Assessing complexity of short-term heart period variability through entropy-based approaches

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Introduction

Several physiological control systems are responsible to the changes of heart period on a beat-to-beat basis.

These control mechanisms interact each other and might even compete

The visible result is the richness of dynamics of heart period when observed on a beat-to-beat basis (i.e. the complexity of heart period series)

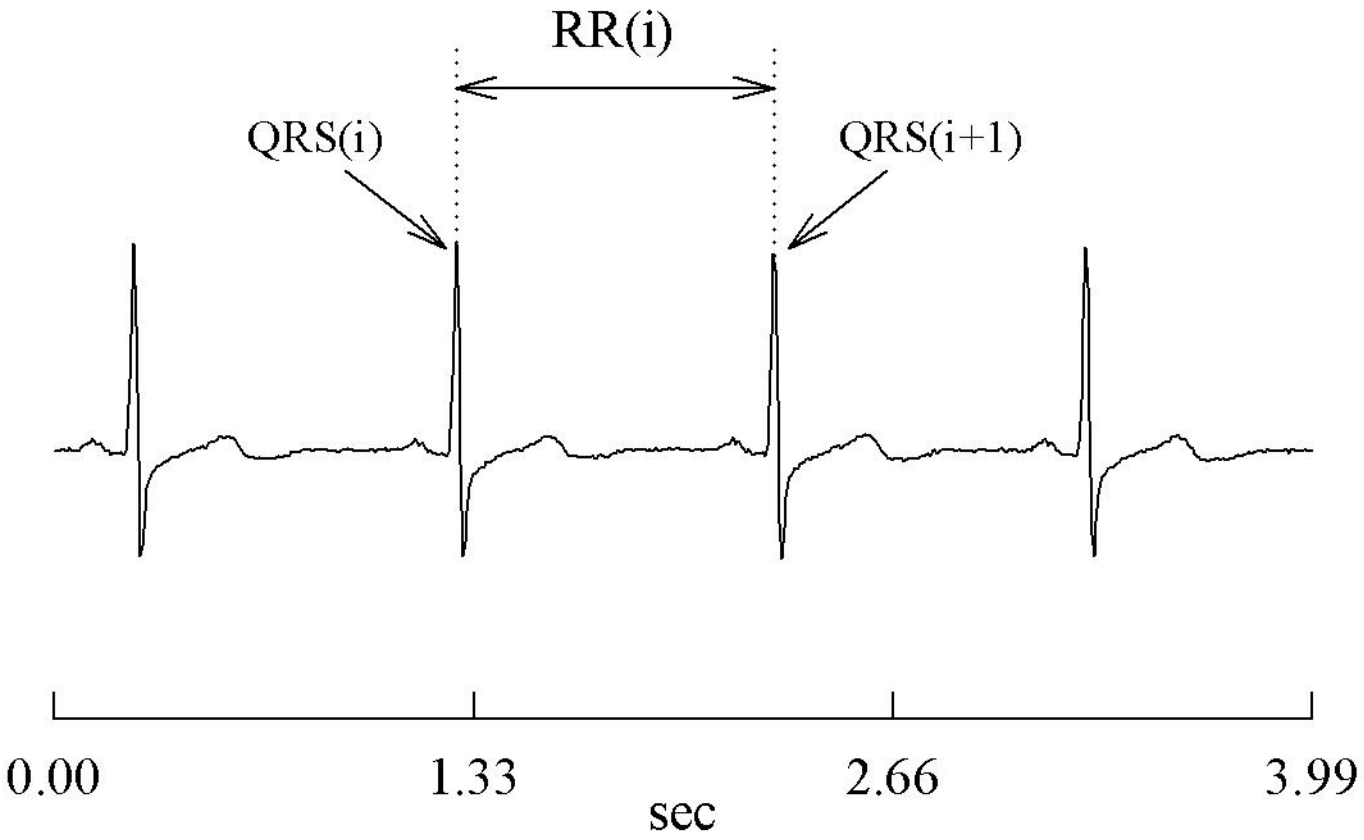
Some observations suggest that measuring complexity of heart period might provide useful clinical information (e.g. it decreases with age and disease)

Primary aim

To monitor complexity of heart period dynamics via entropy-based approaches

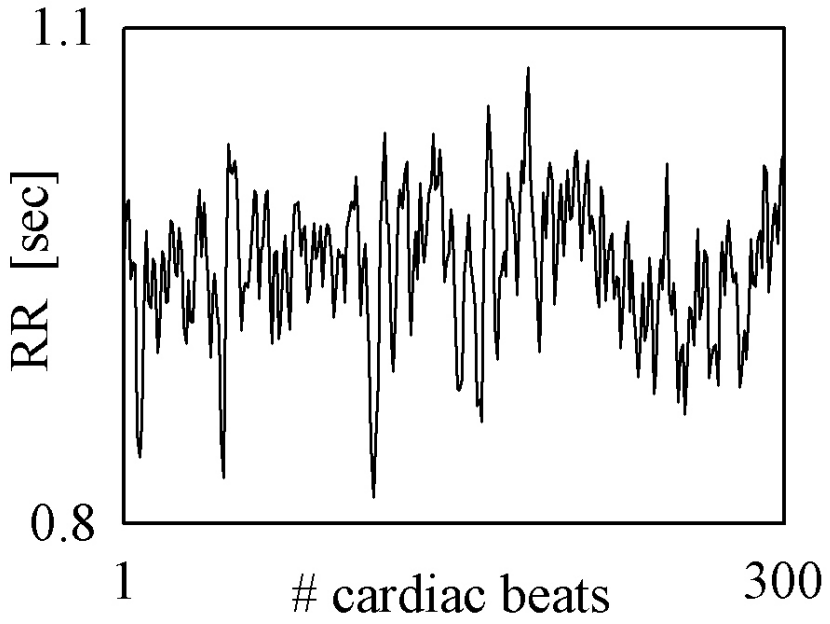
Definition of heart period variability series

ECG



$$RR=\{RR(i),\ i=1,\ldots,N\}$$

Short-term heart period variability

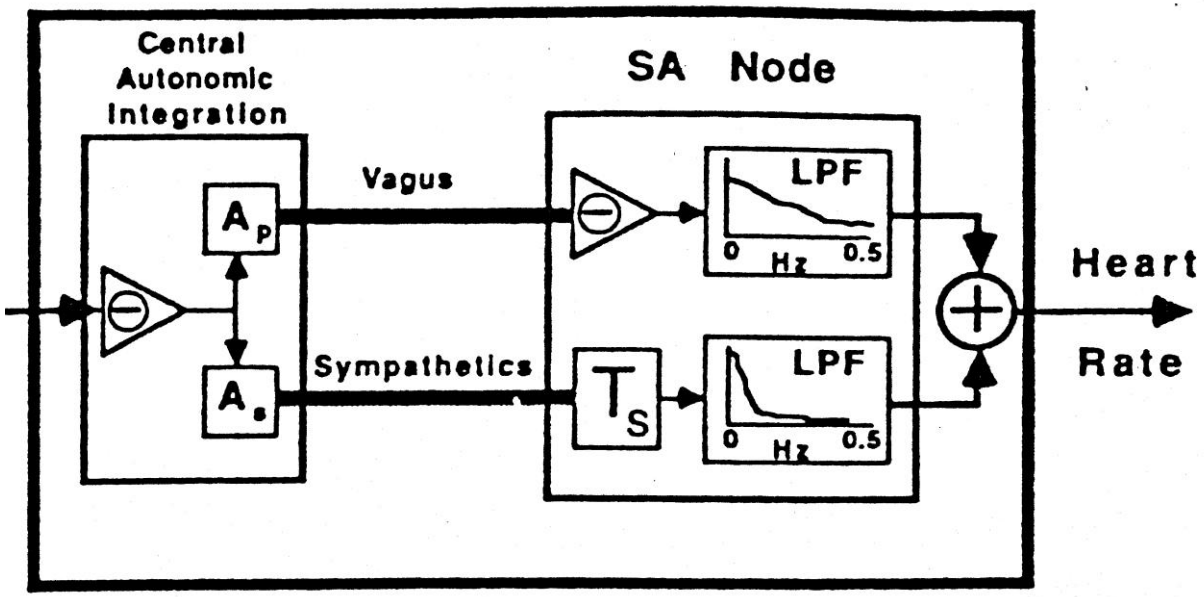


Heart period series exhibits non random fluctuations when observed over a temporal scale of few minutes

These fluctuations are referred to as short-term heart period variability

Autonomic regulation of heart period

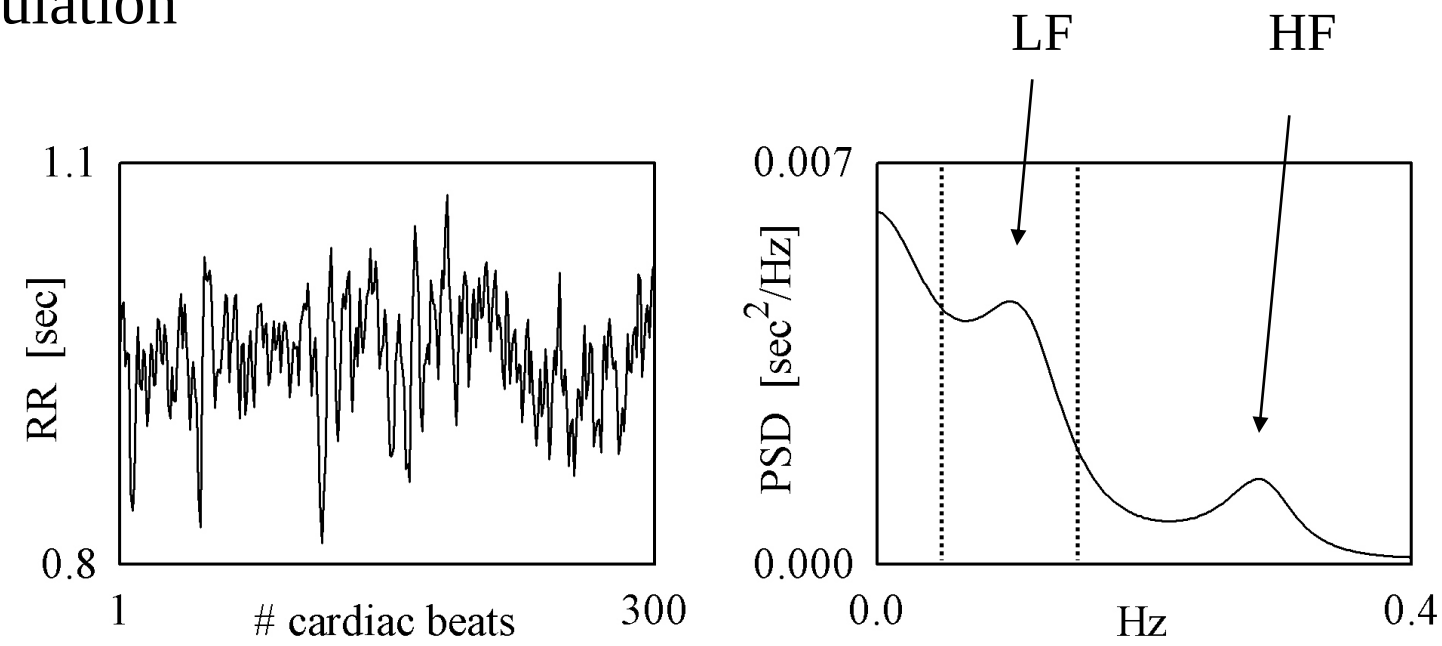
Heart rate variability is under control of the autonomic nervous system



