Copulas: a useful tool for neurosciences?

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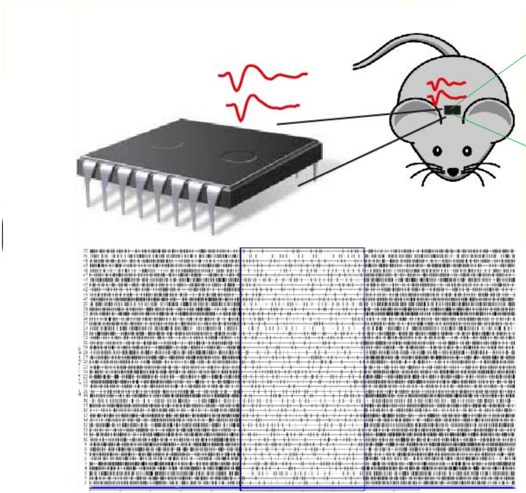
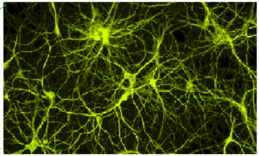
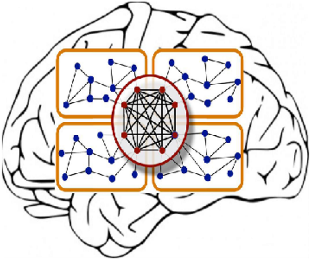
Aims



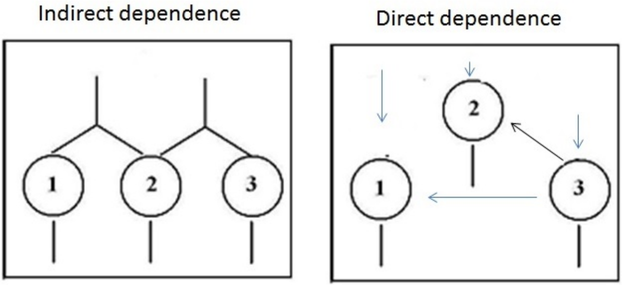




Network connections

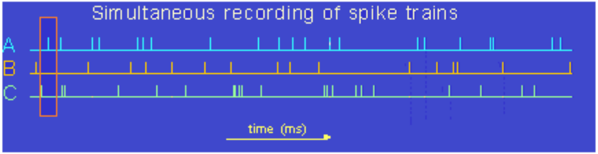
Neural network $\Leftarrow$ interactions between neurons and/or common stimula:

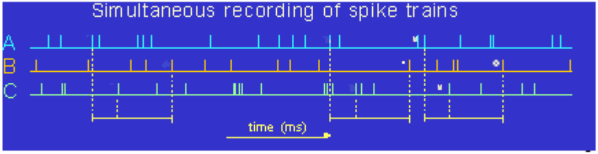
- direct
- indirect



Aims

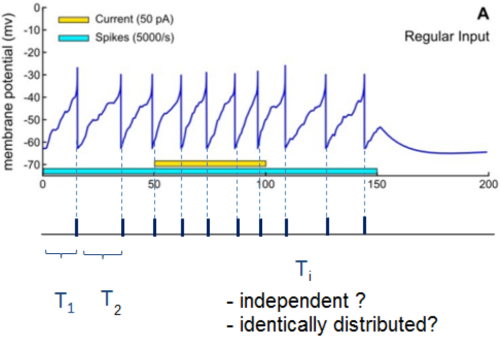
1. How to guess existence of connections in the network?





Aims

2. How to detect dependences between Interspike Intervals?
We need statistical methods to recognize dependent ISIs



SUMMARY

- Copulas
- Problem 1: Guessing about network structure
  - A first approach: forward times dependences
    - Models for Data Simulation
    - Results
  - A second approach: Mutual Information
    - Mutual Information Estimation and Copulas
- Problem 2: Dependence between interspike intervals in a single spike train
  - Models for data generation
  - Copulas and dependence detection: Results

Copulas

Definition

A two-dimensional copula is a function $C : [0,1]^2 \to [0,1]$ with the following properties:

