The clinical and basic significance of studying fluctuations of brain coordinated activity

Physiology characterised by not-so-regular rhythms

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Fluctuations due to external input and intrinsic factors – Allow for a "full search" of the state space — crucial effects near phase transitions (dynamical bifurcations) ⟹ **Adaptability**

"Noise *during rest* enables the exploration of the brain's dynamic repertoire" (Ghosh et al., PLoS Comp. Biol. 4, 2008)

Low variability in physiological records associated with disease many times reported

-*Tidal volume variability* decreases associated with breathing pathologies

-*Hormonal secretion variability* reduced in acute and chronic illness

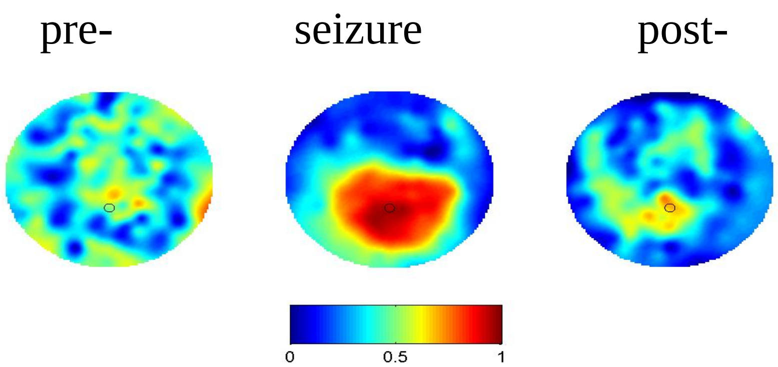
- *Heart rate variability* has been shown to decrease in: cardiac disease and post-traumatic stress disorder; schizophrenia; panic disorder; diabetes

Cardiac transplant patients: lower heart rate variability that increases with time (Koskinen et al., 1996; Chiu et al., 2004)

Sympathetic nerve activity variability is absent in severe heart failure (van de Borne et al., 1997)

With regards to nervous systems…

The nature of the problem



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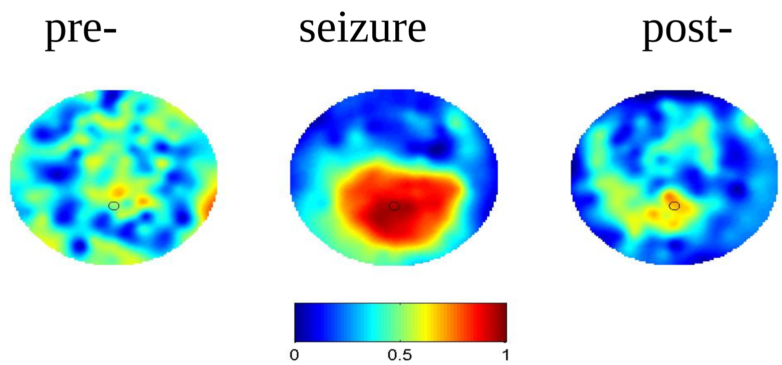

Coordinated activity → **integration and segregation**

Too much/too little synchronised activity not too optimal for information processing…

Existence of flexible formation of neural activity patterns requires TRANSIENT COORDINATION…

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Existence of flexible formation of neural activity patterns requires TRANSIENT COORDINATION…

⬇

FLUCTUATIONS IN COORDINATED ACTIVITY

Erich Von Holst's (1908-1962) **RELATIVE COORDINATION**

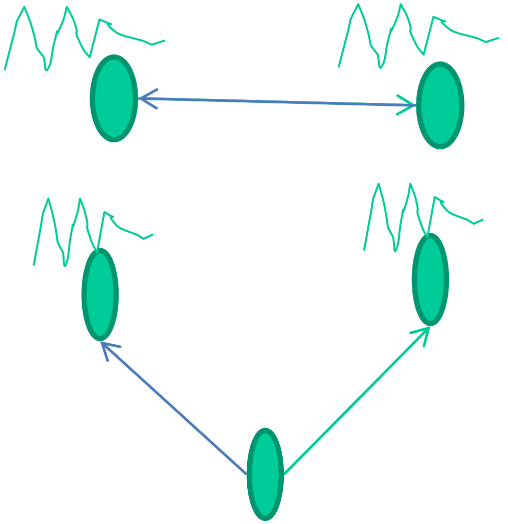
What is measured as Brain Coordinated Activity?

Extracted from macroscopic recordings (EEG, MEG, intracerebral). Main activity recorded is synaptic transmission. The sensors pick up (mostly) cortical activity that reflects:

- Either directly interacting networks

OR

- Interaction via a third network



Regardless of which type, fluctuations in phase synchrony reflect a re-arrangement of coordination ➡ **Relative Coordination**

As an index of brain coordinated activity…

Order parameter: captures the macroscopic behaviour resulting from microscopic fluctuations, thus, they allow for a description of the dynamics using few variables.

