

# Seizure prediction in epilepsy

## outline

- Definition
- Classification
- Methods of identification
- What to do
- Concomitant “symptoms”
- EEG patterns
- Seizure prediction
- In class assignment



Transcending ©2003, Jennifer Hall, All rights reserved

# Sites & videos

- <http://www.ilae-epilepsy.org/> (intl. league against epilepsy)
- <http://www.aesnet.org/> (American Epilepsy Society)
- <http://www.cdc.gov/epilepsy/resources.htm> (Ctr Disease Control & Prevention)
- [http://www.epilepsy.com/epilepsy/main\\_epilepsy.html](http://www.epilepsy.com/epilepsy/main_epilepsy.html) (good animations - First Aid and “what is epilepsy”. Videos on ketogenic diet; AEDs, etc.)
- <http://www.youtube.com/watch?v=ZpsMxejnxUE> (Epilepsy surgery video)
- <http://www.youtube.com/watch?v=mEKrppmHkCg> (better video of surgery)
- <http://www.youtube.com/watch?v=Ws-USSsSPH0> (Canadian Soc. Epilepsy: what to do and not to do if you see somebody having a seizure)
- <http://www.youtube.com/watch?v=5P-FXB--dEM> (National Soc. for Epilepsy)
- <http://www.youtube.com/watch?v=frWcJJkXQFM> (Partial, Tonic, Clonic seizures)
- [http://www.youtube.com/watch?v=TY2FBG39V\\_w](http://www.youtube.com/watch?v=TY2FBG39V_w) (Wada test, in Spanish)
- <http://www.neuropace.com/> (Neurostimulation for epilepsy)

# What is epilepsy?

- *It's a brainstorm.*
- **A seizure** (a fit, an attack, turn or blackout) ***happens when ordinary highly complex brain activity is suddenly disrupted.***
- Seizures take many forms, since the brain is responsible. for such a wide range of functions.
- Personality, mood, memory, sensations, movement and consciousness: any of these functions may be disturbed during the course of an epileptic seizure.

# Can you “provoke” seizures?

- Hyperventilation;
- Photosensitive seizures (flashing light)
- Seizures are more likely during sleep.
- In infants, some seizures are due to metabolic derangements (and don't require AEDs)

# Prevalence and incidence

Epilepsy is a common neurological disorder marked by involuntary, recurrent seizures that arise from excessive discharges of neurons in the brain.

Seizures vary in type, severity and intensity, and can be manifested by changes in consciousness, movement, sensation, or behavior.

1995 data: seizures affect approx 2.3 million people.  
181,000 new cases/year in the U.S.

By age 85, approximately 10% of the population will have experienced at least one unprovoked or acute symptomatic seizure; 4% will have developed epilepsy.

# Seizure classification

One of the first priorities facing the physician when evaluating a patient with seizures is to determine seizure type and, when possible, epileptic syndrome.

Seizure type and epileptic syndrome determine type of evaluation the patient will receive, as well as the therapy.

Seizures are classified into two basic groups, partial and generalized:

- **Partial** seizures involve only a portion of the brain at the onset. They can be further divided:
  - simple partial: consciousness is not impaired
  - complex partial: consciousness is impaired
- Both types of partial seizures can spread, resulting in secondarily generalized tonic-clonic seizures.
- **Generalized** seizures: first clinical changes indicate both hemispheres involved. Consciousness usually impaired, although the myoclonic type may be so brief that impairment of consciousness cannot be assessed.

# Seizure classification – international system

## I. Partial seizures

### A. Simple partial seizures

1. With motor signs
  - a. Focal motor without march
  - b. Focal motor with march (Jacksonian)
  - c. Versive
  - d. Postural
  - e. Phonatory
2. With somatosensory or special-sensory symptoms
  - a. Somatosensory
  - b. Visual
  - c. Auditory
  - d. Olfactory
  - e. Gustatory
  - f. Vertiginous
3. With autonomic symptoms or signs
4. With psychic symptoms
  - a. Dysphasia
  - b. Dismnesic
  - c. Cognitive
  - d. Affective
  - e. Illusions
  - f. Structured hallucinations

### B. Complex partial seizures

1. Simple partial seizures at onset, followed by impairment of consciousness
  - a. With simple partial features
  - b. With automatisms