Saul JP et al, Am J Physiol, 256:H153-H161, 1989

Assessing autonomic balance via spectral analysis

Monitoring heart rate variability has become very popular to assess balancing between parasympathetic and sympathetic regulation



LF band: $0.04 \leq f \leq 0.15$ Hz

HF band: $0.15 < f \leq 0.5$ Hz

$$\text{LF/HF} = \frac{\text{Power in the LF band}}{\text{Power in the HF band}}$$

Task Force, Circulation 93:1043-1065, 1996

Akselrod S et al, Science, 213:220-223, 1981
Malliani A et al, Circulation, 84:482-492, 1991

Drawbacks of the evaluation of the autonomic balance based on spectral analysis

1) LF/HF index is based on a linear analysis

2) LF/HF index depends on the definition of the limits of the frequency bands

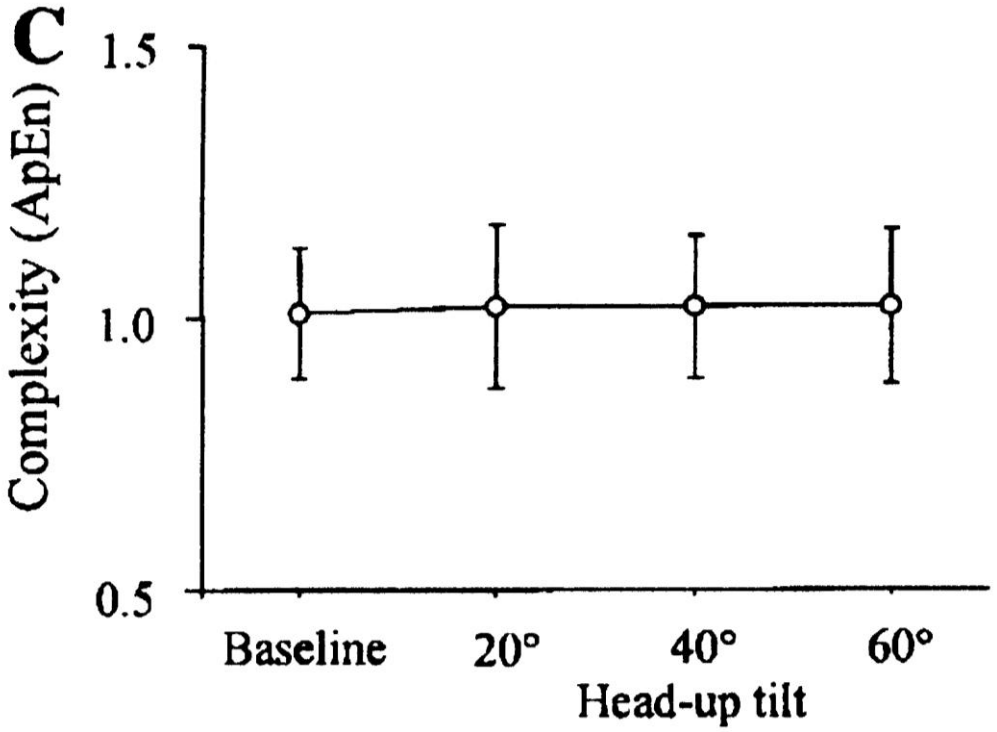
3) The numerator and denominator of the LF/HF index are not independent

4) LF/HF index loses his meaning when respiration drops in the LF band

Secondary aim

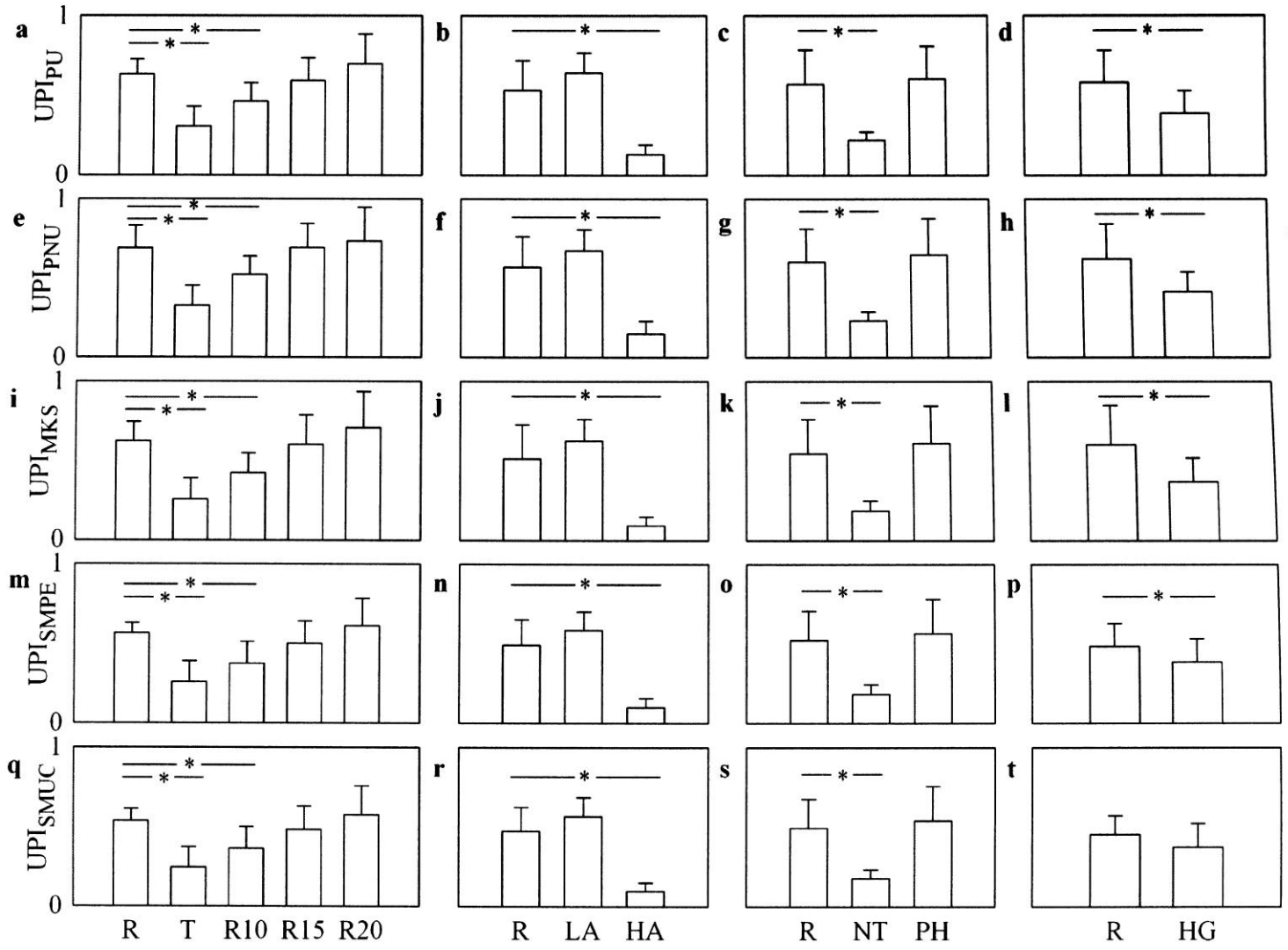
Are entropy-based complexity indexes helpful to infer the state of the autonomic nervous system controlling heart rate?

Short-term heart period variability complexity and autonomic nervous system



Tulppo MP et al, Am J Physiol, 280:H1081-H1087, 2001

Short-term heart period variability complexity and autonomic nervous system



Porta A et al, IEEE Trans Biomed Eng, 54:94-106, 2007

Aims

1) To verify whether complexity indexes based on entropy rates can track the gradual increase of sympathetic modulation (and the concomitant decrease of vagal one) produced by graded head-up tilt test

2) To compare well-established estimates of entropy rates on the same experimental protocol

3) To understand whether normalization of entropy rate with respect to an index of static complexity may bring additional information

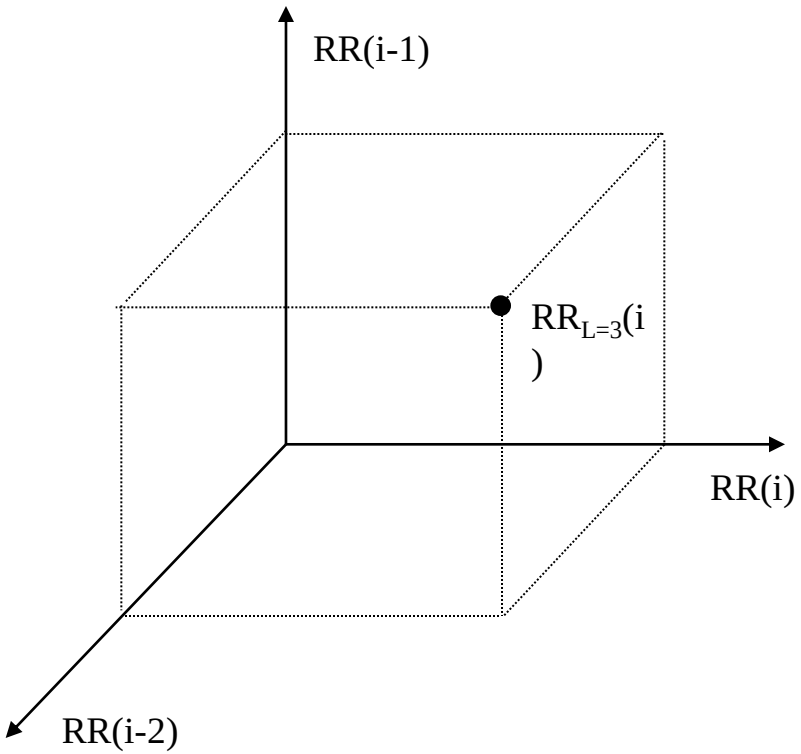
Pattern definition

Given the series RR = {RR(i), i=1,...,N}

Pattern: $RR_L(i) = (RR(i),RR(i-1),...,RR(i-L+1))$

A pattern is a point in a L-dimensional embedding space

With L=3



Shannon entropy (SE) and conditional entropy (CE)

Shannon entropy (SE)

$$SE(L) = -\Sigma p(RR_L(i)) \cdot \log(p(RR_L(i)))$$

Conditional entropy (CE)

$$CE(L) = SE(L)-SE(L-1)$$

Functions playing a role equivalent to the conditional entropy

1) Approximate entropy (ApEn)

Pincus SM, Chaos, 5:110-117, 1995

2) Sample entropy (SampEn)