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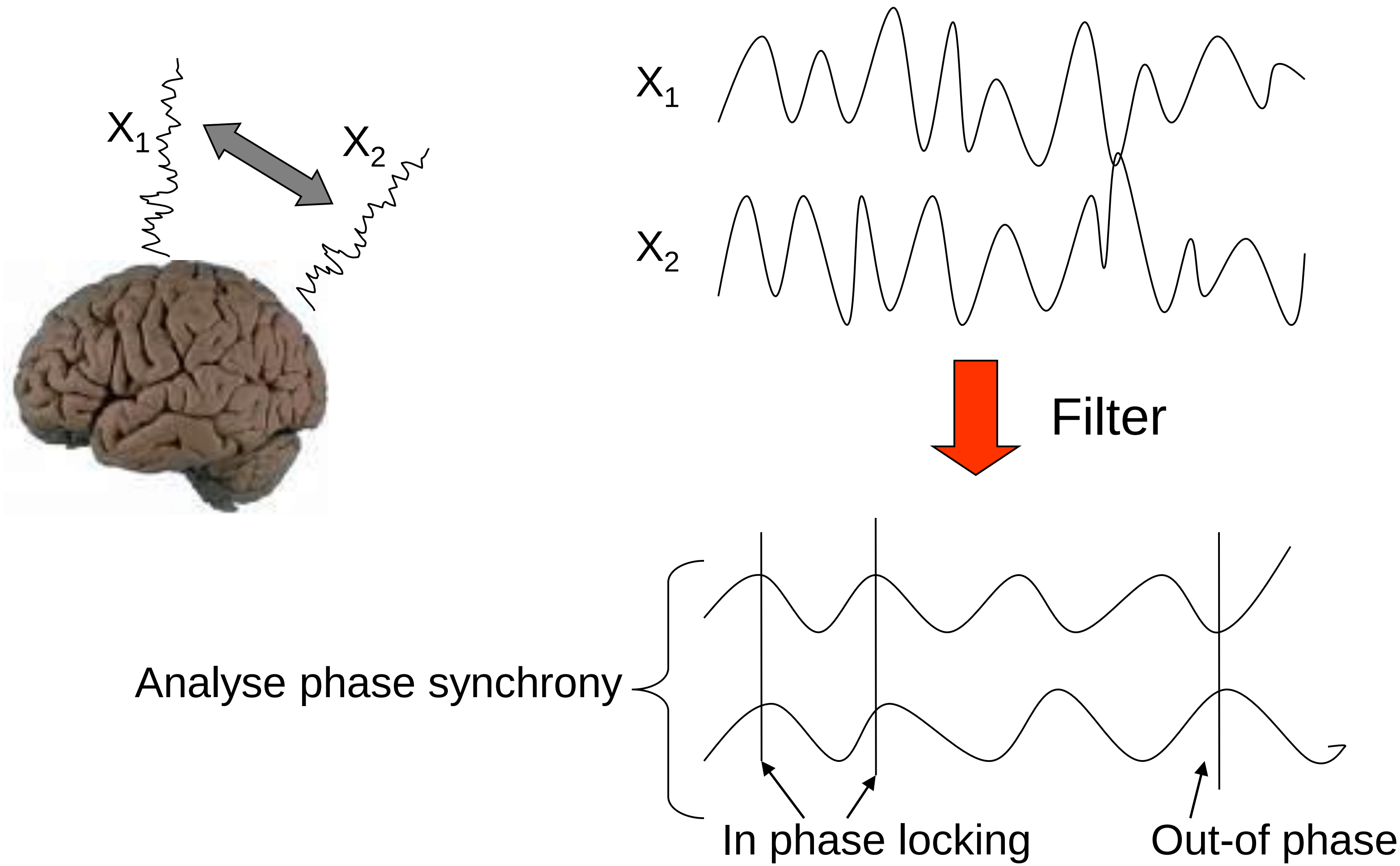
Differences in the oscillating phase: phase relations between oscillating cell groups establish flexible functional coordination of activities and dynamic coupling to allow for **integration** and **segregation** of networks needed to process information.

The activity of one cell acquires ‘meaning’ as it relates to other cells’ activities.

“...one needs to study neurons as members of large ensembles that are constantly disappearing and arising through their cooperative interactions and in which every neuron has multiple and changing responses in a context-dependent manner”
F.J. Varela, E. Thompson, E. Rosch, *The Embodied Mind*, MIT Press, 1991

Phase synchronization of brain waves



Very basics of phase synchrony analysis

Analytic signal concept (Gabor, 1946)

Synchrony index $R = \left| \left\langle e^{(i\Delta\theta)} \right\rangle \right|$

S index (Surrogates when necessary)

Synchrony index: already a representation of variability in relative phase $\Delta\theta$

Fluctuations of phase differences:

-Variability as S.D. …but

R

$SD_1 = SD_2$

- Rate of fluctuations in phase differences $\left| {d(\Delta\theta)}/{dt} \right|$

- “Entropy” of phase differences

- Spatial variability of the phase synchrony pattern

A measure of the spatial heterogeneity
(Garcia Dominguez et al., 2008)

Spatio-temporal fluctuations in cortical coordination patterns associated with cognition and pathologies:

- Epilepsy
- Autism
- Traumatic brain injury
- Cardiac arrest/stroke

Can less fluctuations of phase synchronization be associated with disease?

“Normal” neurophysiologic fluctuations

Fluctuations in synaptic activity enhance reliability of neuronal spike firing (Mainen & Sejnowski, Science, 1995); correlated variability in spike firing improves accuracy of neural population codes (Abbott & Dayan, 1999)

Fluctuations in cell activity in sensory cortices determine perceptual judgments/binocular rivalry (Deco & Romo, Trends Neurosci., 2008)

Fluctuations (reduction) of phase synchronization in brain activity correlate with the subjective experience of visual recognition (Perez Velazquez et al., J. Biol. Phys., 2007)

Variability in brain signals increased with development and is associated with less behavioural variability (McIntosh et al., PLoS Comp. Biol., 2008)

Spontaneous fluctuations in brain activity measured with neuroimaging or electrophysiological methods (Fox & Raichle, Nat. Rev. Neurosci. 2007); fluctuations in baseline fMRI or MEG signals related to subsequent perceptual responses (Palva et al., J. Neurosci., 2005; Boly et al., Hum. Brain Mapp., 2008; Busch et al., J. Neurosci, 2009); variability in evoked responses resulting from ongoing baseline fluctuations (Arieli et al., Science 1996); similar collective states in spontaneous and evoked activity (Tsodyks et al., Science 1999)

etc… etc… etc…

Many origins of fluctuations in the nervous system:

-From outside— Environmental input arrival at sensory terminals

-From inside — Ion channel opening & closing

— Neuronal membrane potential near threshold

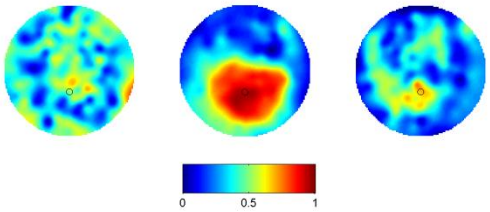
— Poisson-like spike firing

— Synaptic potential arrival at dendrites

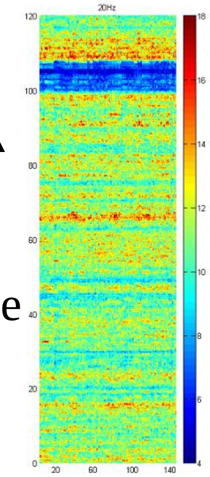
Spatio-temporal fluctuations in phase synchronization during seizures

-Spatial “complexity” of the coordination pattern diminishes during ictal events (Garcia Dominguez et al., 2008)

pre- seizure post-



time



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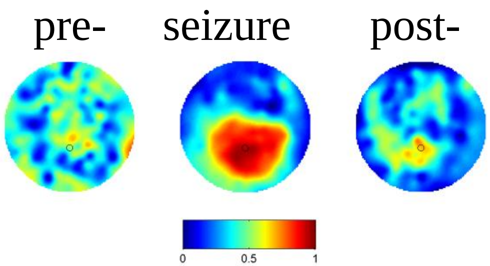
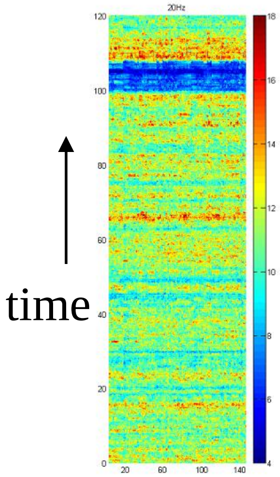
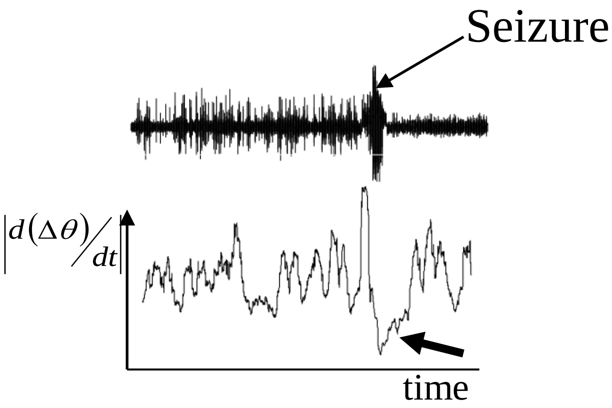


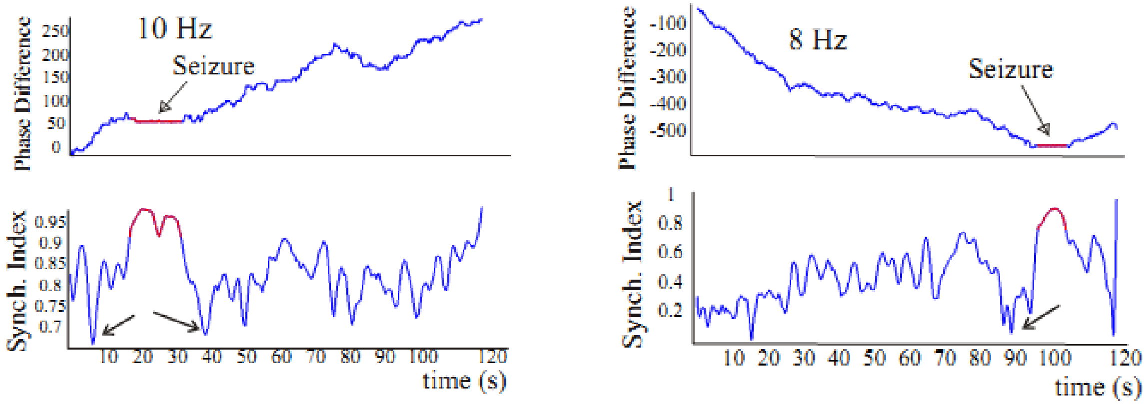


-Temporal variability of the phase difference

Rate of fluctuations in phase difference in intracerebral recordings (amygdala)



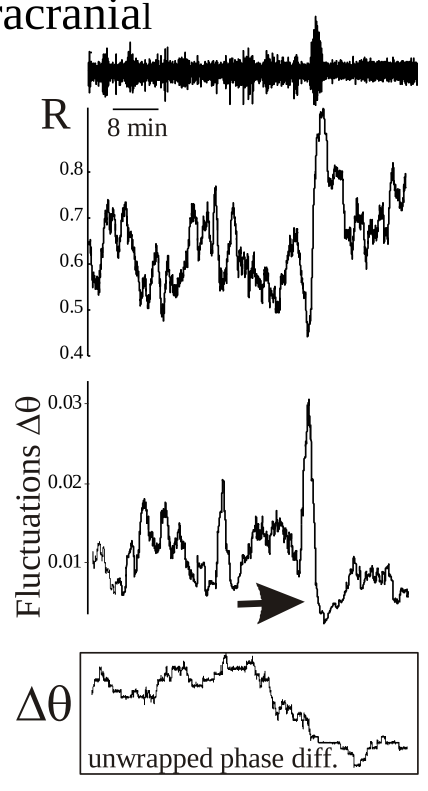
Fluctuations of phase difference, a precursor of seizures?