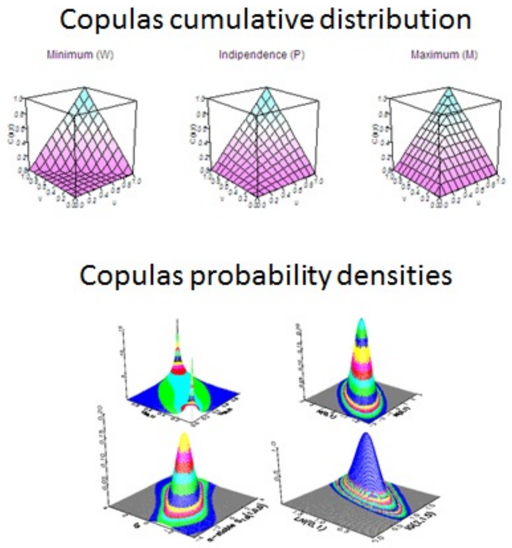
1. $C(u;0) = C(0;v) = 0$ and $C(u;1) = u, C(1;v) = v$ for every $u, v \in [0;1]$;
2. C is 2-increasing, i.e. for every $u_1, u_2, v_1, v_2 \in [0;1]$ such that $u_1 \leq u_2, v_1 \leq v_2$,

$$C(u_1, v_1) + C(u_2, v_2) - C(u_1, v_2) - C(u_2, v_1) \geq 0$$

Remark

C is a $2-$ dimensional copula if C is a joint cumulative distribution function of a $2-$ dimensional vector on the square $[0,1]^2$ with uniform marginals

Copulas distribution and Copulas densities



Sklar Theorem

Theorem

Let F be a two-dimensional distribution function with margins F_1 and F_2. Then F has a copula representation:

$$P(X_1 < x_1; X_2 < x_2) = F(x_1; x_2) = C(F_1(x_1); F_2(x_2))$$

The copula C is unique if the margins are continuous. (Otherwise, only the subcopula is uniquely determined on $RanF_1 \times RanF_2$.)

Sklar theorem

The 3 functions: 1. marginal respect to X_1
2. marginal respect to X_2
3. The copula

Uniquely determine the joint distribution

Copulas

Remark

The copula of independent random variables is $C(u, v) = uv$ *and its scatterplot is uniform on* $[0; 1]^2$

Remark

Consider a random vector X_1, X_2. *Suppose its margins are continuos with marginals* $F_i(x) = P(X_1 < x)$. *Applying the probability integral transform, the random vector* $(U_1, U_2) = (F_1(X_1), F_2(X_2))$ *has uniformly distributed marginals. The copula* C *is defined as the joint cumulative distribtion function of* U_1, U_2.

Copula

Why to use copulas?

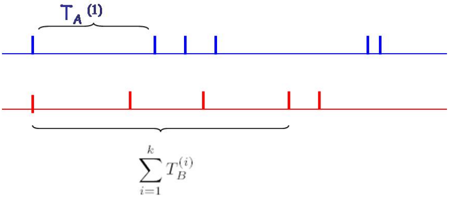
- They catch the joint dependence between r.v.s, separating it from the marginal behaviors.
- Scale free: invariance under strictly increasing transformations.
- They can model independence as well as dependence.
- Measures of dependence, in particular Kendall's τ can be expressed as:

$$\tau = 4\int_0^1\int_0^1 C(u,v)dC(u,v) - 1 = 4\mathbb{E}[C(u,v)] - 1 \in [-1,1]$$

Copulas allow to build models with assigned dependence properties

Copulas: a tool to investigate neural networks structure

Bivariate dependencies



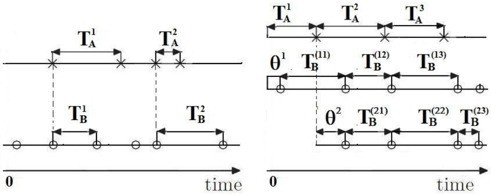
Dependency between an ISI of neuron A and the k-th ISI of neuron B

$$P\left(T_A^{(1)} < t, \sum_{i=1}^{k} T_B^{(i)} < s\right)$$

$$P\left(T_A^{(1)} < t, T_B^{(k)} < s\right)$$

Copulas to detect dependencies

Hypothesis: underlying renewal process



$$P\left(T_A^{(1)} < t, \theta + \sum_{i=1}^{k} T_B^{(i)} < s\right) = C\left(F_{T_A^{(1)}}(t), F_{\theta+\sum_{i=1}^{k} T_B^{(i)}}(s)\right)$$

