin remodelling + DNA repairs + ???



Process time-window (in the thymus):



Allelic exclusion:

- All the following **cell types** are observed **in the thymus**, with different proportions:

D - J / D - J, DJ / D - J, DJ / DJ, VDJ⁺/ D - J, VDJ⁻/ D - J,
VDJ⁺/ DJ, VDJ⁻/ DJ, VDJ⁺/ VDJ⁻, VDJ⁺/ VDJ⁺

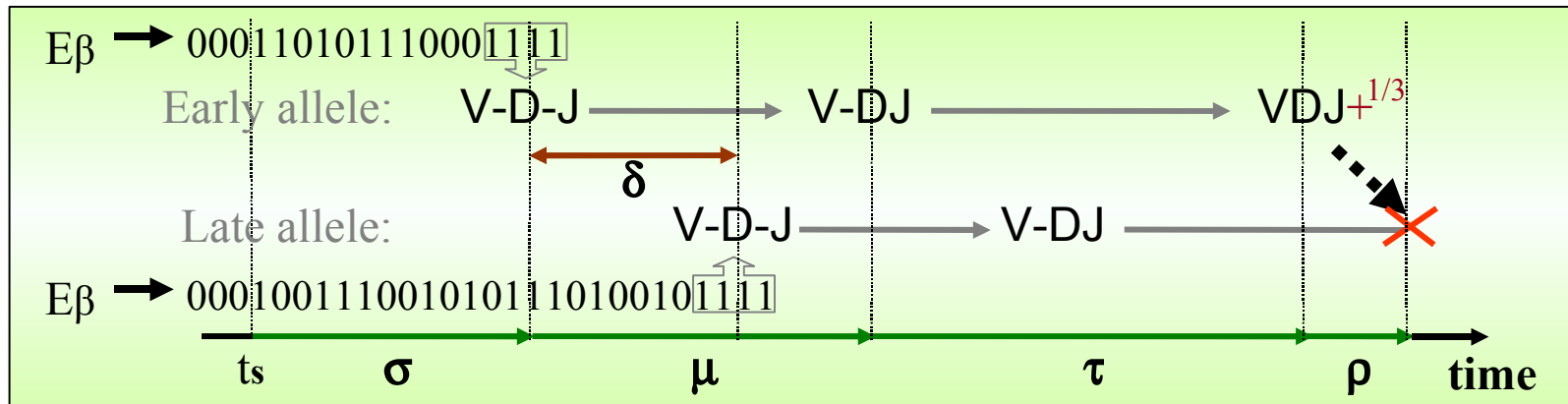
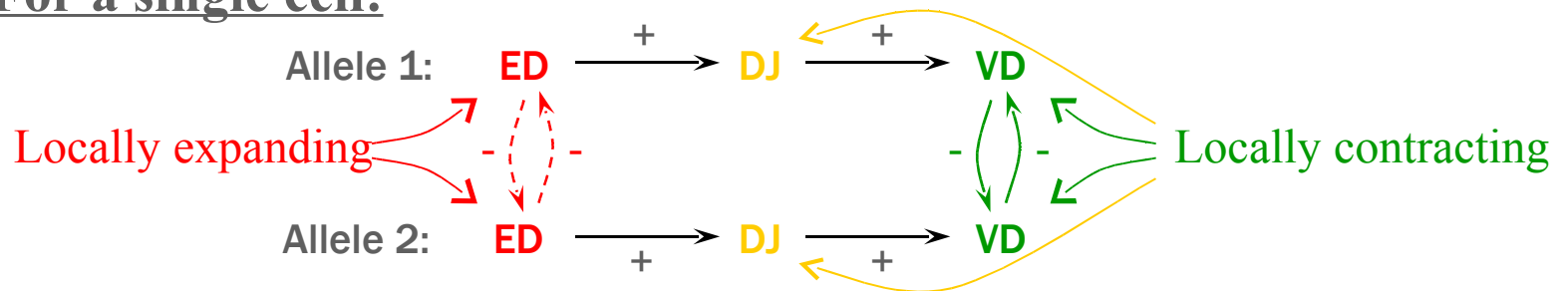
- In a **population** less than 1% of cells with a TCR β are eventually VDJ⁺/ VDJ⁺, and around 60% are VDJ⁺/ DJ.
- In a cell, there are some early common DNA processing activities on both alleles (such as V germline transcript^o) as well as some asynchronous activities (such as DNA demethylation and replication).