Richman JS and Moorman JR, Am J Physiol, 278:H2039-H2049, 2000

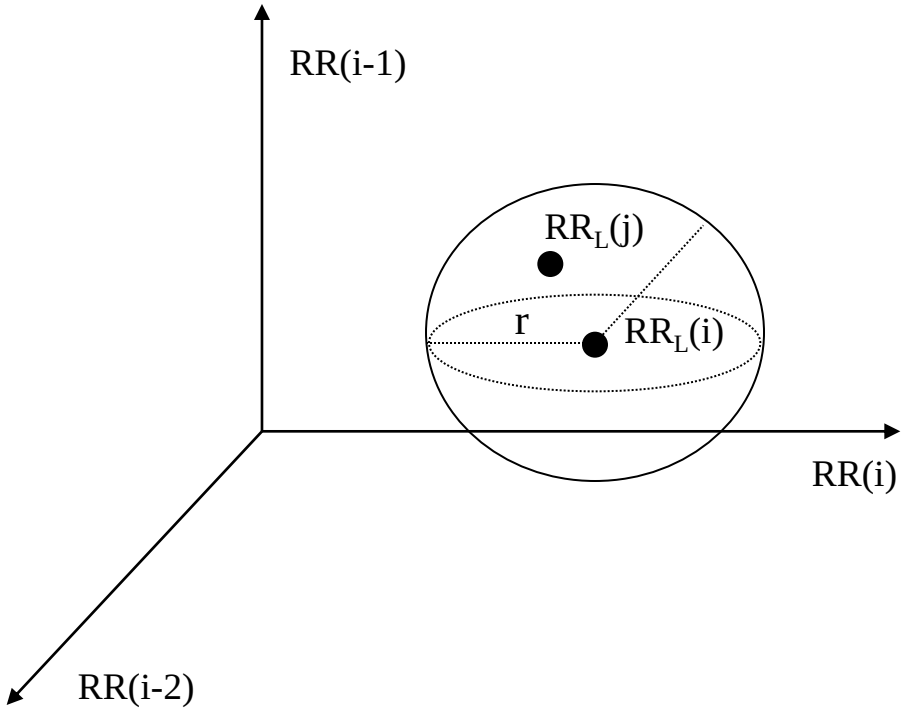
3) Corrected conditional entropy (CCE)

Porta A et al , Biol Cybern, 78:71-78, 1998

Approximate entropy (ApEn)

Pattern similarity within a tolerance r

With L=3



$RR_L(j)$ is similar to $RR_L(i)$ within a tolerance r
if they $RR_L(j)$ is closer than r to $RR_L(i)$

According to the Euclidean norm, $RR_L(j)$ is similar to $RR_L(i)$
if $RR_L(j)$ lies in a hyper-sphere of radius r centered in $RR_L(i)$

Approximate entropy (ApEn)

$$\Phi_{PS}(L,r) = -\frac{1}{N-L+1}\sum_{i=1}^{N-L+1}\log(C_i(L,r))$$

where

$$C_i(L,r) = \frac{N_i(L,r)}{N-L+1}$$

$N_i(L,r)$ = number of points (i.e. patterns) similar to $RR_L(i)$ within a tolerance r

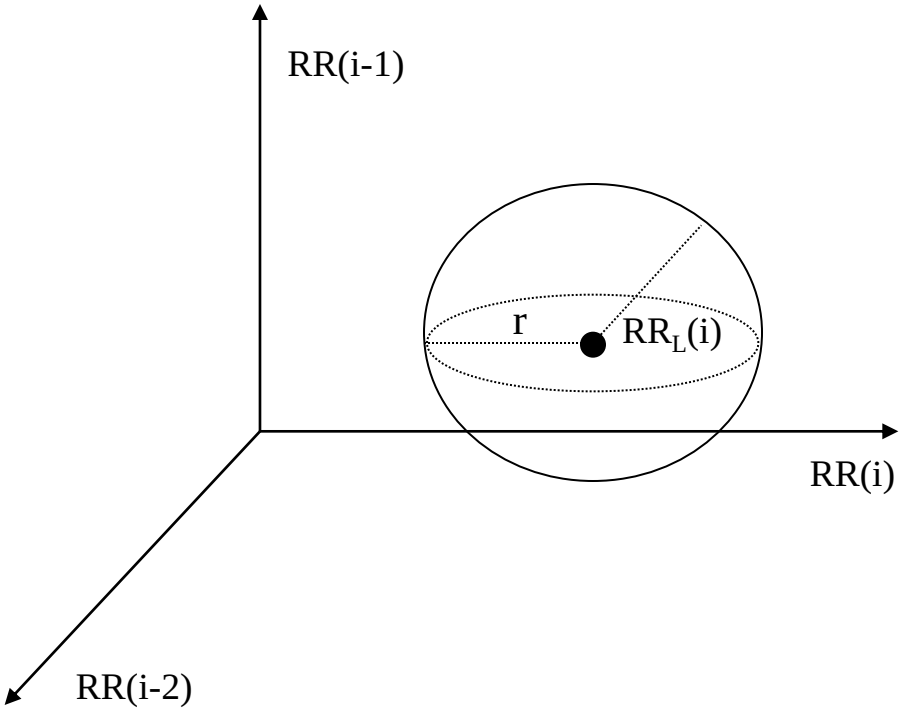
$$ApEn(L,r) = \Phi_{PS}(L,r) - \Phi_{PS}(L-1,r)$$

Pincus SM, Chaos, 5:110-117, 1995

Self-matching

Self-matching is a consequence of the trivial observation that $RR_L(j)$ is always at distance smaller than r from $RR_L(i)$ when i=j

With L=3



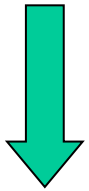
Self-matching occurs when the unique pattern in the hyper-sphere of radius r centered around $RR_L(i)$ is $RR_L(i)$

$RR_L(i)$ is a "self-match" if $N_i(L,r)=1$

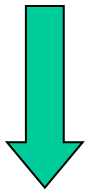
Self-matching and approximate entropy

When calculating $\Phi_{PS}(L,r) = -\frac{1}{N-L+1}\sum_{i=1}^{N-L+1}\log(C_i(L,r))$

self-matching is allowed



$$\frac{1}{N-L+1} \leq C_i(L,r) \leq 1$$



log(0) is prevented

Bias of the approximate entropy

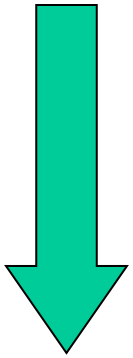
Two factors produce the important bias of ApEn

1) due to the spreading of the dynamics in the phase space

$N_i(L,r) \leq N_i(L-1,r)$

2) due to self-matching

$N_i(L,r) \geq 1$



$N_i(L,r) \rightarrow 1$ while increasing L

Bias of the approximate entropy

Since $N_i(L,r) \rightarrow 1$ while increasing L

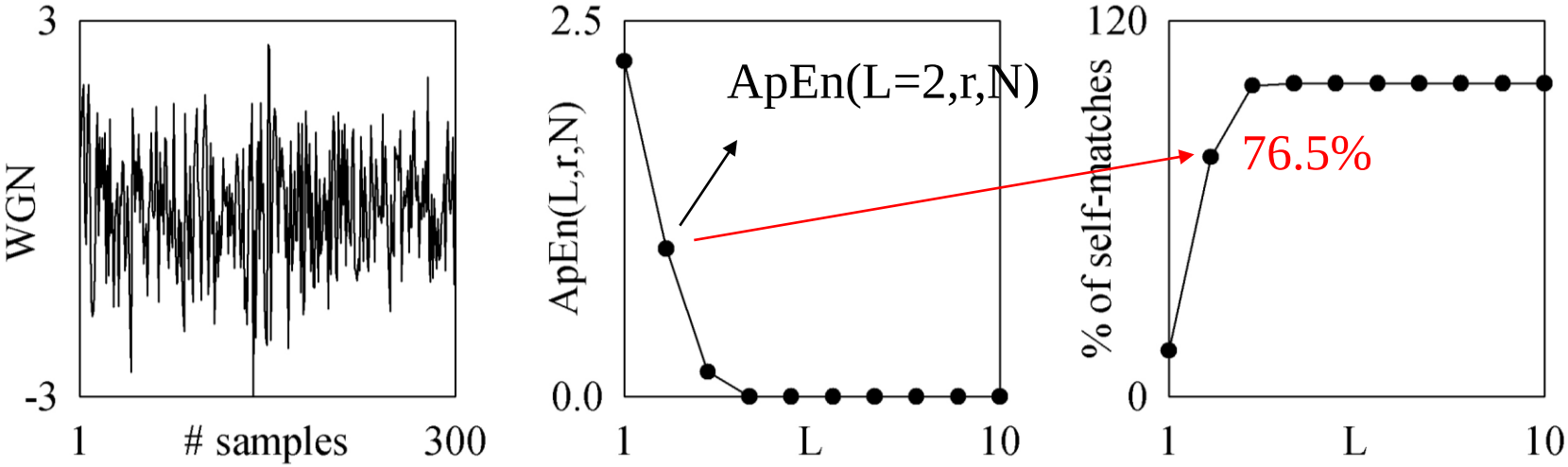
$$\Phi_{PS}(L,r) \rightarrow \Phi_{PS}(L-1,r)$$

$$ApEn(L,r) = \Phi_{PS}(L,r) - \Phi_{PS}(L-1,r) \rightarrow 0$$

thus producing a bias toward regularity

Approximate entropy over a realization of a Gaussian white noise

r=0.2·SD N=300



The high percentage of "self-matches" even at small L makes mandatory their optimal management

Corrected approximate entropy (CApEn)

Correction of the approximate entropy: the corrected ApEn (CApEn)

$$ApEn(L,r)=\Phi_{PS}(L,r) - \Phi_{PS}(L-1,r) = - \frac{1}{N-L+1} \sum_{i=1}^{N-L+1} \log \frac{N_i(L,r)}{N_i(L-1,r)}$$

Correction:

When $N_i(L,r)=1$ or $N_i(L-1,r)=1$, then $\frac{N_i(L,r)}{N_i(L-1,r)}$ is set to $\frac{1}{N-L+1}$

Porta A et al, J Appl Physiol, 103:1143-1149, 2007

Sample entropy (SampEn)

Sample entropy (SampEn)

$$\Phi_{RM}(L,r) = - \log\left(\frac{1}{N-L+1} \sum_{i=1}^{N-L+1} C_i(L,r)\right)$$

where

$$C_i(L,r) = \frac{N_i(L,r)}{N-L+1}$$

$N_i(L,r)$ = number of points (i.e. patterns) that can be found at distance smaller than r from $RR_L(i)$

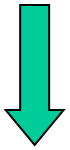
$$SampEn(L,r) = \Phi_{RM}(L,r) - \Phi_{RM}(L-1,r)$$

Richman JS and Moorman JR, Am J Physiol, 278:H2039-H2049, 2000

Self-matching and sample entropy

$$\mathrm{SampEn}(L,r) = \Phi_{RM}(L,r) - \Phi_{RM}(L-1,r) = -\log \frac{\sum_{i=1}^{N-L+1} N_i(L,r)}{\sum_{i=1}^{N-L+1} N_i(L-1,r)}$$

