Computational models of biological systems

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Complexity in biology

- **Molecular level**
  - Regulatory gene networks
  - Protein folding
- **Cellular level**
  - Cell physiology
- **Organism level**
  - Immune system
  - Nervous system
- **Population level**
  - Population dynamics
  - Ecological systems

Does Neural Communication Grow on Trees?

Analysis of interspike intervals sequences to learn and generalize correlations among neurons

The Goals

- To search for discriminating parameters between neural substrates sottending different perceptive states
- To develop analysis strategies applicable to spontaneous neural activities
- To understand neural code
- To infer (thalamocortical) networks of neurons from simultaneous record of their firing activity
- To study the neurophysiology of (cronic) pain

State of the art

- **Gerstein, Aertsen 1985: Crosscorrelograms to study cooperative firing activity in simultaneously recorded populations of neurons**
- **Knierim, McNaughton 2001: analysis of records of hippocampal place-cells firing through embedding in a vector space**
- **Victor, Purpura 2001: metric space based on edit distance**

State of the art

- **Rieke et al. 1997; Borst, Theunissen 1999; Johnson et al 2001: Information theoretical analysis of neural coding**

- **Panzeri et al. 1999: study of the capacity of neural channels**

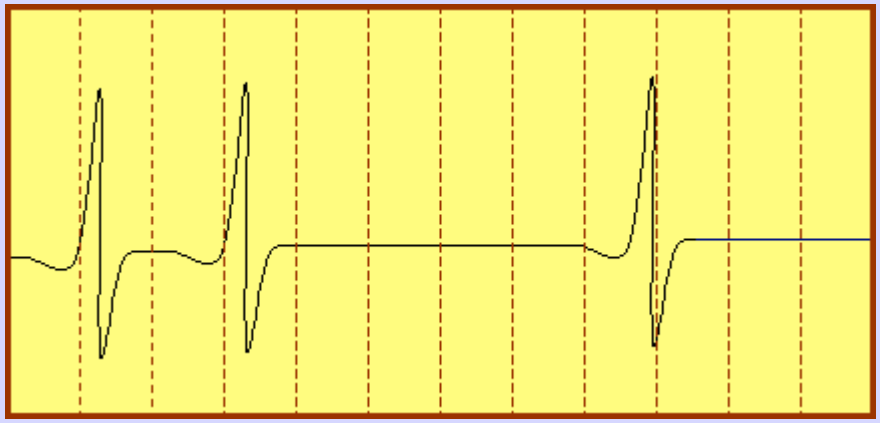
The tools

- **Longest Common Subsequence**
- **Lempel-Ziv complexity and LZ-Trees**
- **Tree Compression**