The method

- Select a reference neuron. [1]
- Consider sample pairs

$$\left(T_A^i, \theta^i + \sum_{k=1}^{m} T_B^{(ik)} \right), \qquad i = 1, \ldots, N, \qquad k = 1, \ldots, M.$$

- Determine their empirical copula and/or the copula scatterplot.
- Test their independence.
- Exchange the role of reference neuron and repeat the analysis.

[1] M. Tamborrino,C. Zucca Brain Research, 2011

Models for data generation

We consider two models of the membrane potential evolution:

- jump diffusion processes (direct dependence*);
- correlated diffusion processes (indirect dependence**).

Different types of interactions

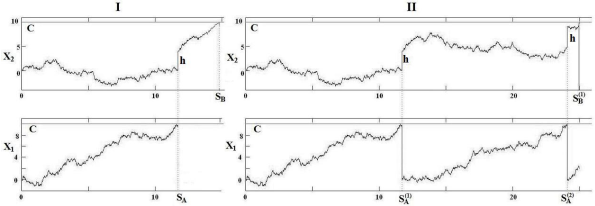
$\Downarrow$

different copulas.

[2]

[2]* LS, C. Zucca Math. Biosciences, 2013; LS, R. Sirovich, A.E.P. Villa, Math. Biosc. for Eng. 2014
**M. Tamborrino, LS, M. Jacobsen, Physica D, 2014

Jump diffusion model

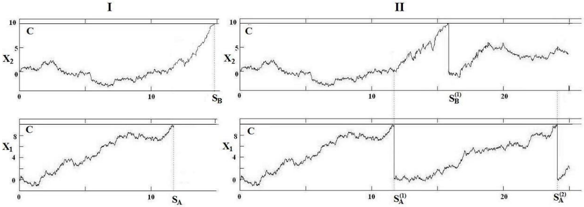


$\mathbf{X}(t) = \{(X_1, X_2)(t); t \geq t_0\}$: two dimensional jump diffusion process. In absence of jumps, the MP of each neuron is modeled as an OU process given by

$$dX_i(t) = \left(-\frac{1}{\tau}X_i(t) + \mu_i\right) dt + \sigma_i dW_i(t), \tag{1}$$

where $W_1(t)$ and $W_2(t)$ are two standard Wiener processes with $Cov(W_1(t), W_2(t)) = 0$.

Correlated diffusion model



$\mathbf{X}(t) = \{(X_1, X_2)(t); t \geq t_0\}$: bivariate diffusion process with correlated components.
The sub-threshold MP evolutions are described through an OU process given by

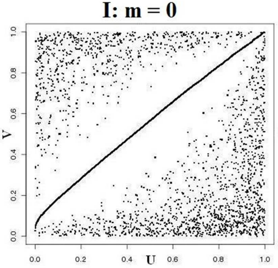
$$dX_i(t) = \left(-\frac{1}{\tau}X_i(t) + \mu_i\right) dt + \sigma_i dW_i(t), \tag{2}$$

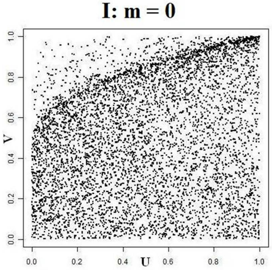
where $Cov(W_1(t), W_2(t)) = \sigma_{12}t$, with $\sigma_{12} \in \mathbb{R}$.