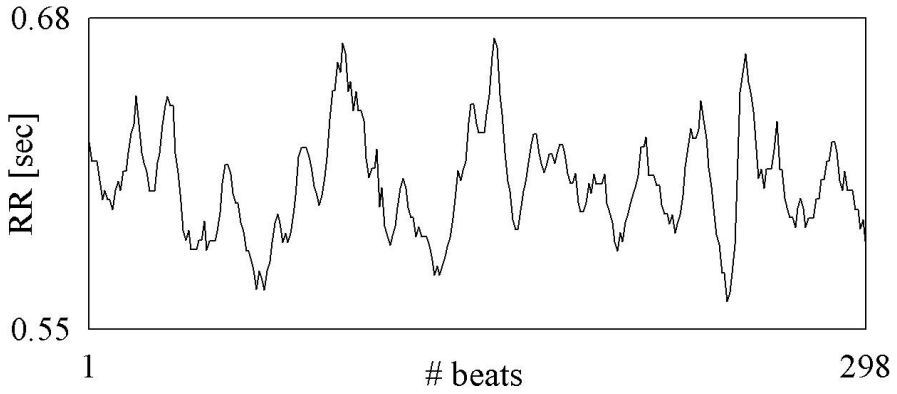
When calculating SampEn(L,r) “self-matches” are excluded



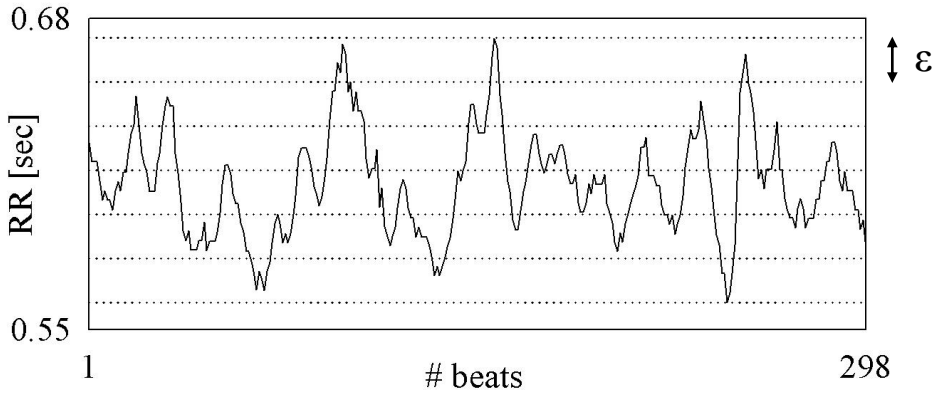
$N_i(L,r)$ and $N_i(L-1,r)$ can be 0

Corrected conditional entropy (CCE)

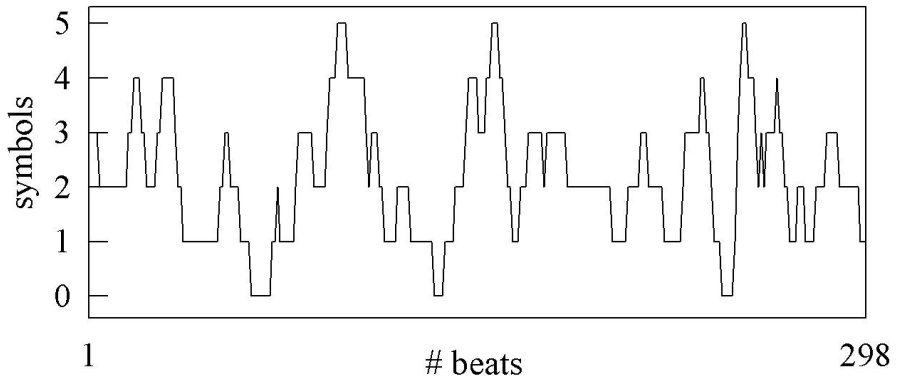
Toward an approximation of Shannon entropy and conditional entropy: uniform quantization



$\{RR(i), i=1,...,N\}$ with $RR(i) \in R$



$$q=6 \text{ with } \varepsilon = \frac{\max(RR)-\min(RR)}{q}$$



$\{RR_q(i), i=1,...,N\}$ with $RR_q(i) \in I$

$0 \leq RR_q(i) \leq q-1$

Estimation of Shannon entropy and conditional entropy

Given the quantized series $RR^q = \{RR^q(i), i=1,...,N\}$ and built the series of quantized patterns $RR_L^q = \{RR_L^q(i), i=L,...,N\}$

with $RR_L^q(i) = (RR^q(i),RR^q(i-1),...,RR^q(i-L+1))$

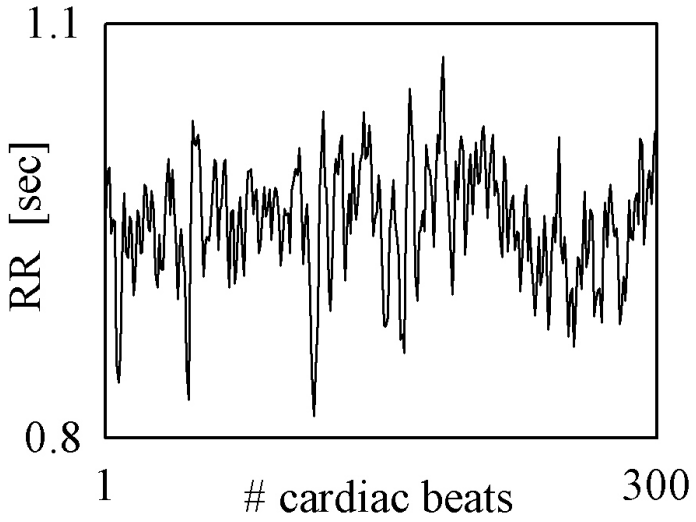
Shannon entropy (SE)

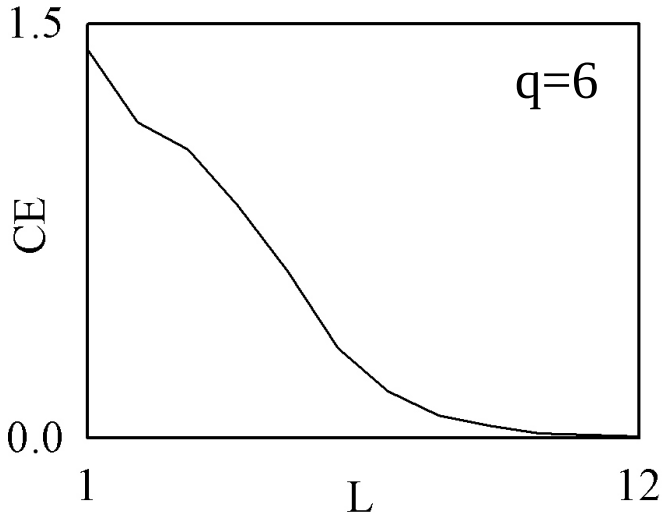
$$SE(L,q) = -\Sigma p(RR_L^q(i)) \cdot \log(p(RR_L^q(i)))$$

Conditional entropy (CE)

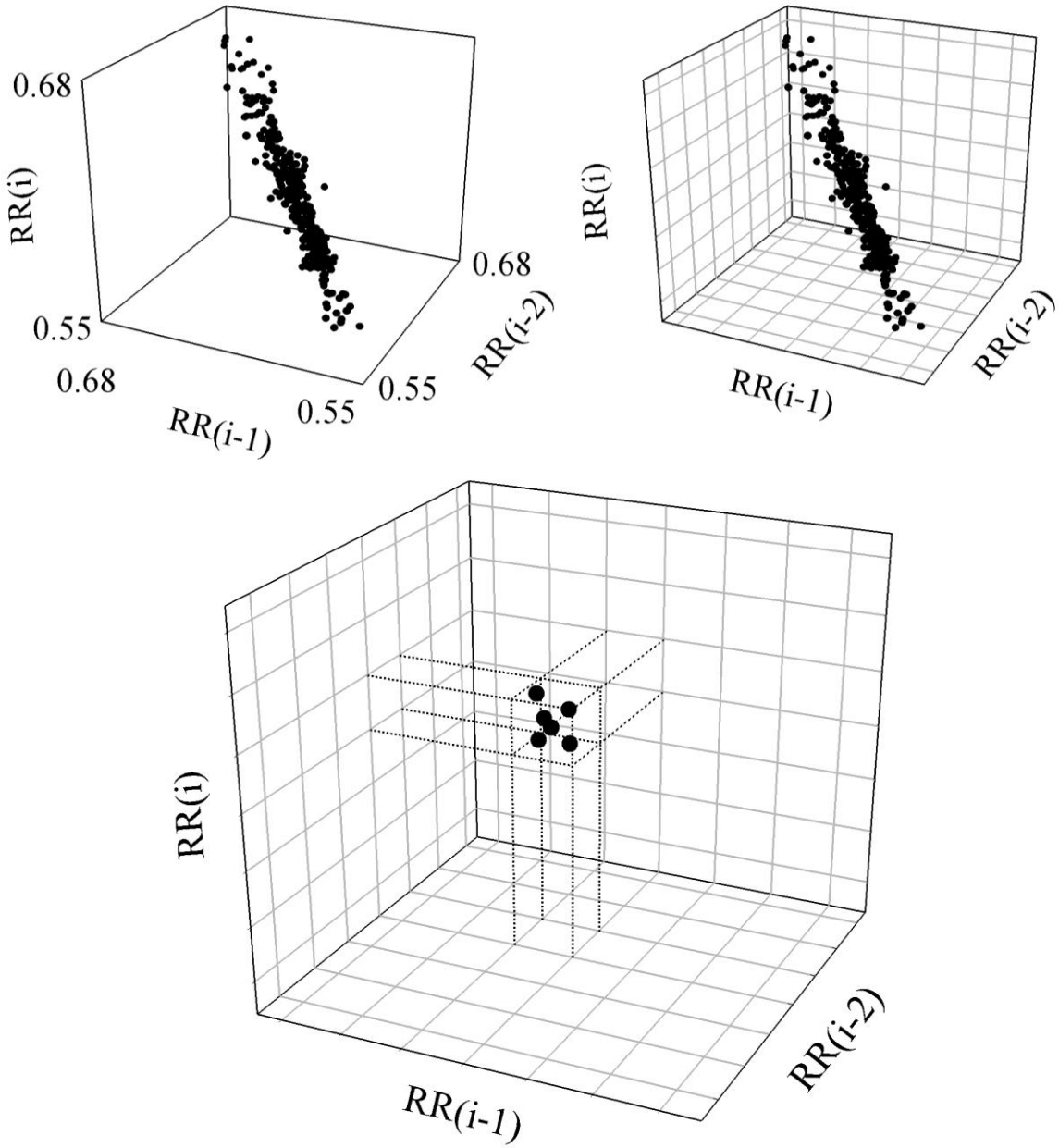
$$CE(L,q) = SE(L,q)-SE(L-1,q)$$

Estimate of the conditional entropy (CE)