Encoding neuron's activity

Time Diagram

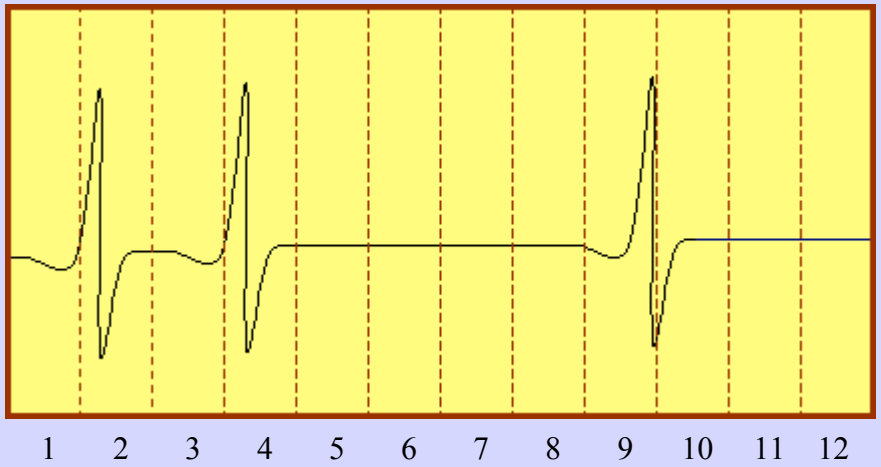
Record



Encoding neuron's activity

Time discretization

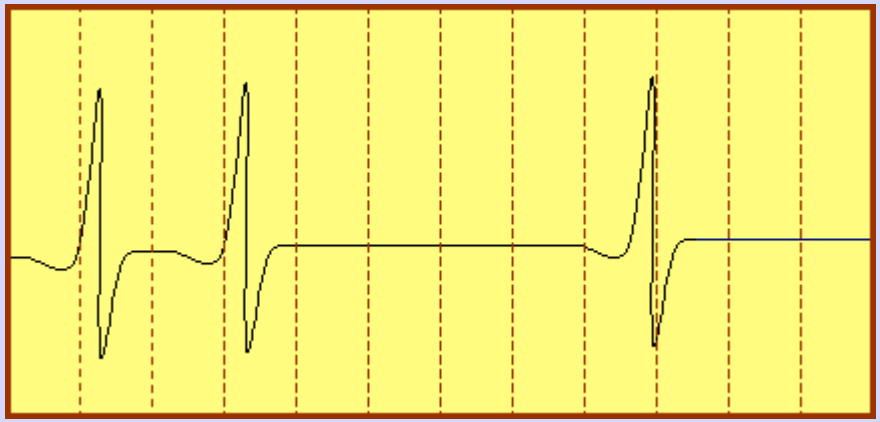
Record



Encoding neuron's activity

Binary encoding

Record

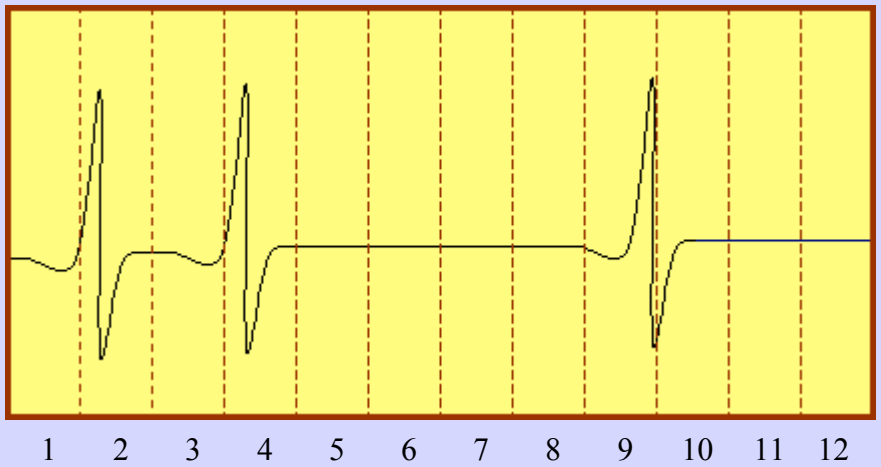


1	2	3	4	5	6	7	8	9	10	11	12
0	1	0	1	0	0	0	0	1	0	0	0

Encoding neuron's activity

Encoding through interspike intervals

Record



Spike Times

2	4	9

Interspike Intervals

1	1	4	3

Alphabets, words, languages

Alphabet

=

finite set Σ of elements called *letters,characters or symbols*

Examples

Σ = {0,1}

Σ = {a, b, c, ..., v, z}

Σ = {A, C, G, T}

Σ = {GLY, ALA, VAL, LEU}

Alphabets, words, languages

Word, string or sequence over □

=

function w from {1,... ,n} to □

- We write w = $a_1\ a_2 \ldots a_n$ where a_i = w(i) □ □
- n is the length of the sequence, denoted by |w|
- □* denotes the set of words over □

EX: **w = AATGCA** **|w| = 6**

Empty word □ **|□ = 0**

Alphabets, words, languages

Concatenation of w and v,

=

word consisting of the characters from w, followed by the characters from v

- **ES: w = AATGCATAGGC**
  v = GGCTACT
  w v = AATGCATAGGCGGCTACT

Alphabets, words, languages

Prefix of w

=

string v such that w = vt for some t Σ^*

Suffix of w

=

string v such that w = tv for some t Σ^*

Longest Common Subsequence

Let S_1 and S_2 be two sequences over □.