2. With impairment of consciousness at onset
  - a. With impairment of consciousness only
  - b. With automatisms

### C. Partial seizures evolving to secondarily generalized seizures

1. Simple partial seizures evolving to generalized seizures
2. Complex partial seizures evolving to generalized seizures
3. Simple partial seizures evolving to complex partial seizures evolving to generalized seizures

## II. Generalized seizures

### A. Absence seizures

1. Typical absence seizures
  - a. Impairment of consciousness only
  - b. With mild clonic components
  - c. With atonic components
  - d. With tonic components
  - e. With automatisms
  - f. With autonomic components

### 2. Atypical absence seizures

### B. Myoclonic seizures

### C. Clonic seizures

### D. Tonic seizures

### E. Tonic-clonic seizures

### F. Atonic seizures

# Generalized seizures

- Whole brain is involved
- Consciousness is lost.
- The seizure may then take one of the forms:
  - Generalised **tonic clonic** convulsive seizure ('grand mal' seizure): person becomes rigid, and may fall if standing. The muscles then relax and tighten rhythmically causing the person to convulse. Breathing is laboured.
  - **Tonic**: is general stiffening of muscles without rhythmical jerking. The person may fall to the ground if standing with consequent risk of injury.
  - **Atonic** (drop attacks): sudden loss of muscle tone, again causing the person to fall if standing.
  - **Myoclonic**: abrupt jerking of the limbs occurs. These often happen within a short time of waking up, either on their own or in company with other forms of generalised seizure.
  - **Absences**: brief interruption of consciousness without any other signs, except perhaps for a fluttering of the eyelids. These occur most commonly in children and are known as "petit mal".



# Partial seizures

- **Partial seizure:** usually determined by the function of the part of the brain that is involved. Also known as 'focal'.
- Three types of partial seizures: simple partial, complex partial, and secondarily generalised.
- **Simple partial** seizures: consciousness not impaired; seizure confined to either rhythmical twitching of one limb, or to unusual tastes or sensations such as pins and needles in a distinct part of the body.
- Simple partial seizures sometimes develop into other sorts of seizures; often referred to as a "warning" or "aura".
- **Complex** partial seizures differ from partial seizures in that consciousness is affected. The seizures may be characterised by change in awareness as well as "semi-purposeful " movements such as fiddling with clothes, wandering about and general confusion.
- Complex partial seizures usually involve the temporal lobes of the brain, however they can also affect the frontal and parietal lobes.
- In some people either of these seizures may spread to involve the whole of the brain: **secondarily generalised** seizure.

# DURING THE SEIZURE

- Prevent others from crowding around.
- Put something soft under the person's head (like a jacket) to prevent injury. Only move them if they are in a dangerous place i.e. at the top of a flight of stairs or in the road.
- Do not attempt to restrain convulsive movements.
- Do not put anything in the person's mouth. There is no danger of swallowing the tongue.