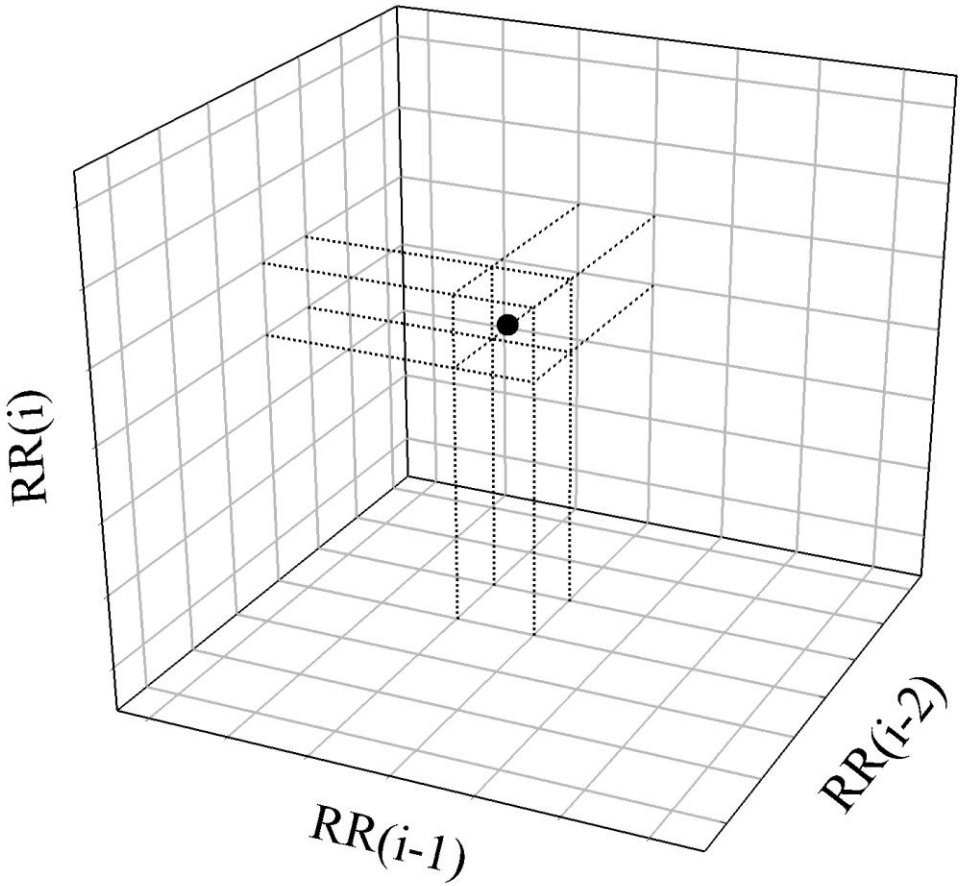


Effects of uniform quantization procedure



Definition of “single” patterns

Let’s define as “single” the quantized pattern $RR_L^q(i)$ such that it is alone in an hypercube of the partition of the phase space imposed by uniform quantization



Bias of the estimate of the conditional entropy

The contribution of each “single” pattern to Shannon entropy is

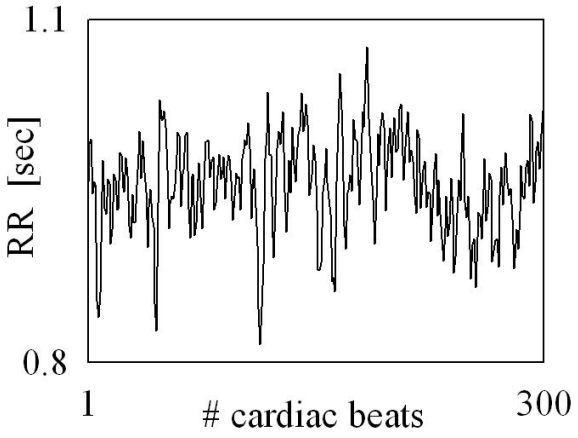
$$-\frac{1}{N-L+1}\log\left(\frac{1}{N-L+1}\right) \approx -\frac{1}{N}\log\left(\frac{1}{N}\right)$$

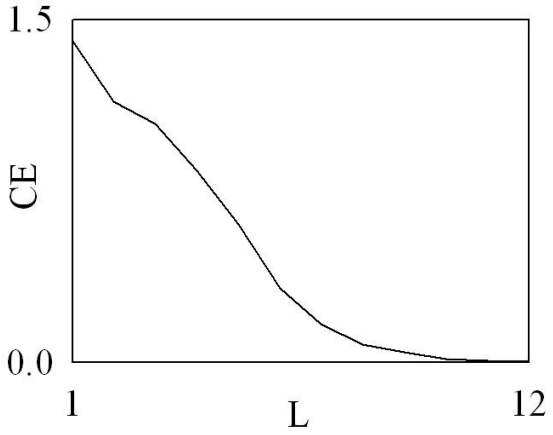
Since it N>>L, it is constant with L and, thus, its contribution to the conditional entropy is 0

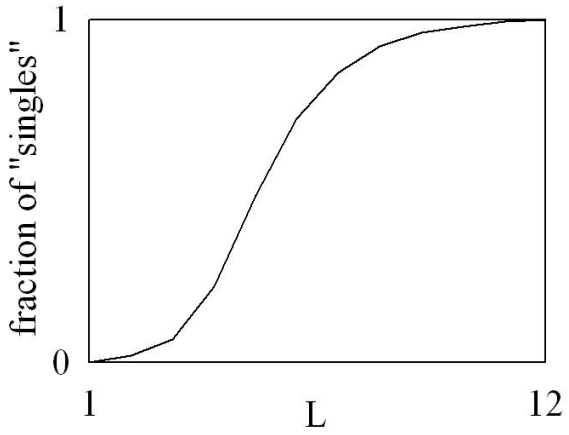
“Single” patterns do not contribute to CE

Bias of the estimate of the conditional entropy and single patterns

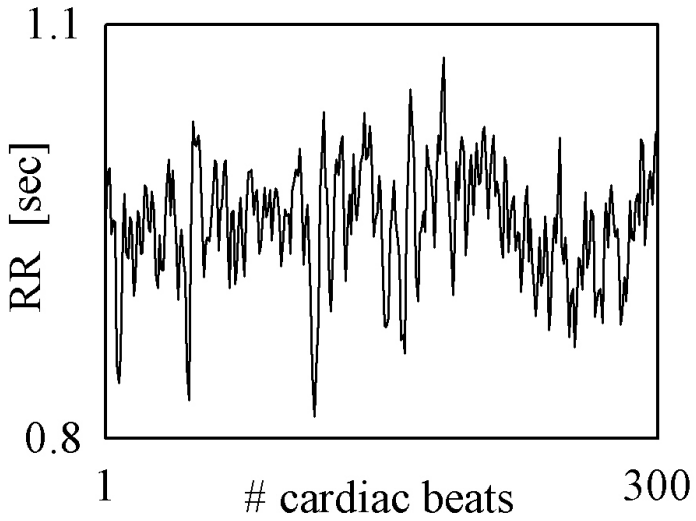
Since the percentage of “single” patterns increases as a function of L, the conditional entropy decreases to 0

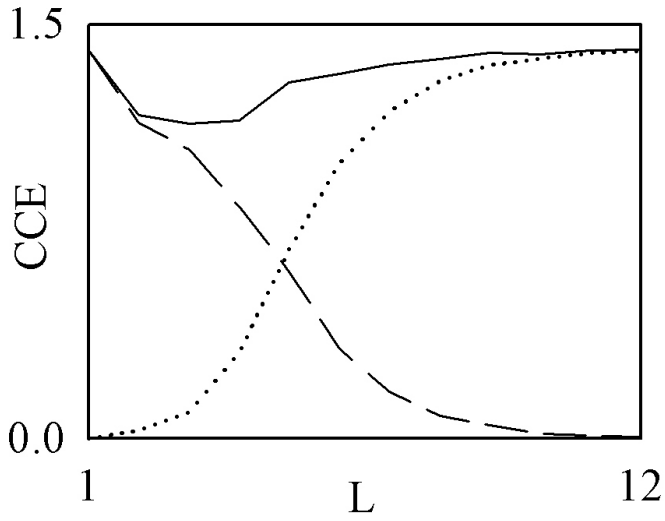






Corrected conditional entropy (CCE)





CCE(L,q)

CE(L,q)

SE(L=1,q) · perc(L)

$$CCE(L,q) = CE(L,q) + SE(L=1,q) \cdot fraction(L)$$

with $0 \leq perc(L) \leq 1$

Porta A et al , Biol Cybern, 78:71-78, 1998

Experimental protocol

17 healthy young humans (age from 21 to 54, median=28)

We recorded ECG (lead II) and respiration (thoracic belt) at 1 kHz during head-up tilt (T)

Table angles were randomly chosen within the set {15,30,45,60,75,90}

Each T session (10 min) was always preceded by a session (7 min) at rest (R) and followed by a recovery period (3 min)

Setting for calculation of the complexity indexes

1) Approximate entropy, ApEn(L,r,N) and Corrected Approximate entropy, CApEn(L,r,N)

L-1=2; r=0.2·SD; N=~250 → CI_{PS} CCI_{PS}

2) Sample entropy, SampEn(L,r,N)

L-1=2; r=0.2·SD; N=~250 → CI_{RM}

3) Corrected conditional entropy, CCE(L,q,N)

$L=L_{min}$; q=6; N=~250 → CI_{P}

Normalized complexity indexes

$$CI_{PS} \rightarrow NCI_{PS} = \frac{CI_{PS}}{\Phi_{PS}(L=1,r)}$$

$$CCI_{PS} \rightarrow NCCI_{PS} = \frac{CCI_{PS}}{\Phi_{PS}(L=1,r)}$$

$$CI_{RM} \rightarrow NCI_{RM} = \frac{CI_{RM}}{\Phi_{RM}(L=1,r)}$$

$$CI_{P} \rightarrow NCI_{P} = \frac{CI_{P}}{SE(L=1,\xi)}$$

Entropy-based complexity indexes during graded head-up tilt

Index	R	T15	T30	T45	T60	T75	T90
CI_{PS}	0.94 (0.90-1.01)	0.97 (0.95-1.03)	1.00 (0.96-1.06)	1.04 (1.00-1.06)	1.03 (0.97-1.04)	1.00 (0.96-1.03)	0.95 (0.87-1.05)
NCI_{PS}	0.41 (0.39-0.45)	0.43 (0.42-0.45)	0.43 (0.42-0.46)	0.46 (0.43-0.47)	0.45 (0.43-0.46)	0.44 (0.42-0.46)	0.42 (0.40-0.46)
CCI_{PS}	4.20 (3.88-4.37)	3.90 (3.59-4.14)	3.57 (3.28-3.93)	3.15# (2.63-3.59)	2.99# (2.61-3.34)	2.87# (2.32-3.18)	2.63# (2.16-3.26)
$NCCI_{PS}$	1.84 (1.76-1.91)	1.71 (1.59-1.82)	1.61 (1.44-1.71)	1.38# (1.15-1.60)	1.39# (1.17-1.44)	1.25# (1.08-1.41)	1.14# (0.95-1.42)
CI_{RM}	2.19 (2.03-2.37)	2.05 (1.78-2.13)	1.88 (1.70-2.00)	1.73# (1.49-1.88)	1.55# (1.10-1.69)	1.54# (1.26-1.64)	1.55# (1.14-1.71)
NCI_{RM}	1.01 (0.96-1.08)	0.95 (0.82-0.98)	0.87 (0.78-0.94)	0.80# (0.71-0.87)	0.73# (0.55-0.81)	0.70# (0.60-0.75)	0.69# (0.53-0.82)
CI_{P}	1.17 (1.12-1.30)	1.13 (1.08-1.19)	1.00 (0.91-1.14)	0.91# (0.83-1.01)	0.87# (0.81-0.99)	0.87# (0.74-0.91)	0.85# (0.75-0.96)
NCI_{P}	0.81 (0.71-0.85)	0.72 (0.70-0.76)	0.66# (0.62-0.73)	0.64# (0.55-0.68)	0.58# (0.52-0.64)	0.54# (0.51-0.60)	0.57# (0.52-0.66)

Values are expressed as median (first quartile – third quartile).
CI = complexity index; NCI = normalized CI; CCI = corrected CI; NCCI = normalized CCI; subscripts PS, RM, P (Pincus, Richman and Moorman, and Porta) indicate the name of the authors who proposed the index. The symbol # indicates a significant difference vs R with $p<0.05$.