S_2 is a **subsequence** of S_1 if it can be obtained from S_1 by removing some of its symbols

S_1 = **T A T A G C G C A A T C G**
S_2 = **T A T G C A T G**

S_2 is subsequence of S_1

Longest Common Subsequence

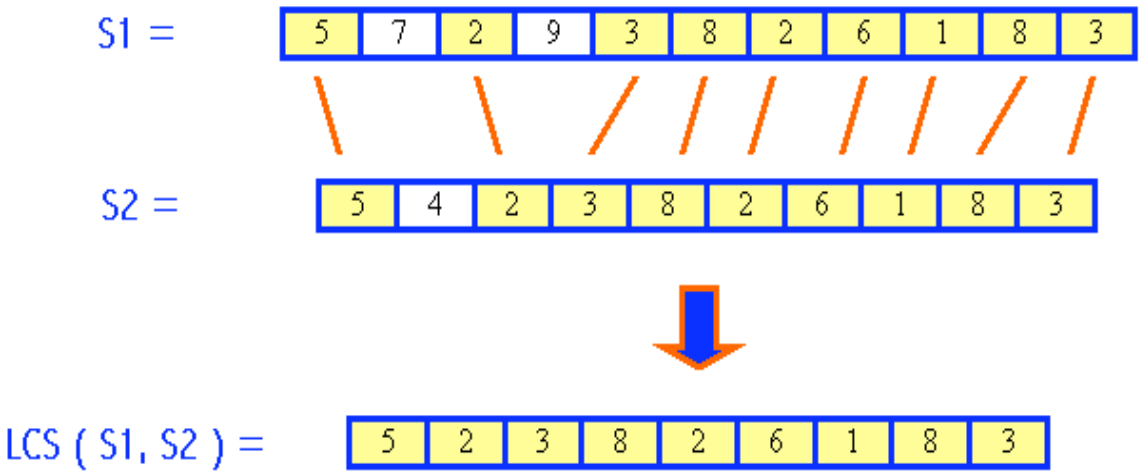
Let $\mathcal{S}$ be a set of sequences.

S is a ***common subsequence*** of $\mathcal{S}$ if it is a subsequence of every sequence in $\mathcal{S}$

Problem (LCS):

Given a set $\mathcal{S}$ of sequences, compute a longest common subsequence lcs($\mathcal{S}$)

Longest Common Subsequence, an example



Longest Common Subsequence

Def: **Given an alphabet Σ and sequences $S_1, S_2 \in \Sigma^*$, lcs(S_1, S_2) is a sequence W such that:**

1) **$\forall i, 1 \leq i \leq |W|-1$,**

$\exists j, j'$: $1 \leq j < j' \leq |S_1|$, $\exists k, k'$: $1 \leq k < k' \leq |S_2|$ <u>such that</u>:

$$W[i] = S_1[j] = S_2[k],$$

<u>and</u>

$$W[i+1] = S_1[j'] = S_2[k'];$$

2) $\neg \exists W' \in \Sigma^*$: (1) <u>and</u> $|W'| > |W|$.

LCS in sequence analysis

The lcs is able to:

- **Measure the similarity among a set of sequences through its length**
- **Exhibit the nature of the similarity through the symbols it contains**

Applications in:

- **data compression**
- **syntactic pattern recognition**
- **file comparison**
- **bioinformatics**

Complexity of LCS

- **Many polynomial time algorithms for LCS on two sequences**
- **Maier 78: LCS among k sequences is NP-hard**
- **Jiang, Li 95: nonapproximability results**
- **Jiang, Li 95: Long Run, approximation algorithm over a fixed alphabet**
- **Bonizzoni, Della Vedova, Mauri 98:better approximation ratio on the average**

LCS, Relaxed

Def: **Given an alphabet Σ, $\Delta \notin \Sigma$, sequences $S_1, S_2 \in \Sigma^*$, $\delta \geq 0$, $LCS_\delta(S_1, S_2)$ is a sequence W such that:**