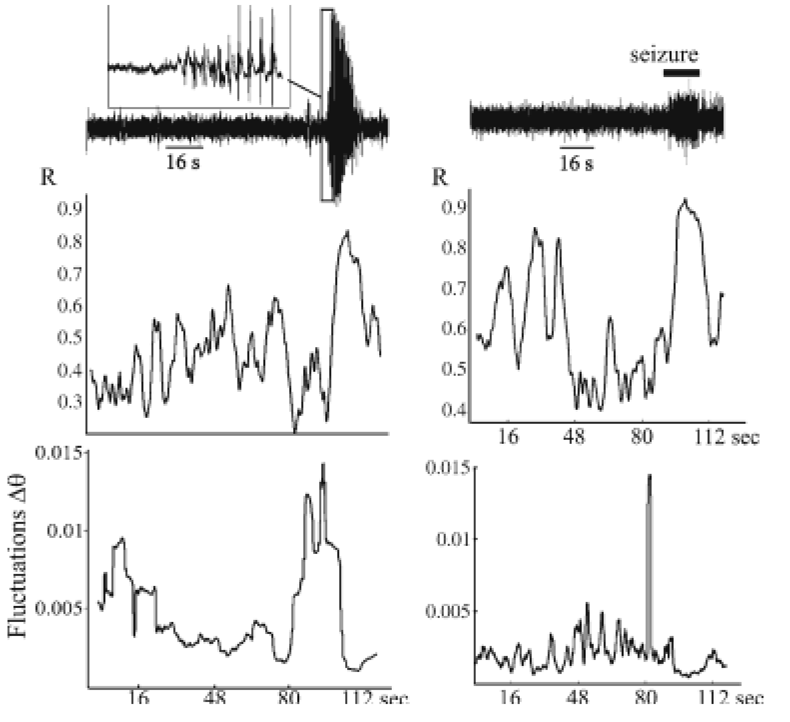
J.L. Perez Velazquez, L. Garcia Dominguez, R. Wennberg, The fluctuating brain: dynamics of neuronal activity, in *Nonlinear Phenomena Research Perspectives*, (C.W. Wang, ed.) pp. 417-444, Nova Science Publishers, 2007

Fluctuations of phase difference, a precursor of seizures?

Intracranial



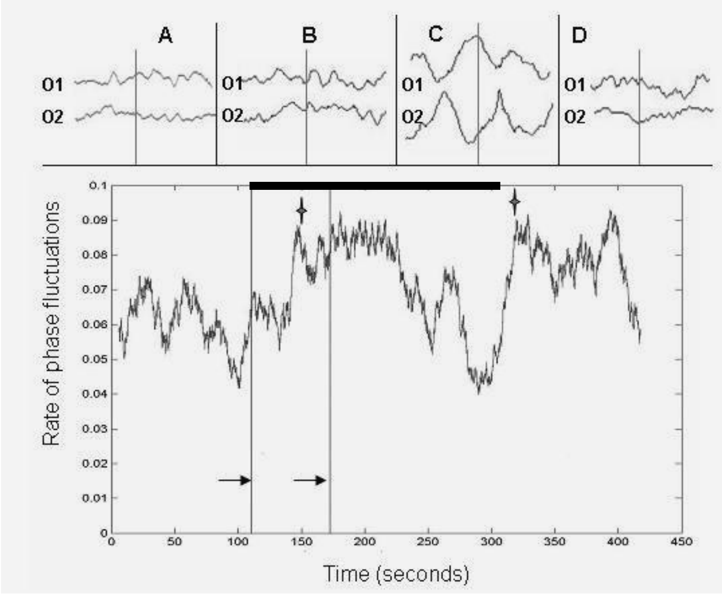
MEG

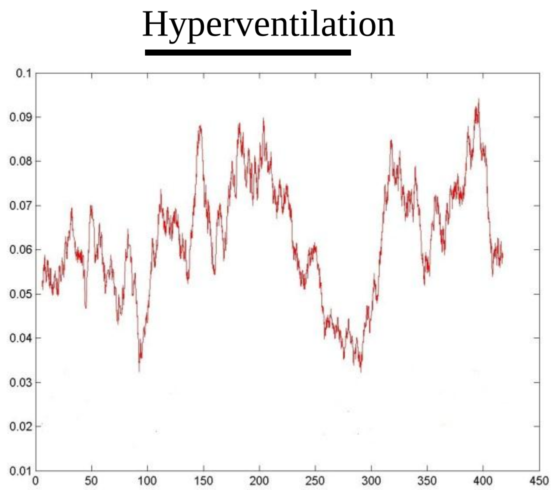


J.L. Perez Velazquez, L. Garcia Dominguez, V. Nenadovic, R. Wennberg (2011)
Experimental observation of increased fluctuations in an order parameter before epochs of extended brain synchronization. J*ournal of Biological Physics* 37, 141-152

Fluctuations of phase difference, a precursor of highly synchronised activity in general?