Porta A et al, J Appl Physiol, 103:1143-1149, 2007

Global linear regression (GLR) analysis of entropy-based complexity indexes on tilt angles

Index	GLR	GLR (up to T75)
CI_{PS}	No	No
NCI_{PS}	No	No
CCI_{PS}	Yes	Yes
$NCCI_{PS}$	Yes	Yes
CI_{RM}	Yes	Yes
NCI_{RM}	Yes	Yes
CI_{P}	Yes	Yes
NCI_{P}	Yes	Yes

Yes/No = presence/absence of a significant global linear correlation.

Porta A et al, J Appl Physiol, 103:1143-1149, 2007

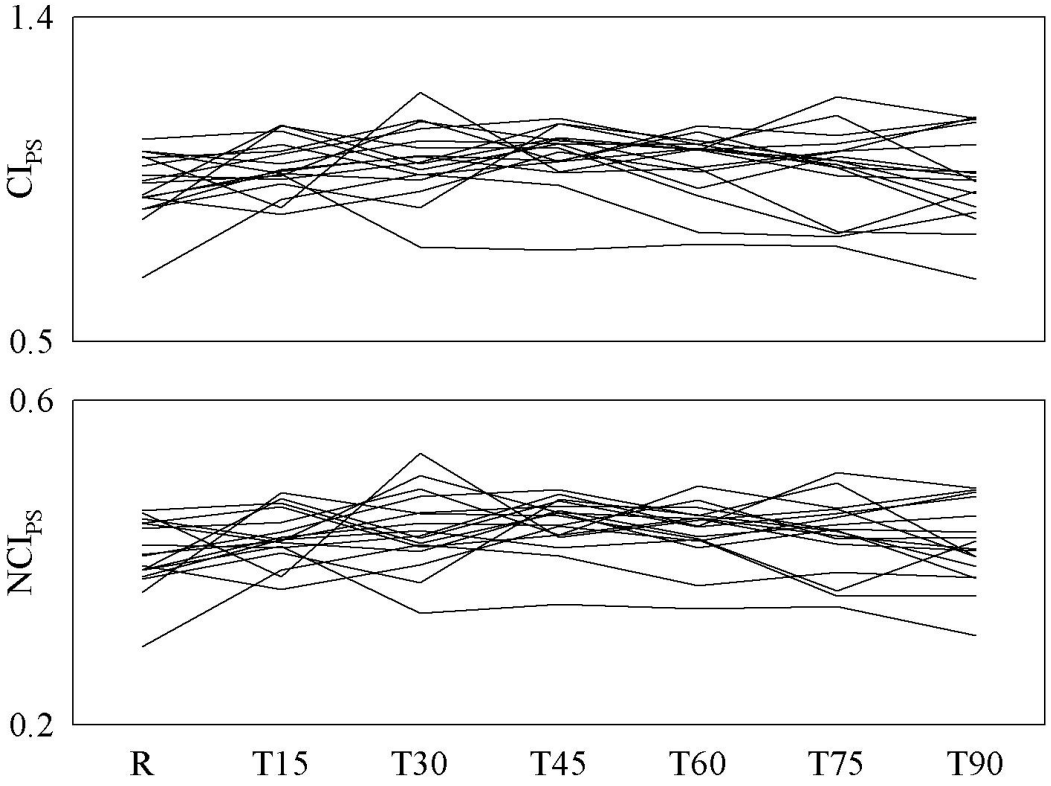
Correlation coefficient of global linear regression (GLR) of entropy-based complexity indexes on tilt angles

Index	r_{GLR}	r_{GLR} (up to T75)
CI_{PS}	-	-
NCI_{PS}	-	-
CCI_{PS}	-0.68	-0.71
$NCCI_{PS}$	-0.69	-0.72
CI_{RM}	-0.63	-0.66
NCI_{RM}	-0.63	-0.65
CI_{P}	-0.66	-0.70
NCI_{P}	-0.70	-0.77

r_{GLR} = global correlation coefficient.

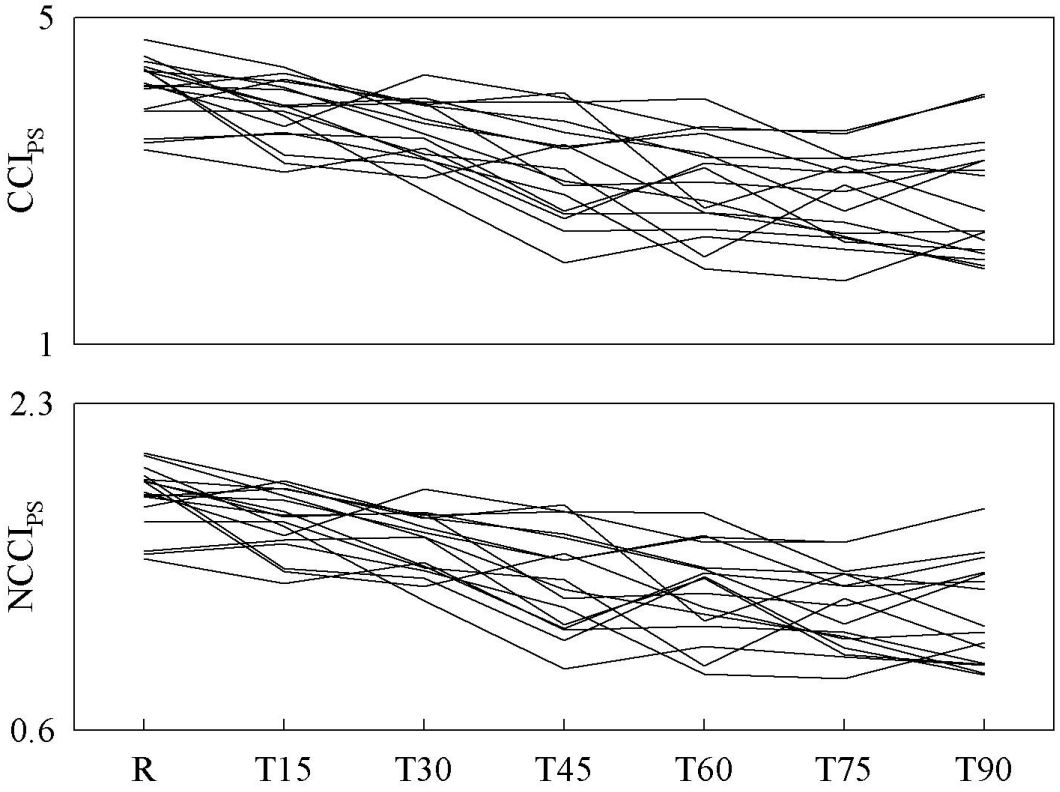
Porta A et al, J Appl Physiol, 103:1143-1149, 2007

Individual trends of entropy-based complexity indexes based on ApEn



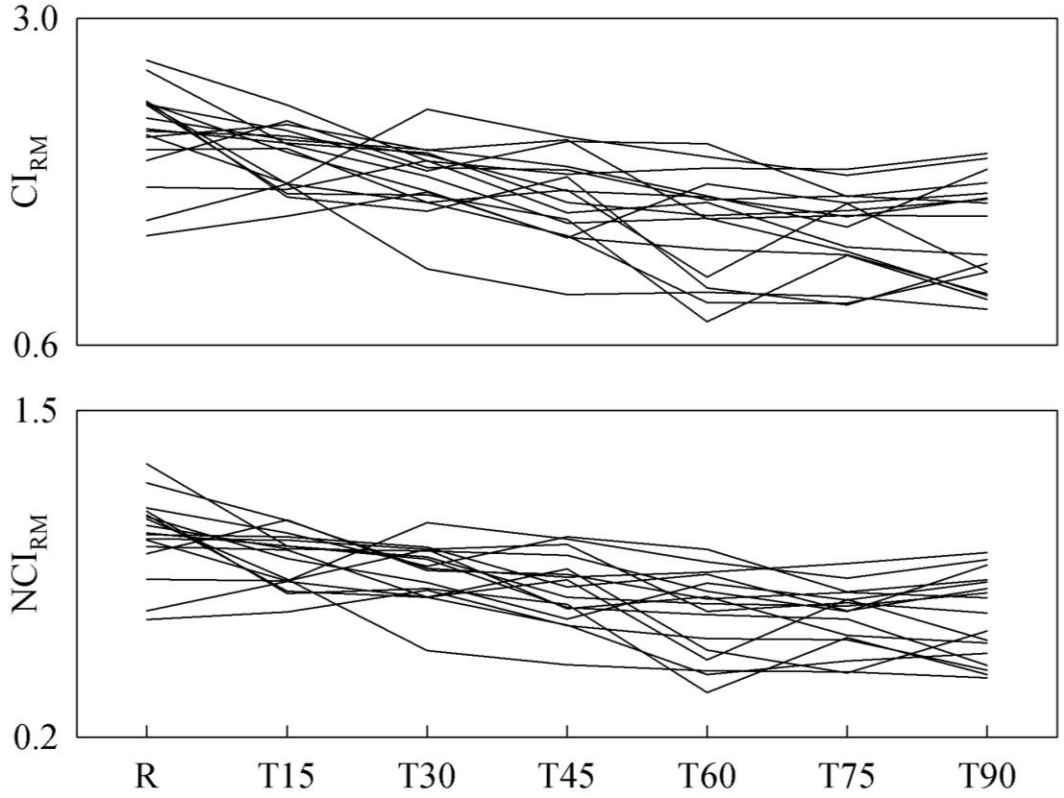
Porta A et al, J Appl Physiol, 103:1143-1149, 2007