Results: comparison I

Parameters: $\tau = 10\ ms^{-1}$, $C = 10mV$, $\mu_A = \mu_B = 1.2mVms^{-1}$, $\sigma_A^2 = \sigma_B^2 = 1.1mV^2ms^{-1}$

Jump amplitude $h = 3\ mV$ $\quad$ $Cov(W_1(t), W_2(t)) = 0.91mV^2ms^{-1}$



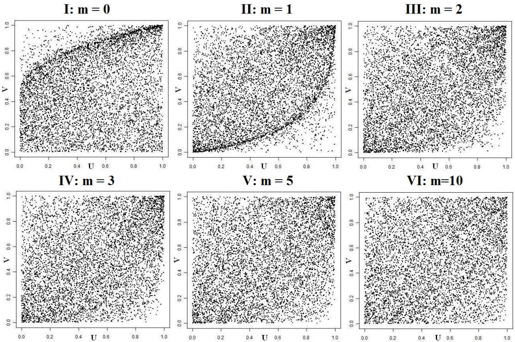


Est. Kendall's tau: $\hat{\tau}_I = 0.42$ $\quad$ Est. Kendall's tau: $\hat{\tau}_I = 0.16$

Copula scatterplots of (T_A, θ), where T_A and T_B have the same distribution (KS test).

Results for covariance diffusion model I

Parameters: $\tau = 10\ ms^{-1}$, $C = 10mV$, $\mu_A = \mu_B = 1.2mVms^{-1}$,
$\sigma_A^2 = \sigma_B^2 = 1.1mV^2ms^{-1}$ $Cov(W_1(t), W_2(t)) = 0.91mV^2ms^{-1}$

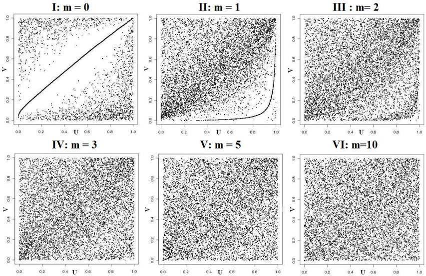


Estimated Kendall's tau:
$\hat{\tau}_I = 0.16$
$\hat{\tau}_{II} = 0.30$
$\hat{\tau}_{III} = 0.25$
$\hat{\tau}_{IV} = 0.22$
$\hat{\tau}_V = 0.18$
$\hat{\tau}_{VI} = 0.14$.

Copula scatterplots of $(T_A, \theta + \sum_{k=1}^{m} T_B^{(k)})$, for $m = 0, 1, 2, 3, 5, 10$, where T_A and T_B have the same distribution (KS test).
$m = 1$: optimal value maximizing the dependency between the involved times.

Results for jump diffusion model I

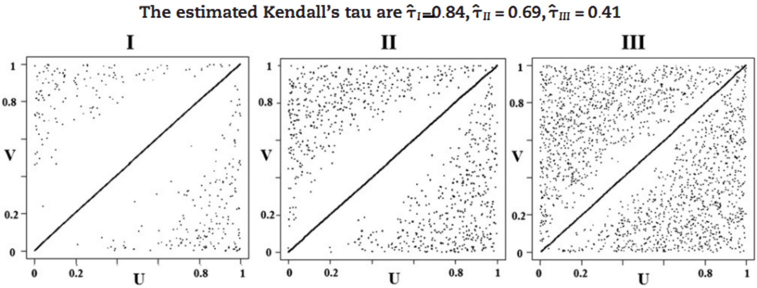
Parameters: $\tau = 10\ ms^{-1}$, $C = 10mV$, $\mu_A = \mu_B = 1.2mVms^{-1}$, $\sigma_A^2 = \sigma_B^2 = 1.1mV^2ms^{-1}$, jump amplitude $h = 3\ mV$



Estimated Kendall's tau:
$\hat{\tau}_I = 0.42$
$\hat{\tau}_{II} = 0.20$
$\hat{\tau}_{III} = 0.15$
$\hat{\tau}_{IV} = 0.12$
$\hat{\tau}_V = 0.10$
$\hat{\tau}_{VI} = 0.07$.

Copula scatterplots of $(T_A, \theta + \sum_{k=1}^{m} T_B^{(k)})$, for $m = 0, 1, 2, 3, 5, 10$,
$m = 0$: optimal value (maximizes the dependency).
Exchange the role of A and B to get hits on the type of structure underlying the dependence.