The lingering enigma:

- How is achieved the production of a single type of antigen receptor in the great majority of T-cells? → **1. Modelling**
- To which activity(ies) (trans-acting proteins, enhancers or another cis-regulatory sequences) is related the establishment of A.E.? → **2. Experimentation**

Our model

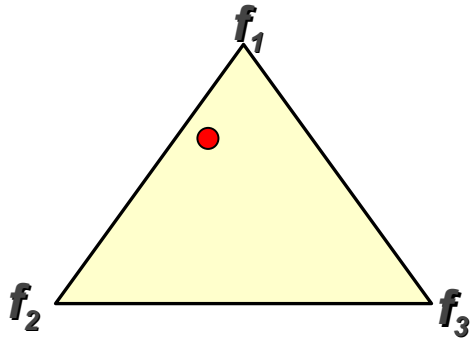
1 - For a single cell:



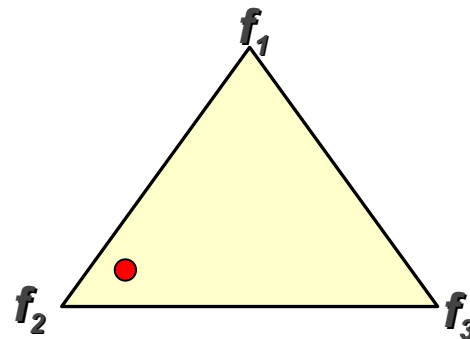
2 - For a cell population:

- **Piecewise expanding dynamics** \Rightarrow proba. distrib. funct. on t_s , σ and δ
 (“stochasticity” in addition to the “1/3 - 2/3” probability rule of (un-)productive rearrangements).
- **Piecewise contracting dynamics** \Rightarrow μ , τ time scales

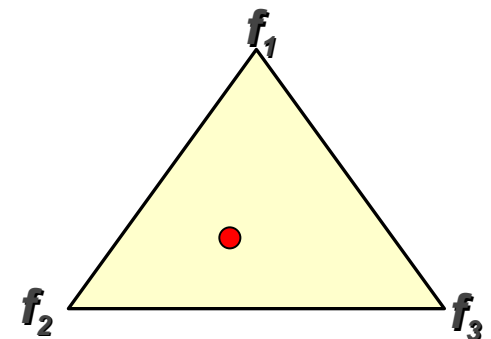
3 - For a synchronous cell population:



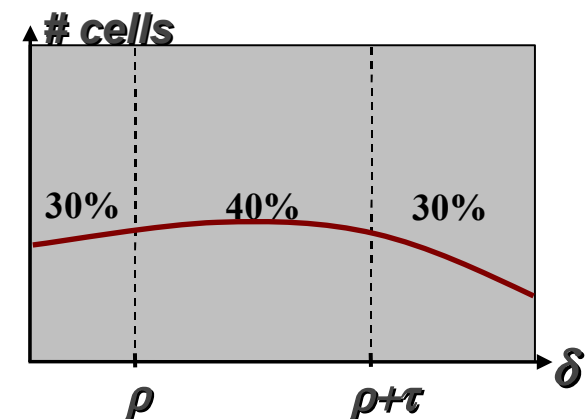
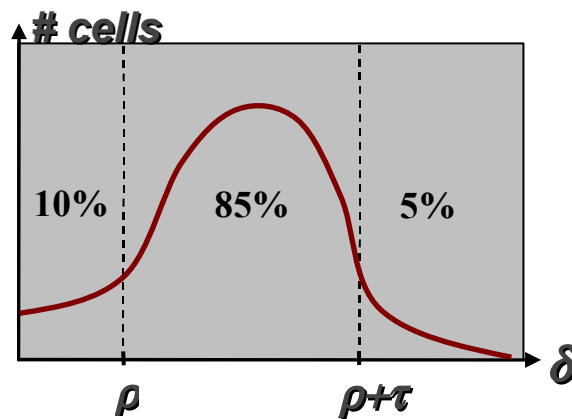
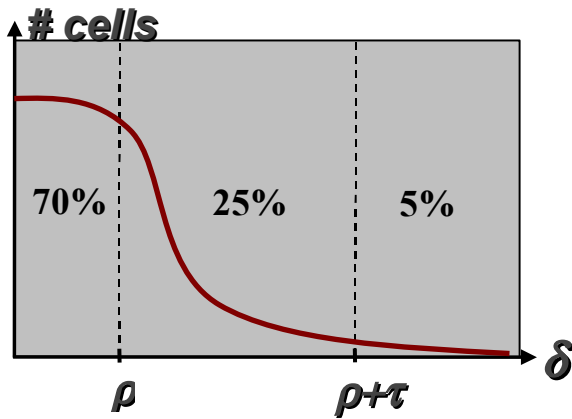
$$0,70 f_1 + 0,25 f_2 + 0,05 f_3$$