1) **$\forall i, 1 \leq i \leq |W|-1$,**
$\exists j, j'$: $1 \leq j < j' \leq |S_1|$, $\exists k, k'$: $1 \leq k < k' \leq |S_2|$ such that:

$$W[i] = S_1[j] = S_2[k] \pm \delta,$$

and

$$W[i+1] = S_1[j'] = S_2[k'] \pm \delta,$$

with $0 \leq \delta \leq \Delta$;

2) $\neg \exists W' \in \Sigma^*$: (1) and $\Delta(M_{W'}, S_1, S_2) > \Delta(M_W, S_1, S_2)$,

where:

LCS, Relaxed

$\forall S_1, S_2, W \in \Sigma^*$,

$M_W(S_1, S_2) := \{(j, k) \mid 1 \le j \le |S_1|, 1 \le k \le |S_2|, \exists i: 1 \le i \le |W|$ **st:**

$W[i] = S_1[j] = S_2[k] \pm \delta$, **with** $0 \le \delta \le \varepsilon$;

and

if $1 \le i \le |W|-1$,

then $\exists j': 1 \le j' \le |S_1|, \exists k': 1 \le k' \le |S_2|$ **such that:**

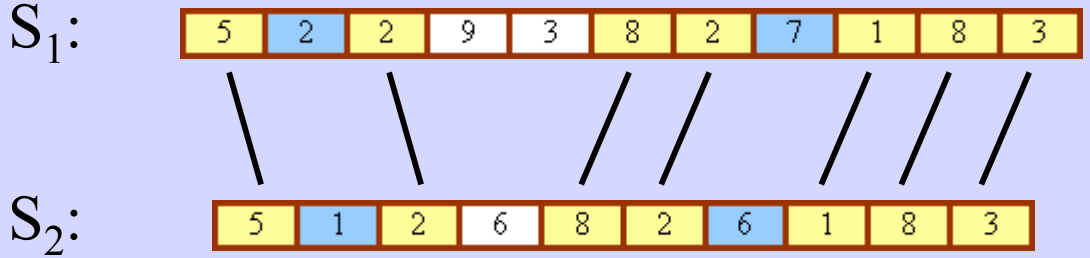
$(W[i+1] = S_1[j'] = S_2[k'] \pm \delta) \wedge (j'>j) \wedge (k'>k)$,

with $0 \le \delta \le \varepsilon$; $\}$

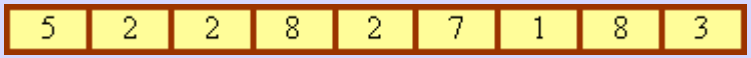
and where: $\Delta(M, S_1, S_2) := \min_{(j, k) \in M} \text{cost}(S[j], S[k])$;

and $\text{cost}(a, b) := 1-|a-b|$, **with** $a, b \in \Sigma$.

LCS (Relaxed), an example



$LCS(S_1,S_2)$:



Lempel-Ziv complexity

- **L. & Z. propose as a complexity measure of a sequence the minimum number of steps needed to produce it from its prefixes using copy and paste operations**
- **L. & Z. give an algorithm to compute the above measure**
- **The complexity notion defined by L. & Z. is compatible with the algorithmic complexity theory (Kolmogorov, Chaitin)**

Lempel-Ziv Algorithm

INPUT: S□□*; OUTPUT: w={Q □□* | □i, j: S[i:j]=Q};

w := □;
w := w □ {□};
curr := 1;
while curr ≤ |S| do
begin
S' := S[curr:n] s.t. S' □ w and S'°S[n+1] □ w;
w := w □ {S'°S[n+1] };
curr := n+2;
end

NOTE: S[i:j]= □for j<i

Lempel-Ziv -Trees

- **The vocabulary w obtained can be organized in a hierarchical (tree) structure through the prefix relation:**