Results for Jump-Diffusion Model II

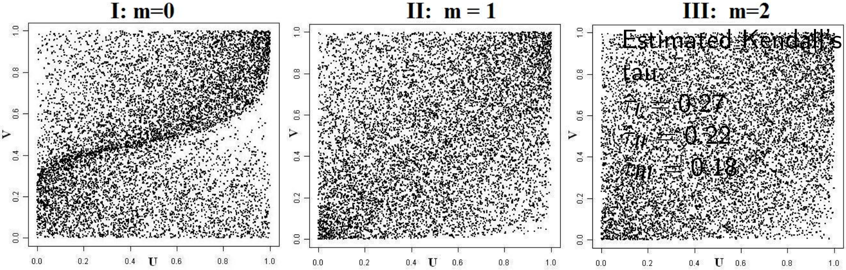


Remark

Higher values of τ increase synchronous spiking.

Results for covariance diffusion model II

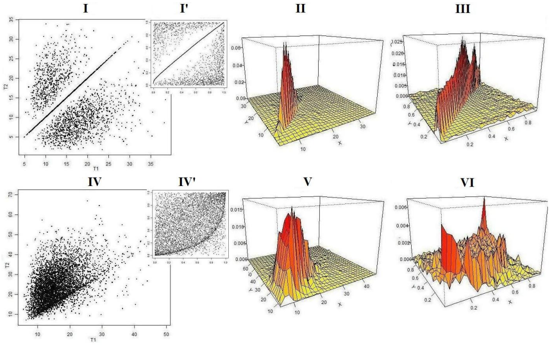
Choice of B as target neuron.



Copula scatterplots of $(T_B, \theta + \sum_{k=1}^{m} T_A^{(k)})$, for $m = 0, 1, 2$
$m = 0$: optimal value maximizing the dependency between the involved times.

Why to use copulas instead of times

Scatterplots and 3-D histograms for times and copulas.



Time scatterplot:

- easily recognize synchronous spikes (straight line)
- informations on the marginal behavior
- merge marginal and joint behaviors (main limit!) hard to distinguish meaningful clusters

An alternative tool to detect dependences: Mutual Information

Mutual Information between two Random Variables

Definition

The mutual information (MI) of a 2-dimensional random vector $X = (X_1, X_2)$ is given by

$$MI(X_1, X_2) = \int_{\mathbf{R}^2} f_{1,2}(x_1, x_2) \log_2 \left[\frac{f_{1,2}(x_1, x_2)}{f_1(x_1) f_2(x_2)} \right] dx_1 dx_2. \tag{3}$$

Remark

- *If X_1 and X_2 are independent $MI(X_1, X_2) = 0$.*
- *MI and entropy in the case $d = 2$ are related through the well known equation*

$$MI(X_1, X_2) = H(X_1) + H(X_2) - H(X_1, X_2). \tag{4}$$

Copulas and Mutual Information

Theorem

(Jenison Reale, 2004) Let $U_1 = F_1(X_1)$ *and* $U_2 = F_2(X_2)$*. The MI (3) of the* 2*-dimensional random vector* $X = (X_1, X_2)$ *can be obtained as*

$$MI(X_1, X_2) = -H\left(U_1, U_2\right) \tag{5}$$

Remark

Entropy of the copula coincides with the mutual information between the random variables!

Estimation of MI

IDEA: Use the relationship between MI and copula to estimate the Mutual Information:

- transform the original sample in a new sample with uniform marginals through $U_1 = F(X_1), U_2 = F(X_2)$;
- Estimate the entropy of the obtained sample;

Estimation of MI

IDEA: Use the relationship between MI and copula to estimate the Mutual Information:

- transform the original sample in a new sample with uniform marginals through $U_1 = F(X_1), U_2 = F(X_2)$;
- Estimate the entropy of the obtained sample;

Problem

Extension to the $d-$ dimensional case

Mutual Information between d Random Variables

The generalization of MI to more than two random variables is not unique: definitions change according to different grouping of the components of the random vector $X = (X_1, \ldots, X_d)$.