Hyperventilation-induced synchronous activity





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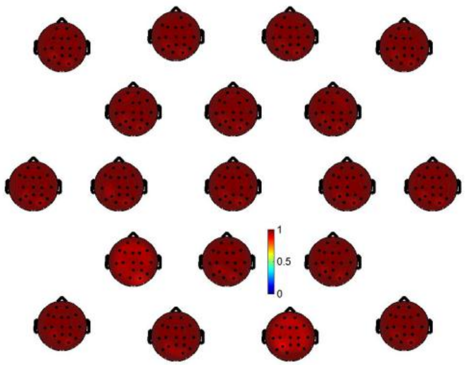
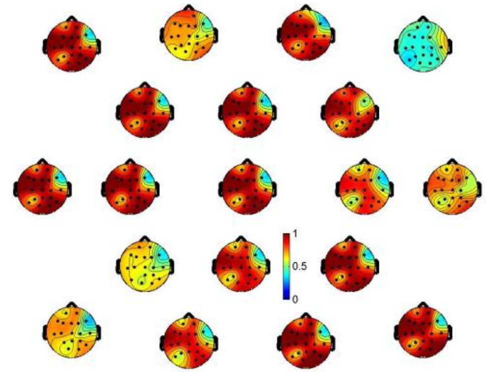
“Simpler” spatial coordination patterns associated with traumatic brain injury (TBI) and cardiac arrest

TBI



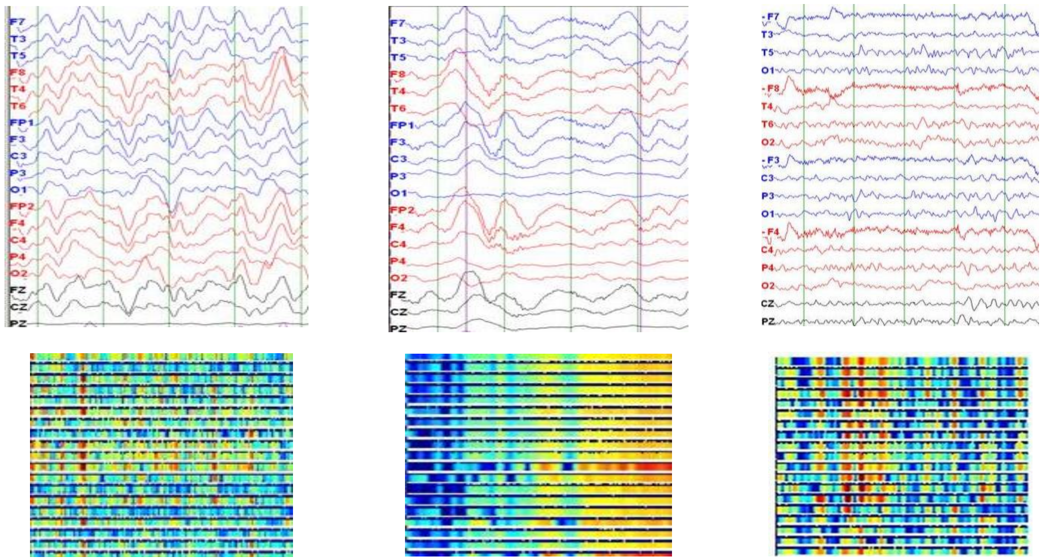
Bad outcome



Good outcome

Introducing the determination of variability in bedside brain monitoring

Appearances are deceiving…

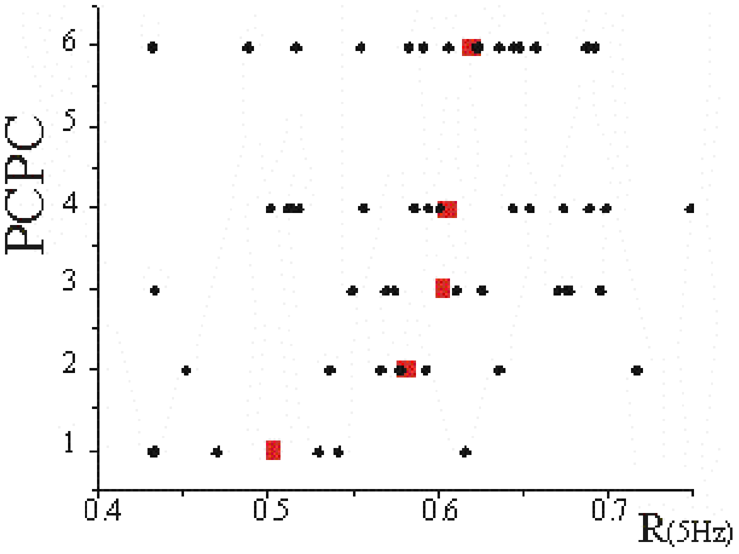


Patient A (PCPC = 1) Patient B (PCPC =4) Control Subject

Variable temporal pattern between synchronization (darkest red) and desynchronization (darkest blue) among EEG channels for patients with good outcome and control participants.

PCPC: Paediatric cerebral performance category score

Correlation between PCPC and synchrony magnitude in TBI and cardiac arrest



Spatio-temporal fluctuations in phase synchronization associated with traumatic brain injury/stroke

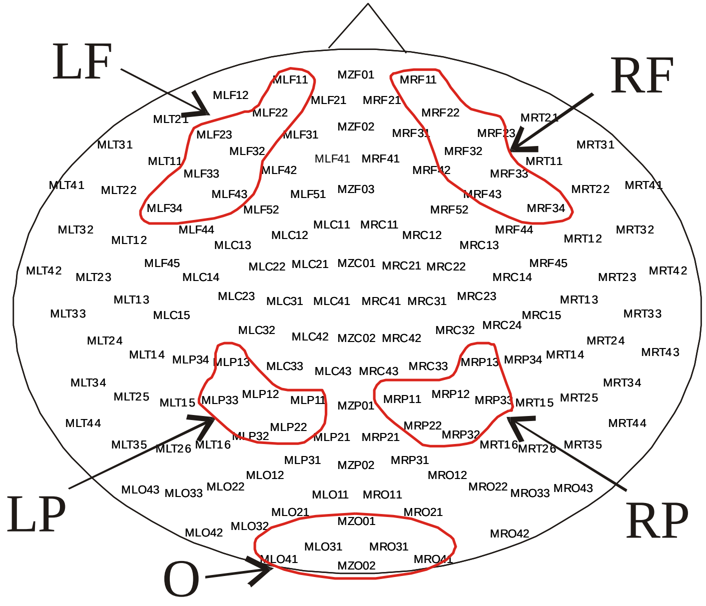
-Lower temporal variability (SD) in cortical coordinated activity, derived from EEG phase synchrony, associated with poor prognosis after traumatic brain injury (Nenadovic et al., 2008)

- Decreased spatial "complexity" of the spatial synchronization patterns associated with worse outcome (PCPC) after cardiac arrest in children (Nenadovic et al., 2009)

- Tendency towards lower spatial "complexity" in patients who died post-stroke/TBI/cardiac arrest.