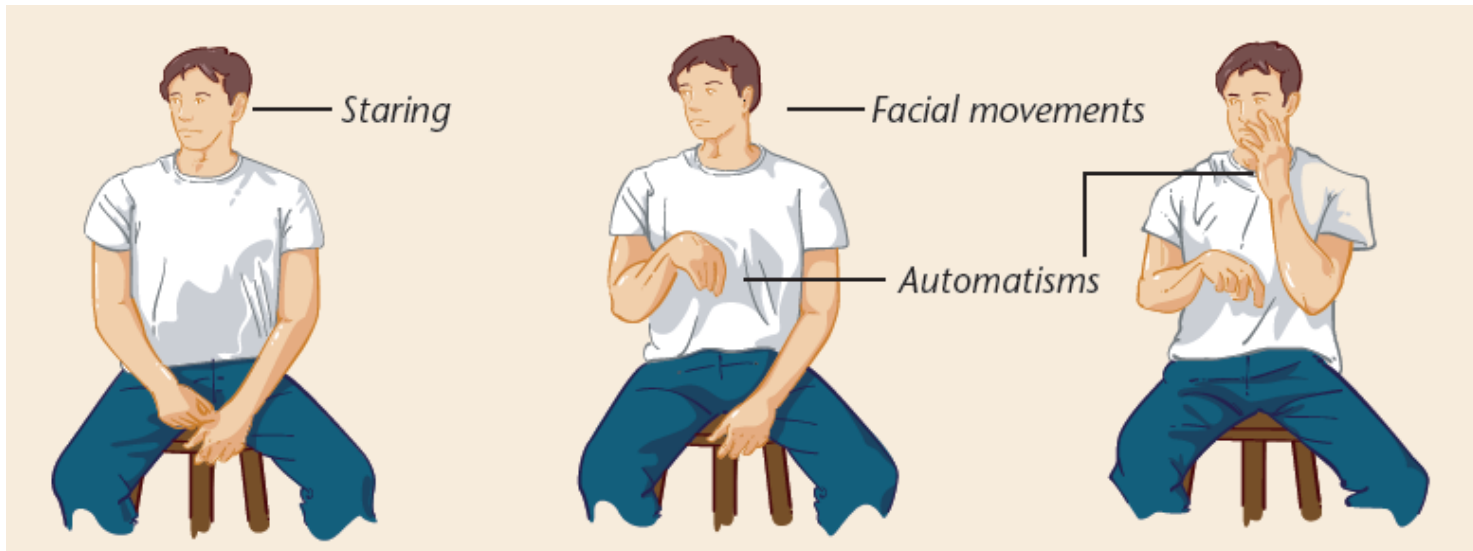
# Concomitant phenomena



# Concomitant phenomena-II

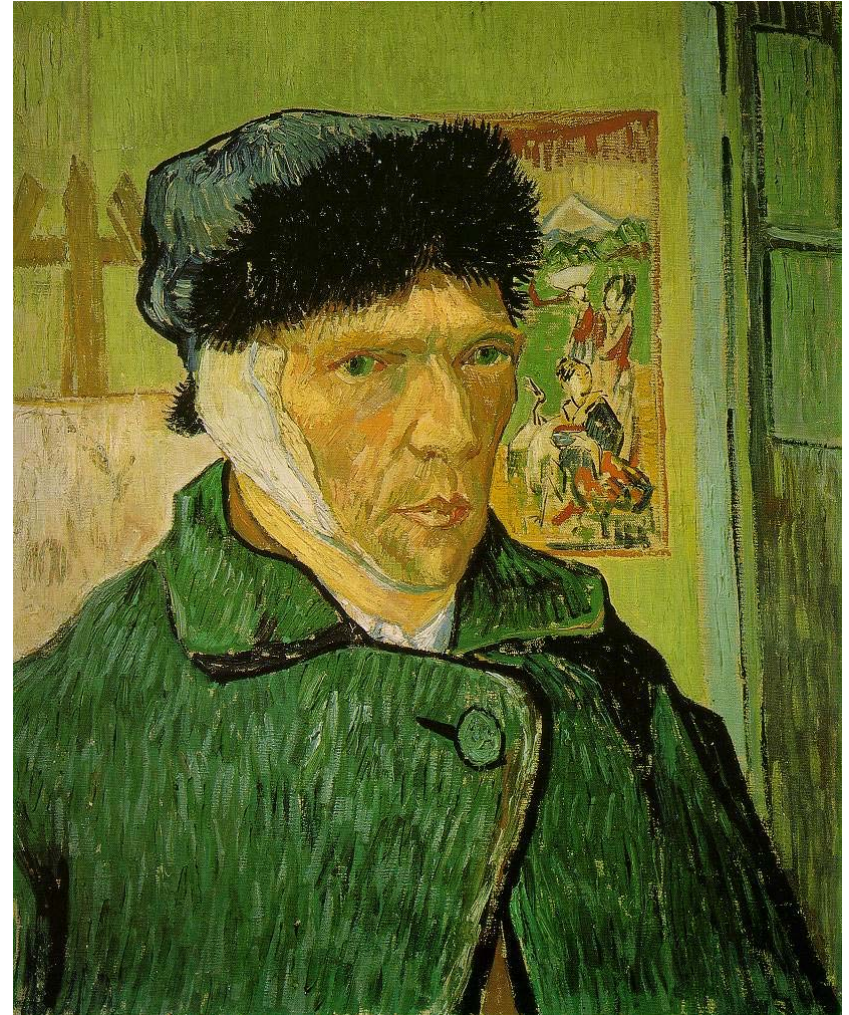
## Myoclonic seizures:

"Myo" means "muscle" and a myoclonic jerk is a brief, shock-like jerk of a group of muscles. People who do not have epilepsy may experience a jerk like this while falling asleep. That's considered normal. Myoclonic seizures in epilepsy involve sudden jerks of the arms, shoulders, neck, body, or upper legs, affecting both sides at the same time. The person may fall. These seizures usually begin in childhood. Often they are part of a pattern of epilepsy that may also include other types of seizures.