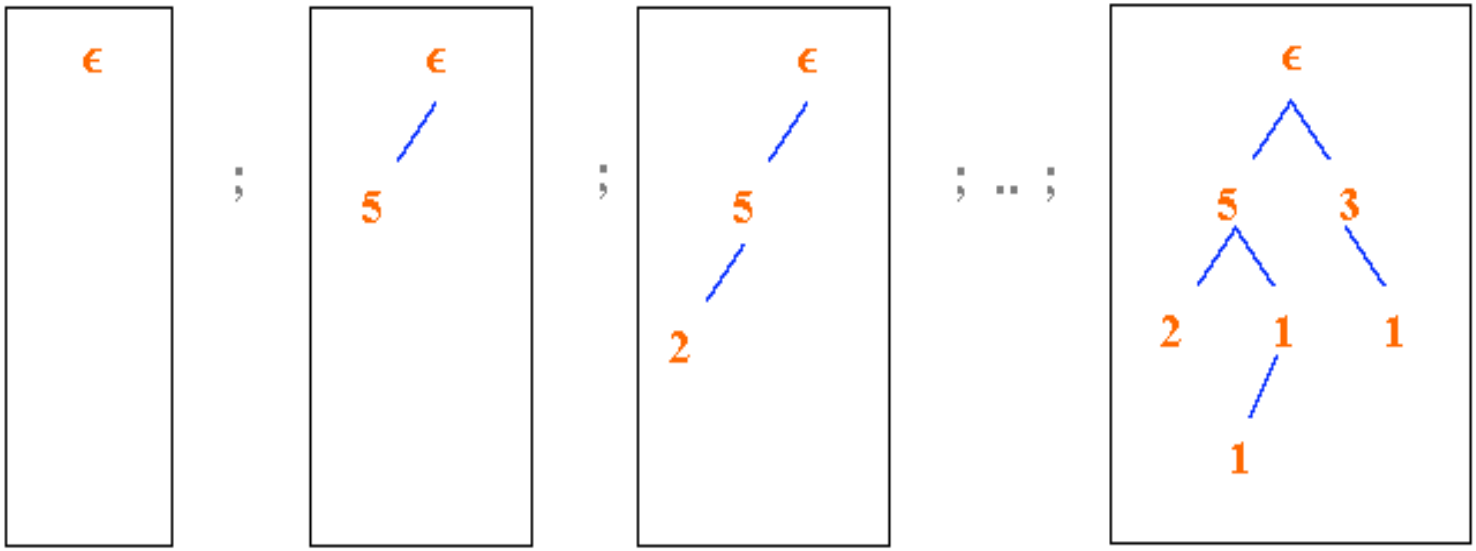
$$\text{prefix} := \{ (u, v) \mid u, v \in w \text{ and } \exists i: u = v[1:i] \};$$

- **Every word in w (except ε) can be obtained by adding a single symbol to another word in w; hence, it can be encoded through a pointer to its maximal prefix, plus the last symbol**