$$0,10 f_1 + 0,85 f_2 + 0,05 f_3$$

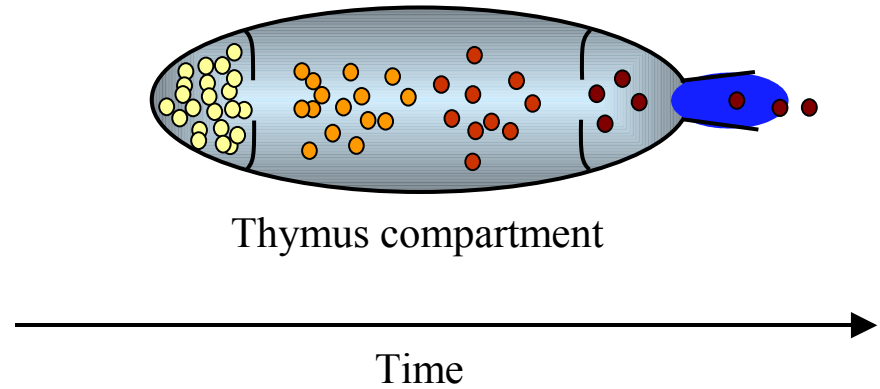
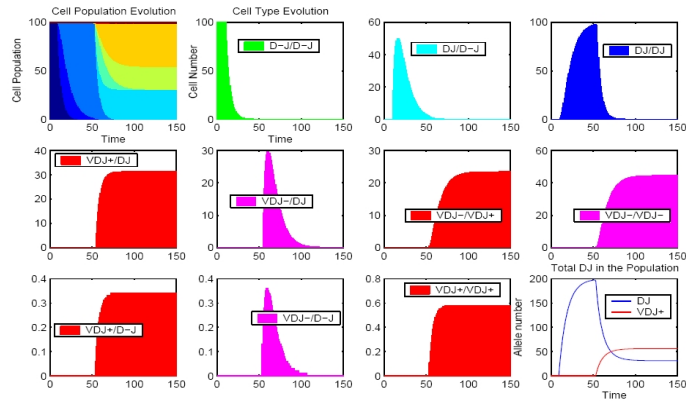


$$0,30 f_1 + 0,40 f_2 + 0,30 f_3$$

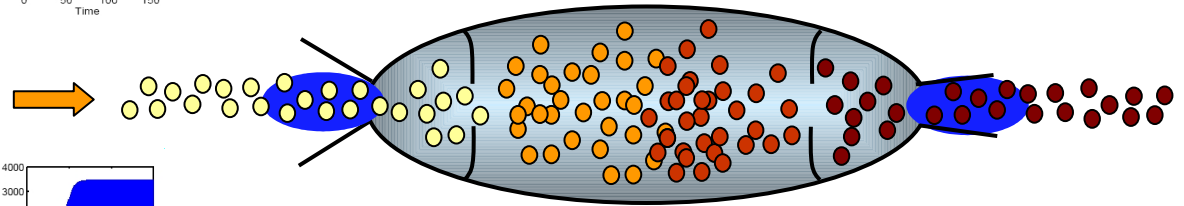
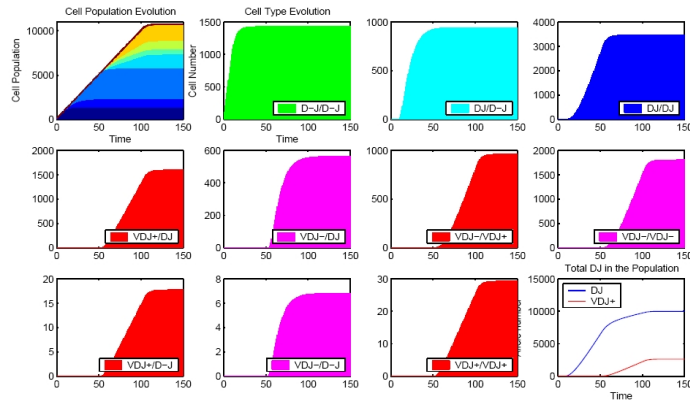


Cell trafficking

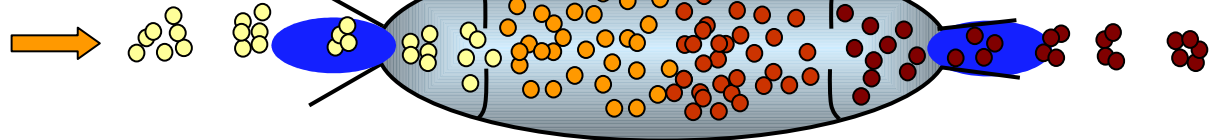
Synchronous population, no flux:



Continuous flux:



Periodic flux:



Conclusions – Prospectives

- The dynamics is rich, well structured, and not trivial
- Show robustness with respect to initial conditions and parameters, which is biologically relevant
- More results on general networks (complexity, ...)
- In our model the whole E β VDJ β locus is involved, and the manifestation of the allelic exclusion at the population level ensues from the single cell recombination dynamics.
- The recombination time τ is the same for each single cell, the allele handicap δ is only due to the stochastic behaviour of the enhancer E β and the signal time ρ is constant.
- A second recombination tentative of D β in each allele is not taken into account...
- More experimental data (to come with murine models: PCR, sequencing, ...) for hypotheses validation and parameters evaluation.
- Experimental temporal series are still not available in full detail. Only « asymptotic » quantities are known for the moment.

References:

- *Discrete time piecewise affine models of genetic regulatory networks*, Coutinho *et al.*, J. Math. Bio., in press.
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