-Less fluctuations (entropy) in inter-hemispheric phase differences in coma.

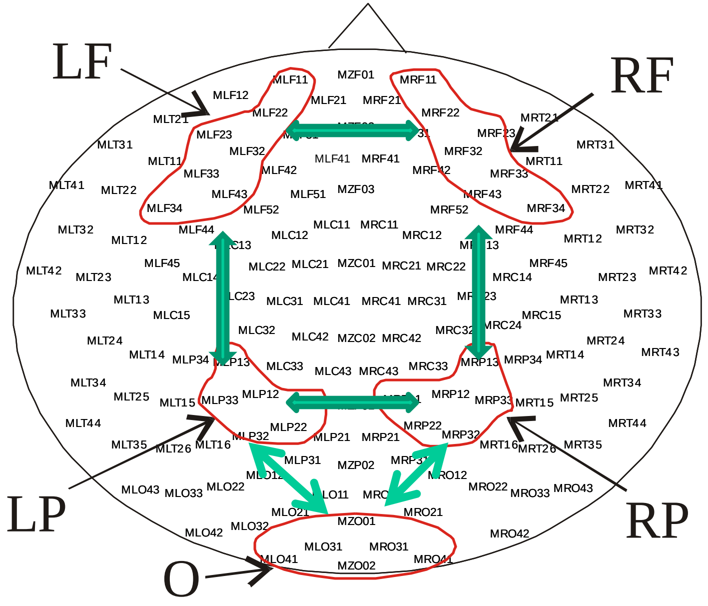
The case of high parietal coordinated activity in autism



The case of high parietal coordinated activity in autism

In “controls”

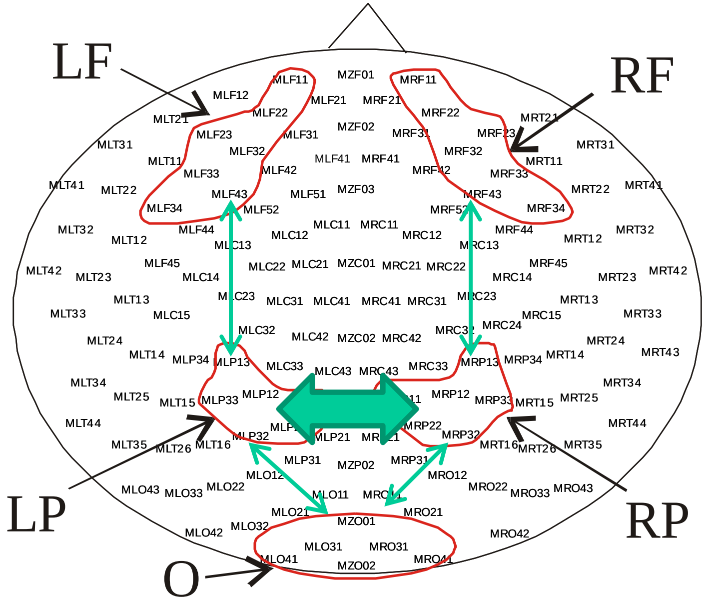
Changes in magnitude of synchrony between any two areas varies with task performance



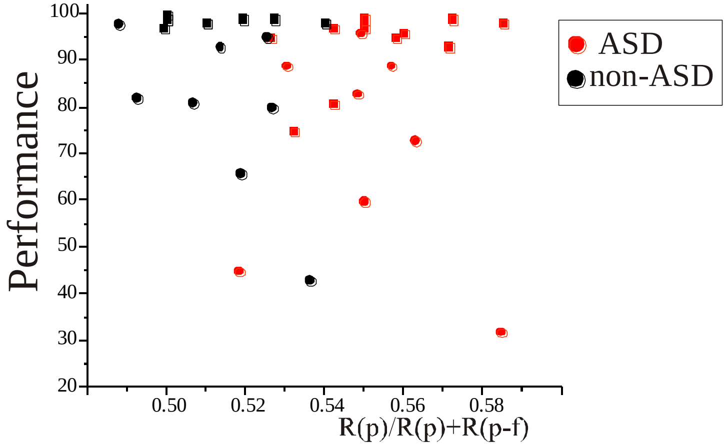
The case of high parietal coordinated activity in autism

In ASD

High intraparietal synchrony regardless of condition



Parietal synchrony relative to parieto-frontal synchrony associated with task performance serves to "classify" normal or ASD individuals