- **LZCompl(S) := |w| / |S|**

Lempel-Ziv-Trees, an example

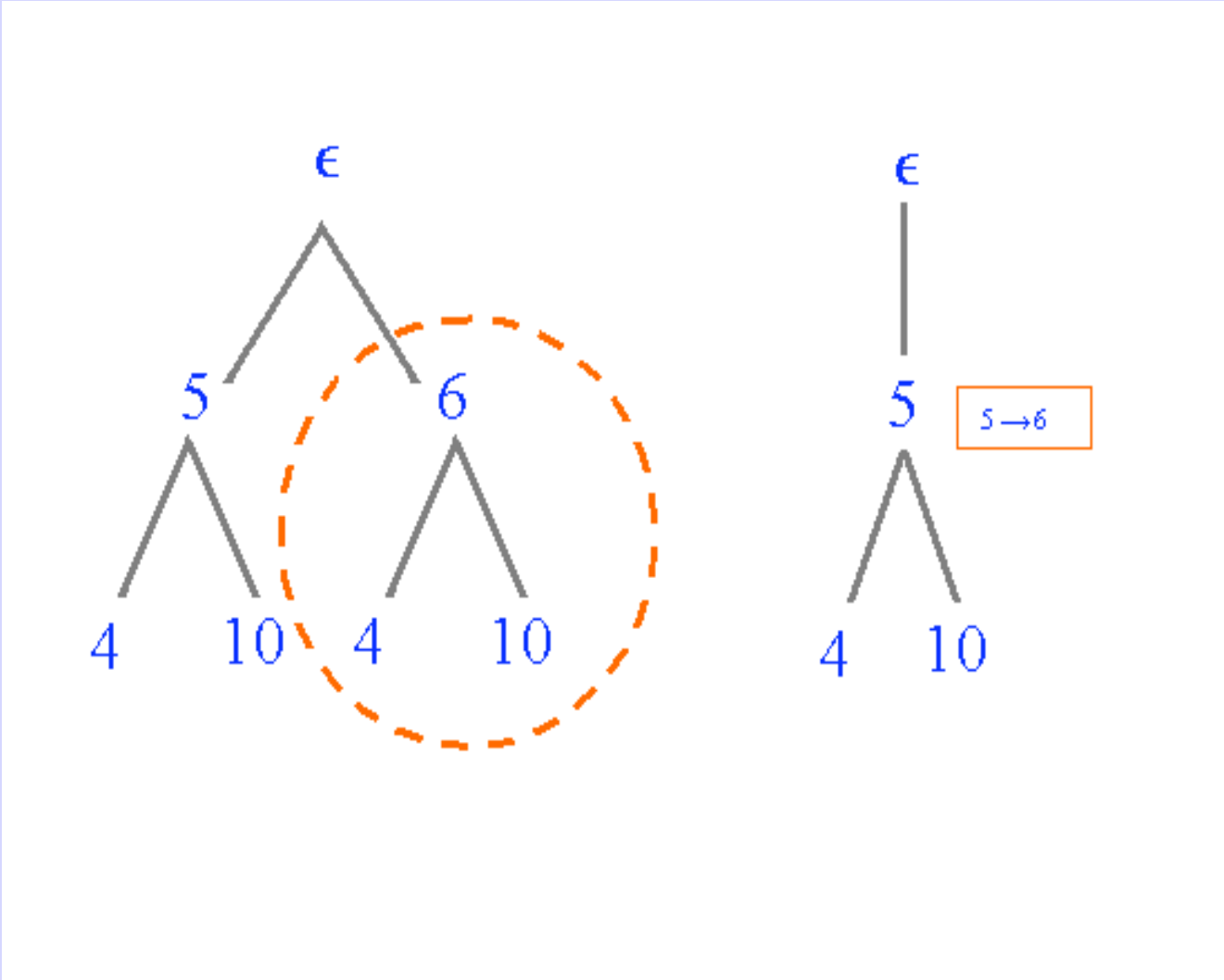
S = 5•52•3•51•31•511•



Lempel-Ziv-Trees, meaning

- **Acquisition of knowledge about the regularity of occurrence of symbol patterns in the sequence**
- **Structuring of knowledge so as to give a representation of the sequence shortest than the list of its symbols.**

Tree Compression, an example



Tree Compression, meaning

- **Reduction of redundancy in the tree structure**
- **Minimization of hierarchical knowledge representations**
- **Abstraction and generalization of the knowledge empirically acquired**

Edit Distance between trees

Let T be a rooted labeled tree over a given alphabet □ :

T = < V, E, r, lab: V□ □ >

and let have the following operations on it :

- Insertion **of an element: □□ a, a□□;**
- Deletion **of an element: a□ □, a□□;**
- Substitution **of the label of an element: a□ b, a, b □□;**

Edit Distance between trees

EditOps := {a→ b | a, b ∈ Σ ∪ {ε} }\{ε→ ε};

Given the (metric) cost function :

γ: EditOps → R^+;

We define the cost of a sequence Sop= EditOps* as

γ(Sop) = $\sum_{i=1,..,|Sop|}$ γ(Sop[i]).