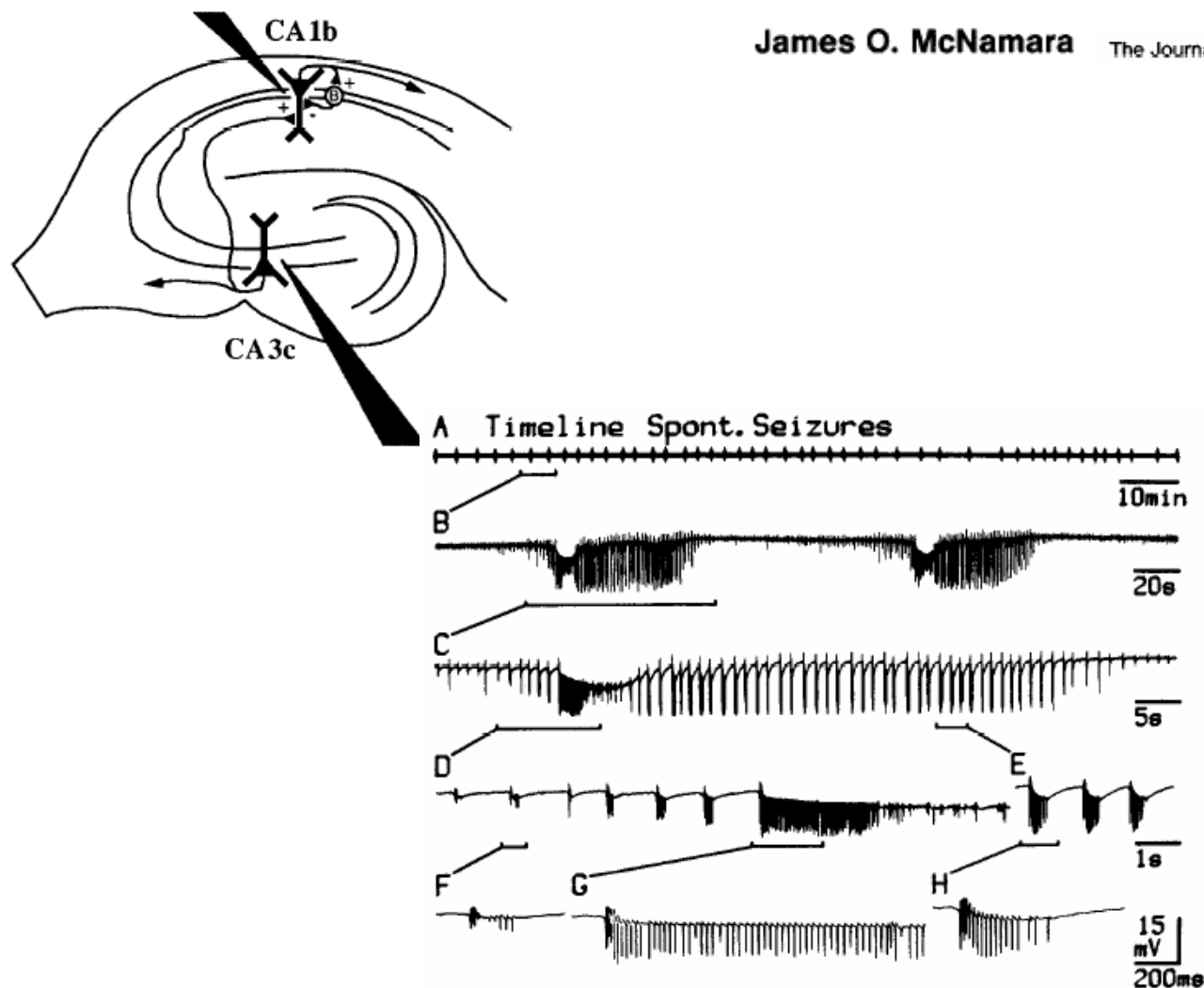
# Famous people

- Van Gogh
- Alexander the Great
- Julius Caesar
- Napoleon
- Dostoyevsky
- Socrates (catalogued by Aristotle)
- Charles Dickens
- Moliere
- Dante Alighieri
- Lewis Carroll
- Edgar Allan Poe
- Handel
- Agatha Christie
- Tchaikovsky (believed to have had)
- Beethoven (may have had)