Individual trends of entropy-based complexity indexes based on CApEn



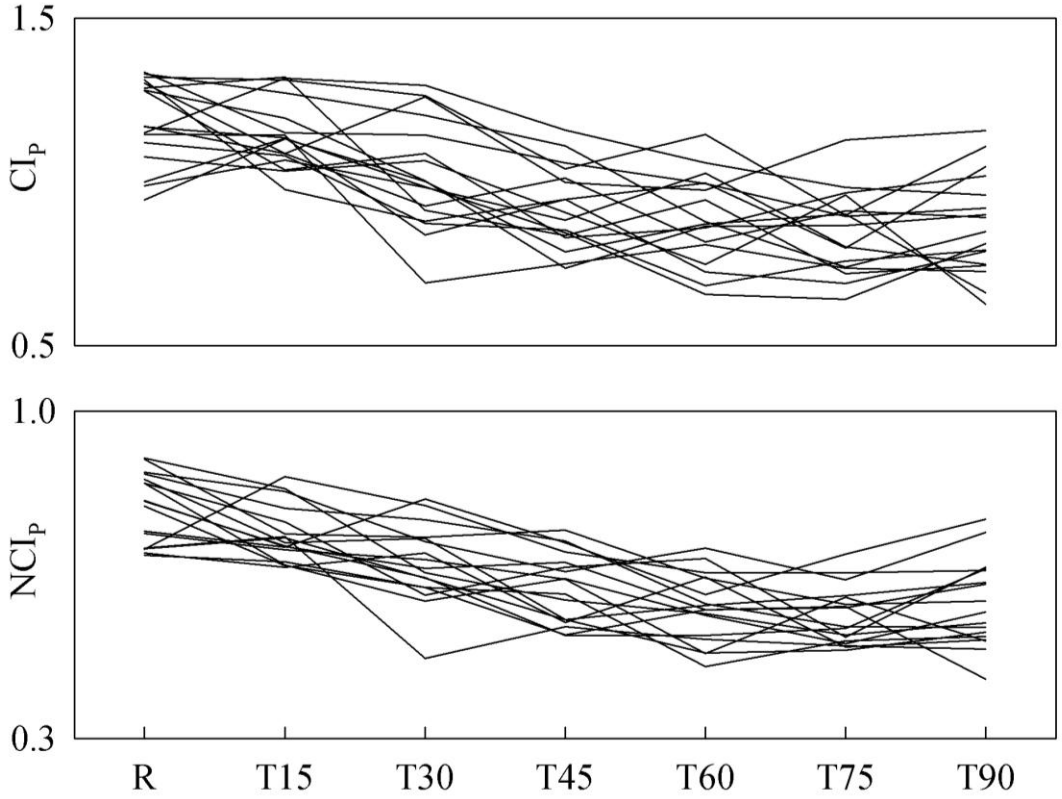
Porta A et al, J Appl Physiol, 103:1143-1149, 2007

Individual trends of entropy-based complexity indexes based on SampEn



Porta A et al, J Appl Physiol, 103:1143-1149, 2007

Individual trends of entropy-based complexity indexes based on CCE



Porta A et al, J Appl Physiol, 103:1143-1149, 2007

Individual linear regression (ILR) analysis of entropy-based complexity indexes on tilt angles

Index	ILR%	ILR% (up to T75)
CI_{PS}	-	-
NCI_{PS}	-	-
CCI_{PS}	82	82
$NCCI_{PS}$	82	82
CI_{RM}	82	76
NCI_{RM}	82	71
CI_{P} (q=5)	65	47
NCI_{P} (q=5)	59	65
CI_{P} (q=6)	71	47
NCI_{P} (q=6)	65	59
CI_{P} (q=7)	82	53
NCI_{P} (q=7)	76	65

ILR% = fraction of subjects with significant individual linear correlation; ξ = quantization levels.

Porta A et al, J Appl Physiol, 103:1143-1149, 2007

Conclusions

Approximate entropy was unable to follow the progressive decrease of complexity of short-term heart period variability during graded head-up tilt

Entropy-based indexes of complexity, when computed appropriately by correcting the bias that arises from their evaluation over short sequences, progressively decrease as a function of tilt table inclination

These indexes appear to be suitable to quantify the balance between parasympathetic and sympathetic regulation

Effects of pharmacological challenges on entropy-based complexity of short-term heart period variability

Introduction

Pharmacological protocol allows a selective blockade of the vagal or sympathetic branch of autonomic nervous system

Challenges can be combined as well to obtain a double blockade of both vagal and sympathetic branches

This protocol could allow to better relate complexity to the functioning of one of the two branches of the autonomic nervous system

Experimental protocol

9 healthy humans (age from 25 to 46)

We recorded ECG (lead II) and noninvasive finger blood pressure (Finapress 2300). Respiratory series was obtained by assessing respiratory-related amplitude changes of the ECG

Experimental sessions were performed in 3 days:

i) on day 1 after parasympathetic blockade with atropine sulfate (AT) to block muscarinic receptors;

ii) on day 2 after β-adrenergic blockade with propranolol (PR) to block β1 cardiac and β2 vascular peripheral adrenergic receptors;

iii) on day 1 PR was administered at the end of the AT session to combine the effect of AT and PR (AT+PR);

iv) on day 3 after centrally block the sympathetic outflow to heart and vasculature with clonidine hydrochloride (CL).

Entropy-based complexity indexes during pharmacological blockade

	B	AT	AT+PR	PR	CL
CI_{CCE}	1.19 (1.07-1.28)	0.62* (0.60-0.72)	0.91 (0.87-1.11)	1.19 (1.07-1.29)	1.39 (1.23-1.44)
NCI_{CCE}	0.77 (0.74-0.81)	0.40* (0.36-0.45)	0.64 (0.55-0.67)	0.79 (0.78-0.89)	0.83 (0.82-0.86)
CI_{CApEn}	4.15 (3.80-4.38)	1.79* (1.45-1.90)	3.20* (2.84-3.68)	4.21 (3.80-4.44)	4.60 (4.31-4.71)
NCI_{CApEn}	1.81 (1.64-1.92)	0.80* (0.64-0.86)	1.39* (1.26-1.60)	1.84 (1.71-1.96)	2.01 (1.89-2.05)
CI_{SampEn}	2.14 (1.99-2.27)	1.13* (0.92-1.29)	1.73* (1.53-1.81)	2.16 (1.83-2.39)	2.41 (2.25-2.57)
NCI_{SampEn}	0.99 (0.91-1.02)	0.55* (0.43-0.60)	0.79* (0.73-0.85)	1.01 (0.85-1.09)	1.08 (1.03-1.19)

Values are expressed as median (first quartile – third quartile).
CCE = corrected conditional entropy; CApEn = corrected approximate entropy; SampEn = sample entropy;
B = baseline; AT = atropine; PR = propranolol; AT+PR = atropine plus propranolol; CL = clonidine.
The symbol * indicates a significant difference ($p<0.05$) vs B.

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Linear correlation analysis between entropy-based complexity indexes during pharmacological blockade

	CI_{CCE}	CI_{CApEn}	CI_{SampEn}
CI_{CCE}		0.844	0.805
CI_{CApEn}	$4.50 \cdot 10^{-17}$		0.967
CI_{SampEn}	$1.58 \cdot 10^{-14}$	$1.96 \cdot 10^{-35}$	

Correlation coefficient, r, and probability of type I error, p, are above and below the main diagonal respectively.
CCE = corrected conditional entropy; CApEn = corrected approximate entropy; SampEn = sample entropy

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Linear correlation analysis between entropy-based normalized complexity indexes during pharmacological blockade

	NCI_{CCE}	NCI_{CApEn}	NCI_{SampEn}
NCI_{CCE}		0.947	0.908
NCI_{CApEn}	$1.09 \cdot 10^{-29}$		0.950
NCI_{SampEn}	$3.54 \cdot 10^{-23}$	$2.11 \cdot 10^{-30}$	

Correlation coefficient, r, and probability of type I error, p, are above and below the main diagonal respectively.
CCE = corrected conditional entropy; CApEn = corrected approximate entropy; SampEn = sample entropy

Porta A et al, Physiol Meas, 34:17-33, 2013

Conclusions

Entropy-based indexes correcting the bias that arises from their evaluation over short sequences are equivalent in assessing complexity of heart period variability

Pharmacological protocol confirms the involvement of the autonomic nervous system is modulating the entropy-based complexity of heart period variability

Since vagal blockade reduces complexity, while sympathetic blockade (central or peripheral) does not affect it, it can be concluded that complexity of heart period variability is under vagal control

Entropy-based complexity of short-term heart period variability: comparison between coarse graining and ranking approaches

Introduction

CApEn, SampEn and CCE are based on coarse graining

Entropy-based complexity indexes based on ranking do not require coarse graining

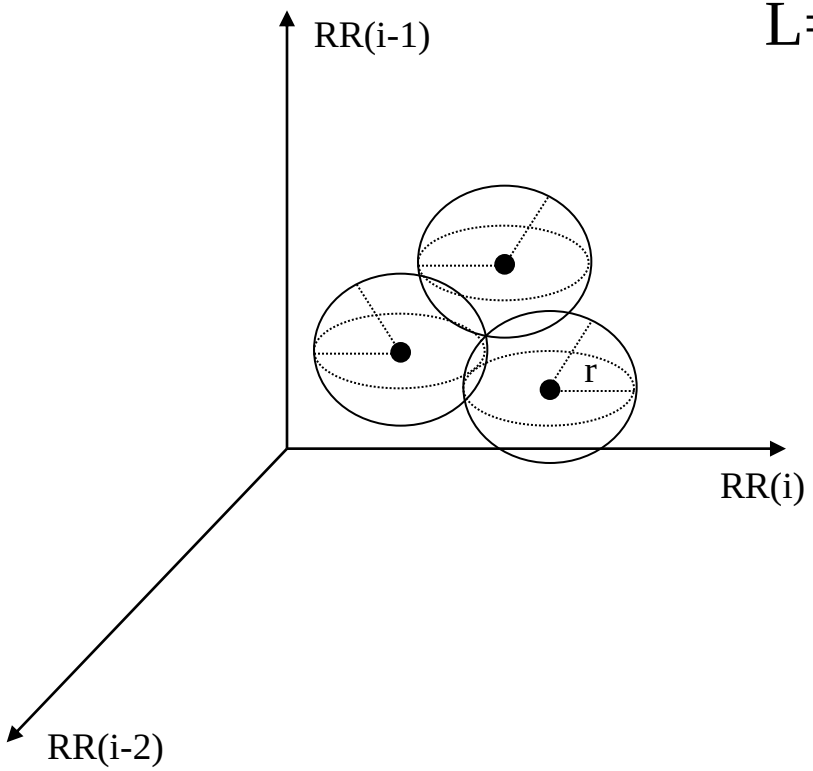
Comparison between coarse graining and ranking approaches is needed to better understand the possibility offered by entropy-based complexity indexes based on ranking