Definition

(couple of multi-indices) For any couple of multi-indices (α, β) of dimensions h and k respectively, with $h + k = d$ and partitioning the set of indices $\{1, 2, \ldots, d\}$, the $MI(X_1, \ldots, X_d)$ can be defined as

$$MI(X_\alpha, X_\beta) = \int f_{\alpha,\beta} \log_2 \frac{f_{\alpha,\beta}}{f_\alpha f_\beta} \tag{6}$$

$$= \int_{\mathbf{R}^d} f_d(x_1, \ldots, x_d) \log_2 \left[\frac{f_d(x_1, \ldots, x_d)}{f_\alpha(x_{\alpha_1}, \ldots, x_{\alpha_h}) f_\beta(x_{\beta_1}, \ldots, x_{\beta_k})} \right] dx_1 \ldots dx_d.$$

where $X_\alpha = (X_{\alpha_1}, \ldots, X_{\alpha_h})$ and $X_\beta = (X_{\beta_1}, \ldots, X_{\beta_k})$.

Mutual Information between d Random Variables

Definition

For any n multi-indices $(\alpha^1, \ldots, \alpha^n)$ of dimensions $h_1, \ldots, h_n$ respectively, such that $h_1 + \cdots + h_n = d$ and partitioning the set of indices $\{1, 2, \ldots, d\}$ the following quantities

$$\mathrm{MI}(X_{\alpha^1}, \ldots, X_{\alpha^n}) = \int_{\mathbf{R}^d} f_{\alpha^1,\ldots,\alpha^n} \log_2 \frac{f_{\alpha^1,\ldots,\alpha^n}}{f_{\alpha^1} \cdots f_{\alpha^n}} \quad (7)$$

$$= \int_{\mathbf{R}^d} f_{1,\ldots,d}(x_1, \ldots, x_d) \times$$

$$\log_2 \left[\frac{f_{1,\ldots,d}(x_1, \ldots, x_d)}{f_{\alpha^1_1,\ldots,\alpha^1_{h_1}}(x_{\alpha^1_1}, \ldots, x_{\alpha^1_{h_1}}) \cdots f_{\alpha^n_1,\ldots,\alpha^n_{h_n}}(x_{\alpha^n_1}, \ldots, x_{\alpha^n_{h_n}})} \right] dx_1 \ldots dx_d$$

are all d–dimensional extensions of the bidimensional MI.

Mutual Information and Entropy

Remark

The $d-$dimensional MI can be expressed as a sum of Entropies

$$MI(X_{\alpha^1}, \ldots, X_{\alpha^n}) = H(X_{\alpha^1}) + \cdots + H(X_{\alpha^n}) - H(X_1, \ldots, X_d). \quad (8)$$

Remark

Reliable statistical estimators for the entropy are available but their use to estimate MI in (7) is discouraged by the presence of a sum of entropy terms (the variances of the sums add up!)

$d-$dimensional copulas and MI

Remark

It is not possible to use copula functions to handle multivariate distribution with given marginal distributions of general dimensions. ***The only copula compatible with any assigned multidimensional marginal distributions is the independent one.***
A generalization of the copula concept is necessary to deal with conditional distributions.

Linkage Functions

Definition

The linkage function corresponding to the d-dimensional random vector $(X_{\alpha^1}, \dots, X_{\alpha^n})$ is defined as the joint p.d.f. L of the vector $(U_{\alpha^1} \dots, U_{\alpha^n})$

$$(U_{\alpha^1_1}, \dots, U_{\alpha^1_{h_1}}, \dots, U_{\alpha^n_1}, \dots, U_{\alpha^n_{h_n}}) = (\Psi_{\alpha^1}(X_{\alpha^1}), \dots, \Psi_{\alpha^n}(X_{\alpha^n})) \,. \quad (9)$$