James O. McNamara

The Journal of Neuroscience, June 1994, 14(6): 3413-3425



*Figure 1. a*, Schematic depicts sites of recording electrodes in pyramidal cell layers of CA3 and CA1 regions of rat hippocampal slice. The axon collateral of the neuron in CA3c is a Schaffer collateral that evokes an EPSP in the dendrite of the neuron in CA1b. Also depicted is a recurrent inhibitory loop whereby the axon collateral of the CA1b pyramidal cell excites the GABAergic basket cell, which in turn projects to and inhibits the CA1b pyramidal cell. This schematic is intentionally simplified and deletes many important connections including feedforward inhibitory circuits. *b*, Spontaneous seizures evident in field potential recordings from CA1 region of hippocampal slice bathed in media containing 8.5 mM  $K^+$ . *A*, Occurrence of spontaneous seizures, denoted by vertical lines superimposed on the horizontal line. *B-H*, Progressively greater expansions of selected portions of record in *A*, highlighting the tonic (*G*) and clonic (*H*) components. *c*, Simultaneous field potential (CA3 and CA1) and intracellular (CA1 pyramidal cell) recordings during spontaneous seizure lasting approximately 35 sec. In-



# What causes a seizure?

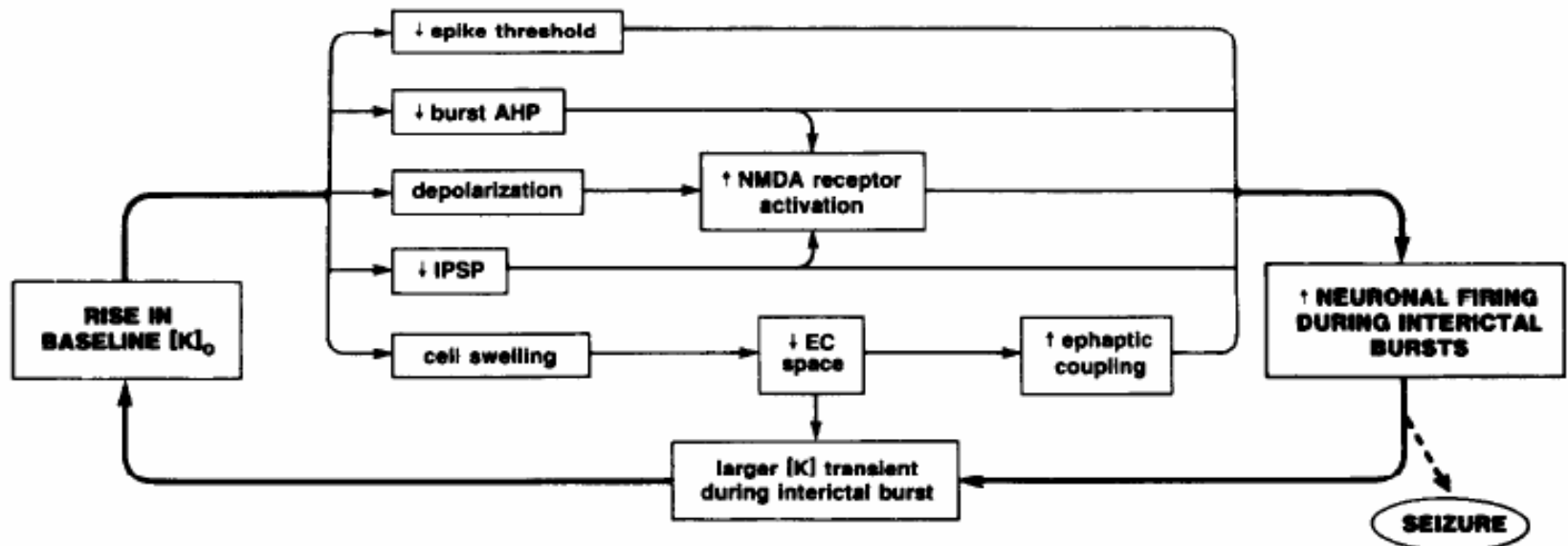
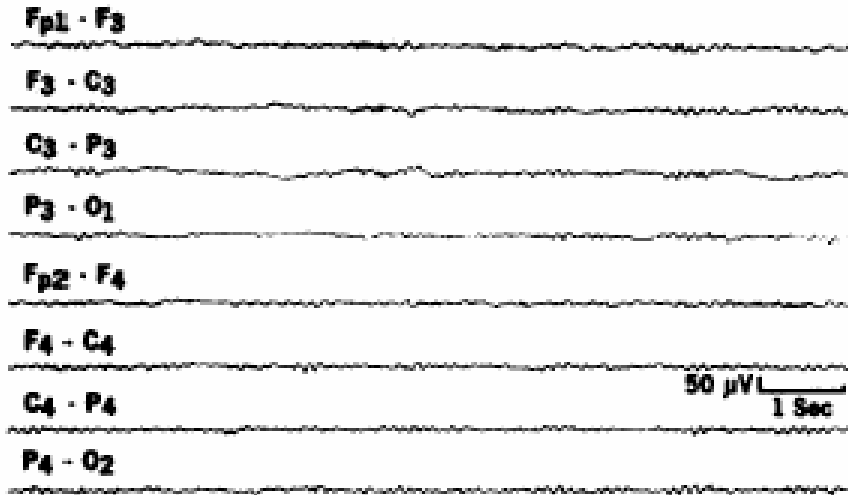