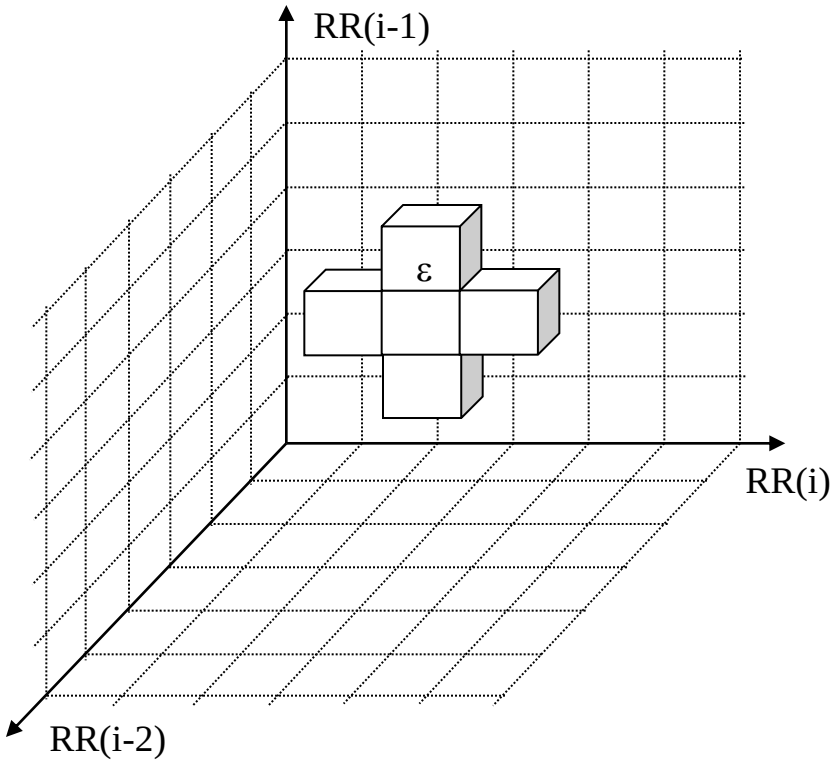
Entropies based on coarse graining

CApEn and SampEn

CCE

L=3





L-dimensional embedding space is coarse grained with hyper-spheres of radius r

L-dimensional embedding space is coarse grained with hyper-cubes of side ε

Permutation entropy

Permutation entropy is based on ranking procedure

Main advantages are:

1) Coarse graining is avoided

2) Calculation can be rendered very fast via sorting procedure

3) Unbiased by the presence of outliers

4) Invariant with respect to non linear monotone transformation

Permutation entropy

Permutation entropy is based on the transformation

$$f: RR_L(i) \longrightarrow r_L(i)$$

where $r_L(i) = (\text{rank}(RR(i)), \text{rank}(RR(i-1)), \ldots, \text{rank}(RR(i-L+1)))$ and rank of each sample is assessed inside the set of samples forming $RR_L(i)$

$r_L(i)$ corresponds to one of the possible L! permutations of (1, 2, …, L)

If equal values of RR are present, leading to tied rank, they are considered all different according to their diverse occurrence in time

Permutation entropy and permutation conditional entropy

Given the series of pattern $r_L = \{r_L(i), i=1,...,N-L+1\}$ and defined as

$$p(r_L(i)) = \frac{\text{number of i with } i=1,\ldots,N-L+1 \mid r_L(i) \text{ is found in } r_L}{N-L+1}$$

permutation entropy (PE) of order L with $L \geq 2$ is

$$PE(L) = -\Sigma p(r_L(i)) \cdot \log(p(r_L(i)))$$

and permutation conditional entropy (PCE) of order L with $L \geq 3$ is

$$PCE(L) = PE(L)-PE(L-1)$$

Normalized permutation entropy and normalized permutation conditional entropy

The normalized (PE) is

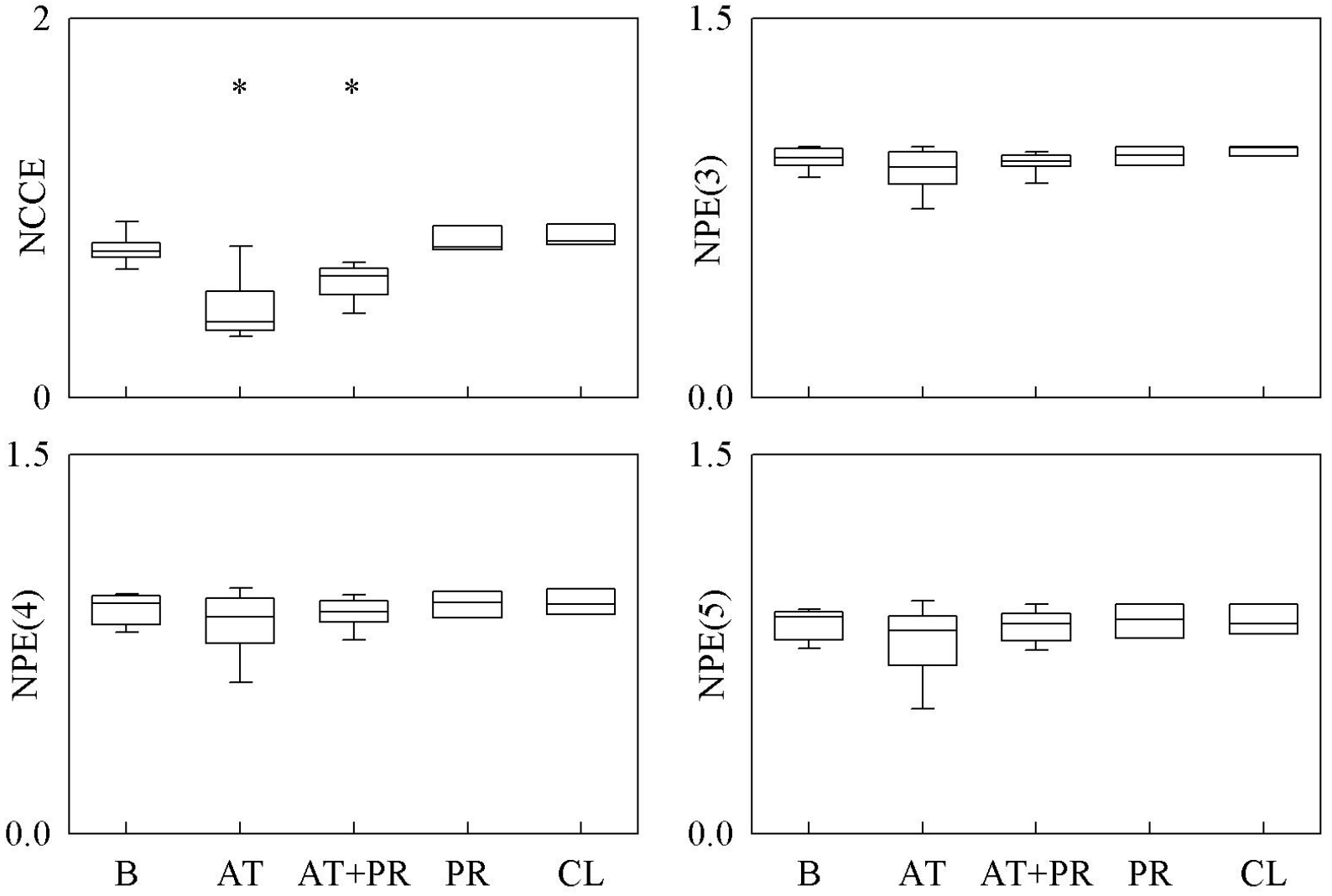
$$NPE(L) = \frac{PE(L)}{\log(L!)}$$

where log(L!) is the PE(L) in the case of uniform distribution of the L! permutations

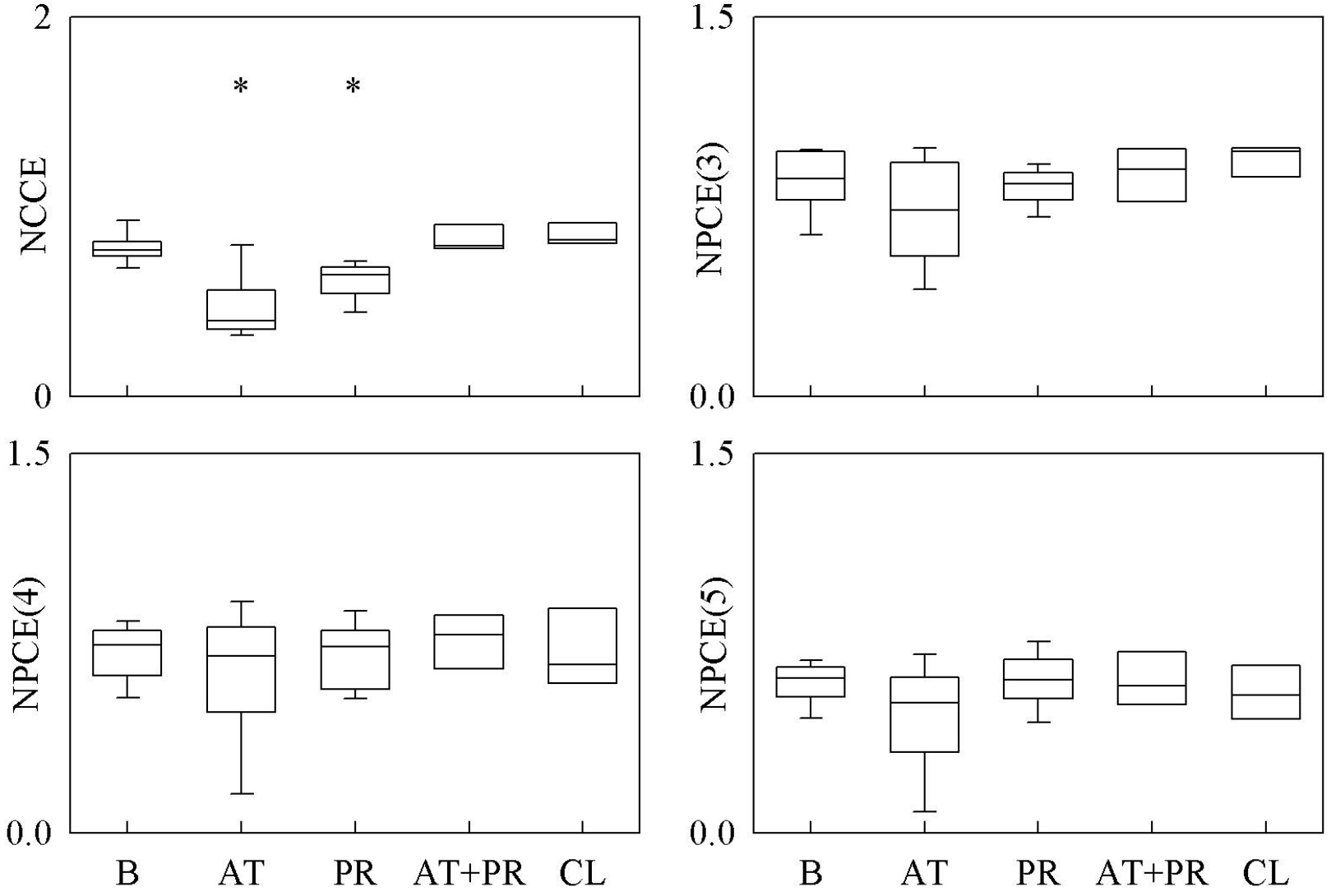
The normalized PCE is

$$NPCE(L) = NPE(L)-NPE(L-1)$$

Comparison between entropy-based complexity indexes derived from CCE and PE



Comparison between entropy-based complexity indexes derived from CCE and PCE



Conclusions

Entropy-based complexity indexes based on ranking are less powerful than those based on coarse graining techniques in detecting changes of the state of the autonomic nervous system