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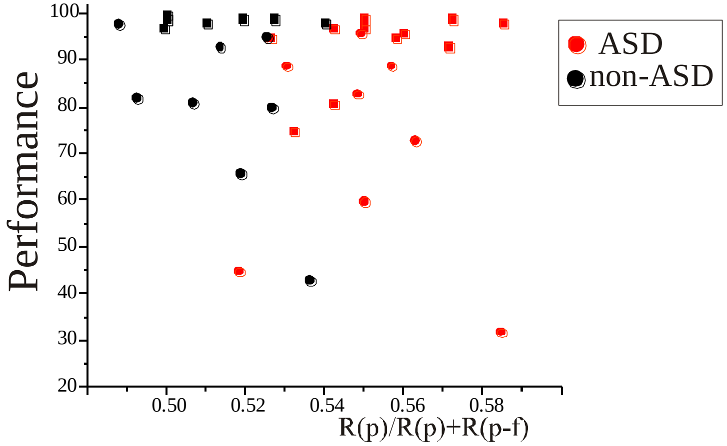
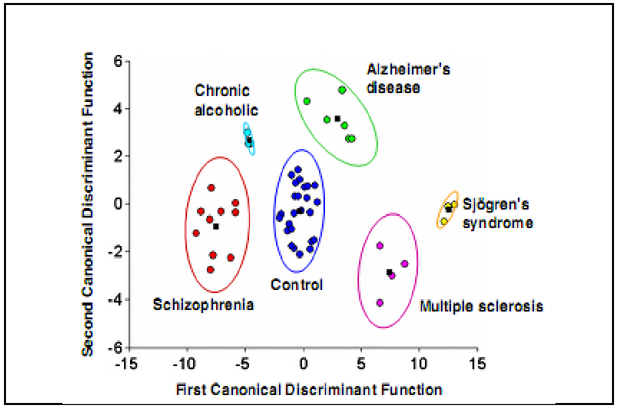


Cross-correlations from MEG signals serves to classify patients



Georgopoulos et al., 2007

Our Summary of Variability in Brain Synchrony

Reduced spatio-temporal variability in

- seizures
- traumatic brain injury
- stroke and cardiac arrest
- autism

More evidence for higher brain synchronised activity associated with disease

Parkinson's disease: enhanced tendency to synchronised activities in cortico-thalamic areas and basal ganglia (EEG, MEG, intracerebral recordings in patients and animals)

Schizophrenia: Increased bilateral coherence between auditory cortices during auditory hallucinations (Sritharan et al., 2005); altered coordination dynamics (Breakspear et al., 2003, Spencer et al., 2003; Uhlhaas et al., 2006)

Chronic hypoxia in patients with obstructive sleep apnea syndrome: enhanced global synchronization (Toth et al., 2009)

Depression: slower decay of long-range correlations in EEG signals (Lee et al., 2007)

Alzheimer's disease: increased local synchronization (but loss of long-distance coordination, Stam et al., 2006)

Considerations on the high synchronized activity associated with "pathology"

Time scales: -length of periods of high synchronization
-slow or fast time scale synchrony
[Maximal information exchange when units sychronise in slow time scale and desynchronise at fast (Baptista & Kurths, 2008)]

State dependency: behavioural context

Control parameters: - alterations in subcortical inputs
- alterations in excitability

Bounds in the variability of brain coordinated activity in health and disease?

Relative bounds in magnitude of the synchrony index

Long-lasting (several seconds):

Deviation/pathology	*Control/baseline*
-Seizures: R>0.7	R<0.3
-ASD: R(intraparietal) >0.34	Non-ASD < 0.3
-Coma (post cardiac arrest) >0.6	R<0.52
-Coma-TBI (entropy of phase angles) S<2.15	S>2.17
-Hyperventilation: R>0.55	R<0.4

Short-lasting (associated with task performance) :

ASD: R(Prefrontal) <0.28	Non-ASD >0.32

Further questions

- How can physiological cycles work despite fluctuations? (Bounds of variability?)

- How can cycles “use” fluctuations to tune rhythms to changing stimuli?

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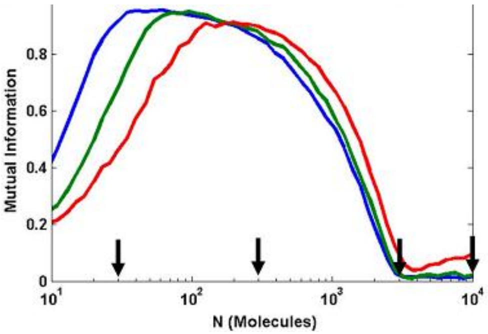
Models of biochemical cycles – the 'inverted U'



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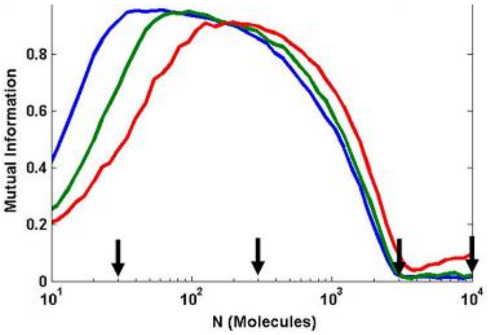
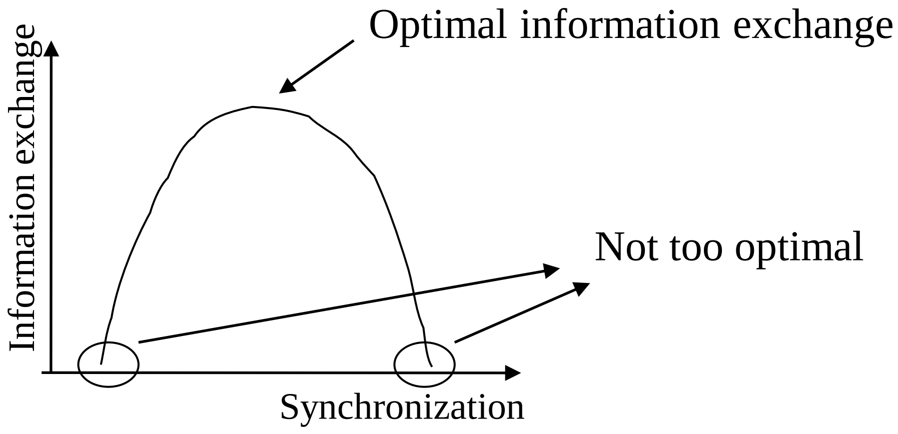
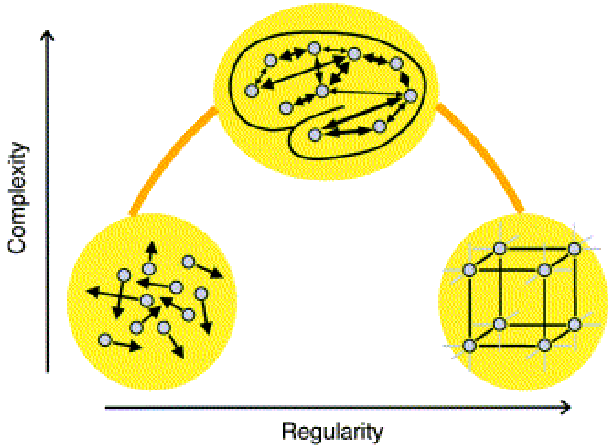