Edit Distance between trees

Def: **Given two labeled trees T e T', the edit distance between them is defined by:**

$$Edist(T, T') := \min_{Sop \in EditOps^*} \{ \gamma(Sop) \mid T' = Sop(T) \}.$$

Tree Compression, Algorithm

proc TreeCompr(**tot** □ **R, < &T, &Sop >**) :

if ($V_T \neq \square$){
    if (**Edist(Tdx(r_T), Tsx(r_T)) < threshold**) {
        Prune(Tdx(r_T));
        TreeCompr(tot, < Tdx, Sop°$Sop_{Edist(Tdx(rT), Tsx(rT))}$ >);
    } **else** {
        TreeCompr(tot, < Tdx, Sop >);
        TreeCompr(tot, < Tsx, Sop >);
    }
}

Tree Complexity

Def: **given a tree T, let T' and Sop□ EditOps the results of the compression of T through** TreeCompr**; the Tree Complexity of T is:**

$$TC(T) := (|T'| / |T|) + \square \cdot \square(Sop)$$

where 0 □ □ □ 1

Tree Complexity

Teorema: **The computation of the tree complexity ofa tree T based on an Edit Distance *Structure Respecting* has time complexity :**

$$O(D^3 \cdot |T|^2),$$

where D is the maximum degree of nodes in T.

Application

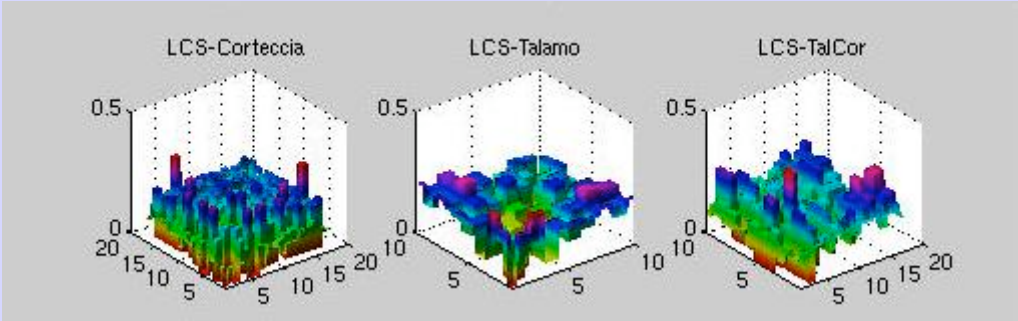
Analysis of sequences of *Interspike Intervals* from simultaneous recordings of talamic and cortical cells populations.

Motivation: **key role of talamocortical areas in the elaboration of somatosensorial stimuli.**

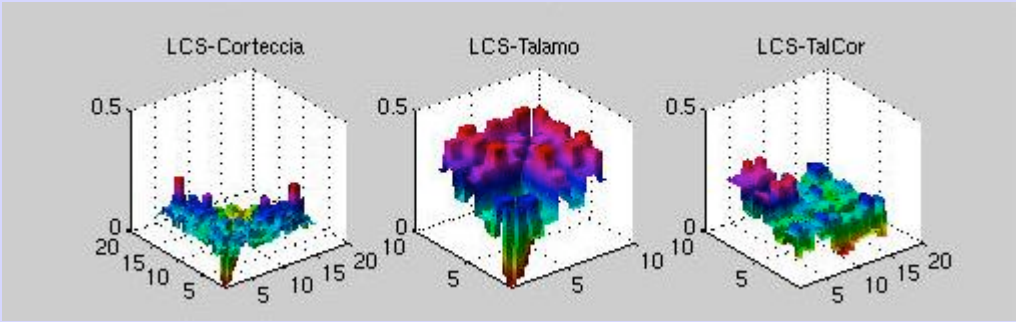
Goal: **to discover rythmic correlations among cells activities.**

Application, LCS

NORM:

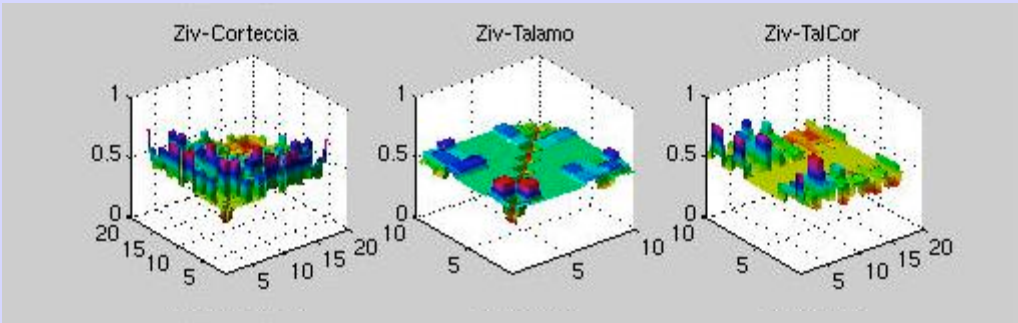


CCI:



Application, LZ-Complexity

NORM:



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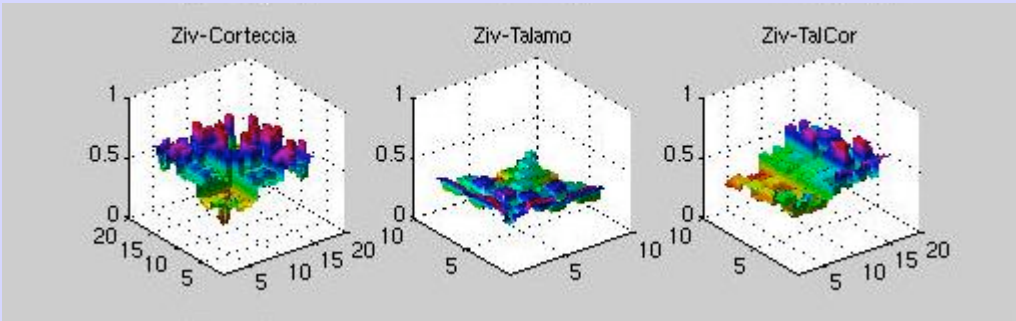

Applicazione, CplArb

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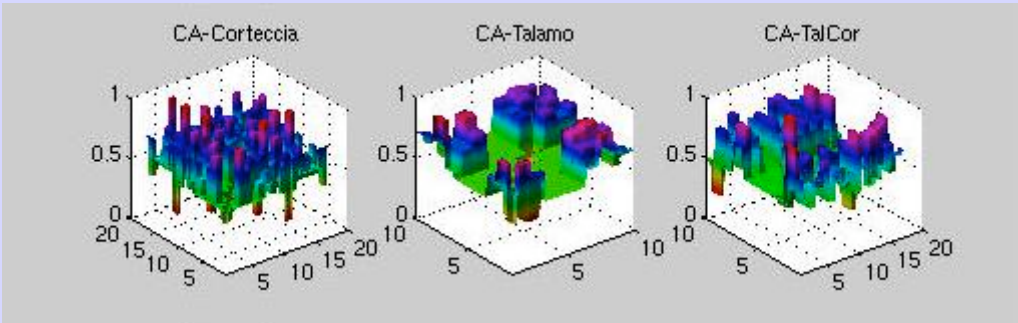

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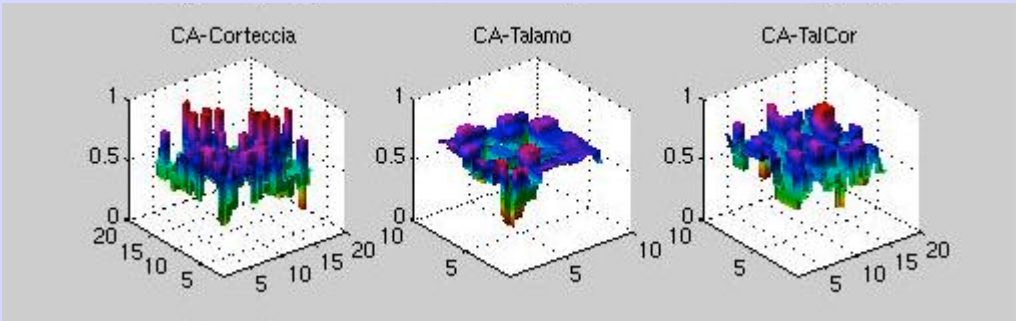

Application, conclusions

The three kinds of di analysis help us to enlightening different aspects of the process we are observing:

- **LCS** — **Omogeneity**
- **Ziv-Tree** — **Monotonicity**
- **Tree compression** — **Fault Tolerance**