where

- $\Psi_{\alpha^i} : \mathbf{R}^{h_i} \to [0,1]^{h_i}$, $i = 1, \dots, n$ with $\Psi_{\alpha^i}(x_{\alpha^i_1}, \dots, x_{\alpha^i_{h_i}}) = (F_{\alpha^i_1}(x_{\alpha^i_1}), F_{\alpha^i_2|\alpha^i_1}(x_{\alpha^i_2}|x_{\alpha^i_1}), \dots, F_{\alpha^i_{h_i}|\alpha^i_1,\dots,\alpha^i_{h_i-1}}(x_{\alpha^i_{h_i}}|x_{\alpha^i_1}, \dots, x_{\alpha^i_{h_i-1}}))$;
- $(\alpha^1, \dots, \alpha^n)$ multi-indices of dimensions $(h_1, \dots, h_n)$ respectively, such that $h_1 + \dots + h_n = d$ partitioning the set $\{1, 2, \dots, d\}$;
- $F_{\alpha^i}, i = 1, \dots, n$: h_i-dimensional c.d.f. of $X_{\alpha^i} = (X_{\alpha^i_1}, \dots, X_{\alpha^i_{h_i}})$
- $F_{\alpha^1,\dots,\alpha^n}$: $d-$dimensional joint c.d.f. of $X_{\alpha^1}, \dots, X_{\alpha^n}$.

Linkage Functions and MI

Theorem

(Li, H.; Scarsini, M.; Shaked, M.,1996) The vectors

$$U_{\alpha^i} = (U_{\alpha^i_1}, \dots U_{\alpha^i_{h_i}}) = \Psi_{\alpha^i}(X_{\alpha^i_1}, \dots, X_{\alpha^i_{h_i}}) = \Psi_{\alpha^i}(X_{\alpha^i}) \qquad (10)$$

are h_i-dimensional vectors of independent uniform $[0,1]$ random variables.

Theorem

Let $X = (X_1, \dots, X_d)$ be a d–dimensional random vector. For any n multi-indices $(\alpha^1, \dots, \alpha^n)$ of dimensions $(h_1, \dots, h_n)$ respectively, such that $h_1 + \cdots + h_n = d$ and partitioning the set of indices $\{1, 2, \dots, d\}$, it holds

$$MI(X_{\alpha^1}, \dots, X_{\alpha^n}) = -H(U_{\alpha^1}, \dots, U_{\alpha^n}), \qquad (11)$$

where $(U_{\alpha^1}, \dots, U_{\alpha^n}) = (\Psi_{\alpha^1}(X_{\alpha^1}), \dots, \Psi_{\alpha^n}(X_{\alpha^n}))$.

The Method

IDEA: Estimate the $MI(X_{\alpha^1}, \ldots, X_{\alpha^n})$, with the elements of the vector $(X_1, \ldots, X_d)$ grouped according to the multi–indices $(\alpha^1, \ldots, \alpha^n)$, as the Shannon entropy in eq. (11). [3] The random vector $(U_{\alpha^1}, \ldots, U_{\alpha^n})$ is obtained from $(X_1, \ldots, X_d)$ by means of the following transformations:

$$\left\{\begin{array}{lcl} U_{\alpha_1^1} & = & F_{\alpha_1^1}(X_{\alpha_1^1}) \\ U_{\alpha_2^1} & = & F_{\alpha_2^1|\alpha_1^1}(X_{\alpha_2^1}|X_{\alpha_1^1}) \\ & \vdots & \\ U_{\alpha_{h_1}^1} & = & F_{\alpha_{h_1}^1|\alpha_1^1,\alpha_2^1,\ldots,\alpha_{h_1-1}^1}(X_{\alpha_{h_1}^1}|X_{\alpha_1^1}, X_{\alpha_2^1}, \ldots, X_{\alpha_{h_1-1}^1}) \\ U_{\alpha_1^2} & = & F_{\alpha_1^2}(X_{\alpha_1^2}) \\ & \vdots & \\ U_{\alpha_1^n} & = & F_{\alpha_1^n}(X_{\alpha_1^n}) \\ & \vdots & \\ U_{\alpha_{h_n}^n} & = & F_{\alpha_{h_n}^n|\alpha_1^n,\ldots,\alpha_{h_n-1}^n}(X_{\alpha_{h_n}^n}|X_{\alpha_{h_1}^n}, \ldots, X_{\alpha_{h_n-1}^n}). \end{array}\right. \tag{12}$$