More inverted Us…



Complexity lies between order and disorder (Badii & Politi, 1997)



Tononi et al., 1998

~Statistical complexity (Crutchfield & Young 1989)

Spatio-temporal patterns as expressions of the tendency to maximal information exchange constrained by the conditions.

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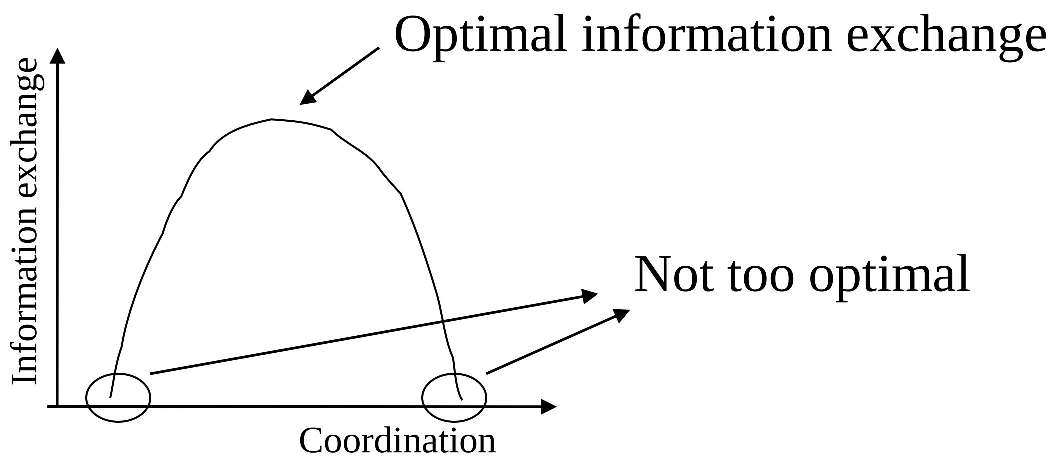


Coordination = Probability of interaction

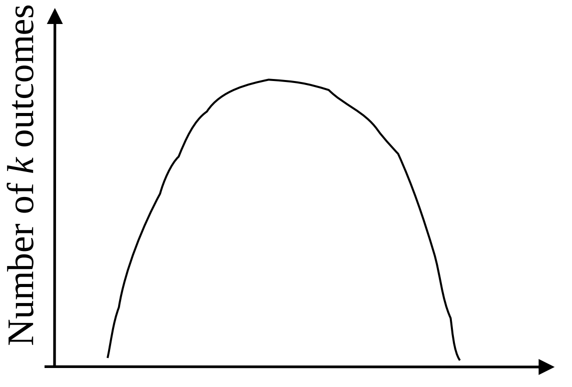
Information exchange ~ *F*(probability of interaction)

P(int)=1 ➡ No segregation

P(int)=0 ➡ No integration

The easiest manner to obtain an inverted U: binomial coefficient

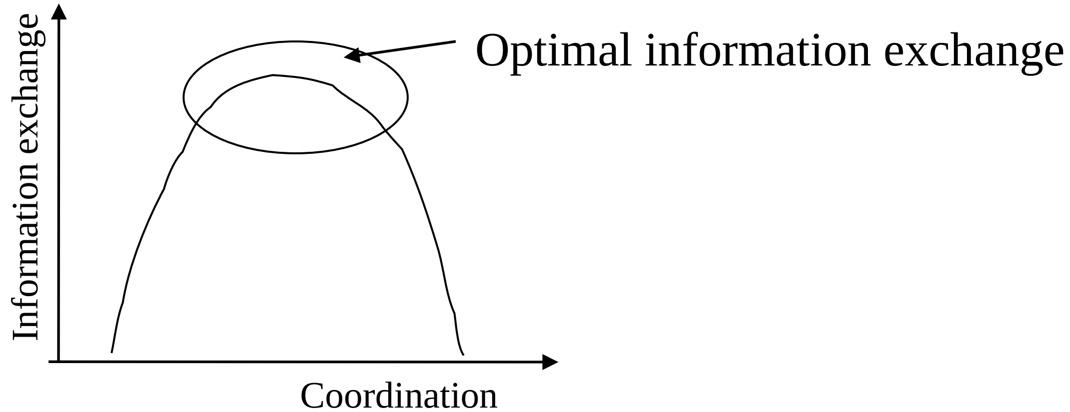
$$\binom{N}{k} = \frac{N!}{k!\,(N-k)!}$$



Number of combinations of *k* items that can be selected from a set of *N* items

The easiest manner to obtain an inverted U: binomial coefficient

$$\binom{N}{k} = \frac{N!}{k!(N-k)!}$$



Number of (k-element) arrangements of units exchanging information from a set of N units – Does **maximising the number of configurations of units exchanging information** make the system more viable?