[3] MT Giraudo, LS, R. Sirovich Entropy, 2014

The estimation algorithm

1. Estimate the conditional c.d.f.'s in eq. (12). Denote these functions as $\hat{\Psi}_{\alpha^i} = (\hat{F}_{\alpha^i_1}, \hat{F}_{\alpha^i_2|\alpha^i_2}, \ldots, \hat{F}_{\alpha^i_{h_i}|\alpha^i_{h_i-1}})$, for $i = 1, \ldots, n$;
2. For $k = 1, \ldots, N$ calculate $U^k = (U^k_{\alpha^1}, \ldots, U^k_{\alpha^n})$, where $U^k_{\alpha^i} = (\hat{\Psi}_{\alpha^1}(X^k_{\alpha^1}), \ldots, \hat{\Psi}_{\alpha^n}(X^k_{\alpha^n}))$, for $i = 1, \ldots, n$;
3. Estimate the $MI(X_{\alpha^1}, \ldots, X_{\alpha^n})$ as the Shannon entropy in eq. (11) of the transformed sample $(U^1, \ldots, U^N)$.

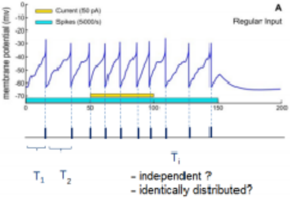
Remark

For the particular case when $d = 2$ the procedure becomes the following:

1. *estimate the c.d.f.'s $U_1 = F_1(X_1), U_2 = F_2(X_2)$. Denote the estimated functions as $(\hat{F}_1, \hat{F}_2)$;*
2. *calculate $U^k = (\hat{F}_1(X^k_1), \hat{F}_2(X^k_2))$, for $k = 1, \ldots, N$;*
3. *estimate $MI(X_1, X_2)$ as the Shannon entropy in eq. (5) of the transformed sample $(U^1, \ldots, U^N)$.*

A second application

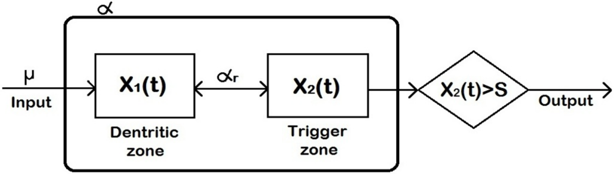
Problem 2: Dependencies between ISIs



Identically distributed ISIs. Method:

- Test the value of τ of Kendall
- Test the uniform distribution of the copula between successive ISIs
- Best fit on specific distributions of the copula between successive ISIs

A model for data generation: two compartment model.[4]



Dendritic component

Input mean

Wiener process

$$\begin{cases} dX_1(t) = \{-(\alpha + \alpha_r)X_1(t) + \alpha_r X_2(t) + \mu\}dt + \sigma dB(t) \\ dX_2(t) = \{-(\alpha + \alpha_r)X_2(t) + \alpha_r X_1(t)\}dt \end{cases}$$

Somatic component

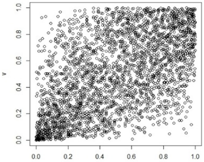
Inverse of the membrane time constant

Junctional constant

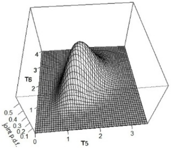
Input variance

Dependence between ISIs

Marginals can be computed solving a new integral equation [5]



Scatterplot of the copula between T_6 and T_7 for $\mu=5$.
Hypothesis: Normal Copula (goodness of fit test : p-value >0.2)



Joint probability density of T_6 and T_7 for $\mu=5$, using a Normal copula

The copula methods

- Problem 1:
  - non parametric method (only request iid ISIs)
  - recognizes the duration of the effect of a coupling phenomenon through the investigation of m
  - recognizes the presence of similar underlying dynamics for the membrane potential when the copula scatterplots or densities have similar shapes
  - allows to detect the presence of a delay in the coupling
  - it might be extended to capture dependencies in triplets, quartets, etc.
- Problem 2
  - allows to determine the presence of dependence between identically distributed ISIs
  - in some cases allows to specify the dependence structure

Thank you for your attention