Figure 2. This schematic depicts a hypothesis of how synaptic and nonsynaptic factors might interact to initiate a seizure evoked by elevated  $K^+$  in CA1 pyramidal cells (see text for elaboration). From Traynelis and Dingledine (1988).

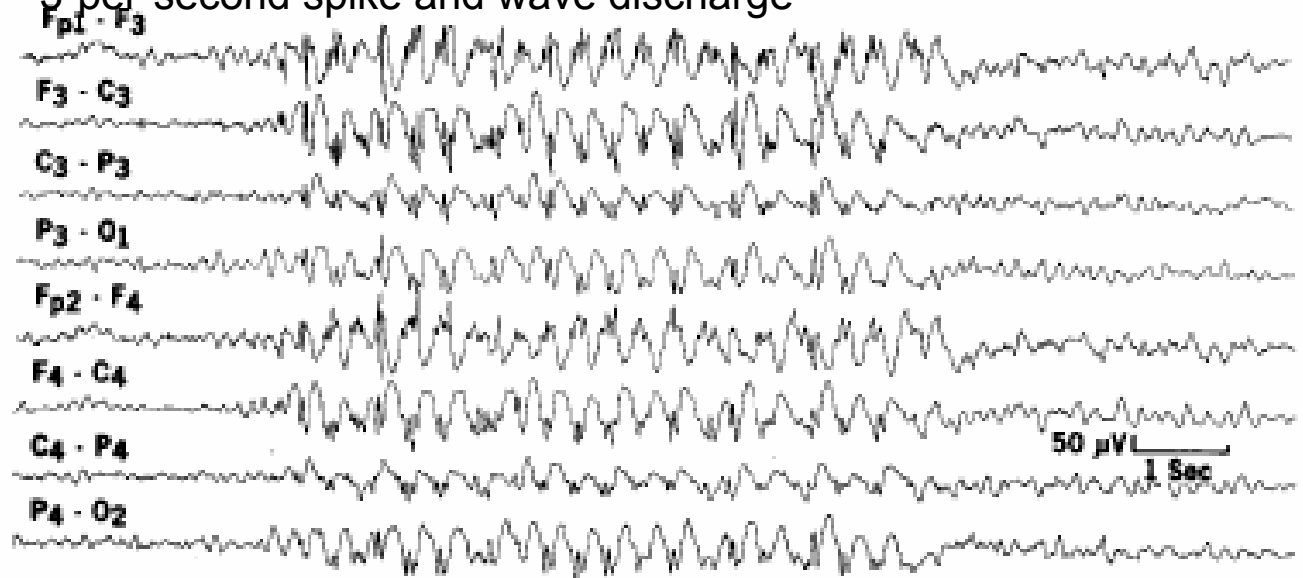
- Ko = extracellular potassium
- AHP = after hyper-polarization
- NMDA = *N-methyl-D-aspartate*
- IPSP = inhibitory post-synaptic potential
- EC = extracellular
- Interictal = between seizures

EEG recording of a normal brain showing no unusual activity



# EEG patterns

EEG recording of an absence seizure showing the distinctive 3-per-second spike and wave discharge





# Absence seizures

Opening initial

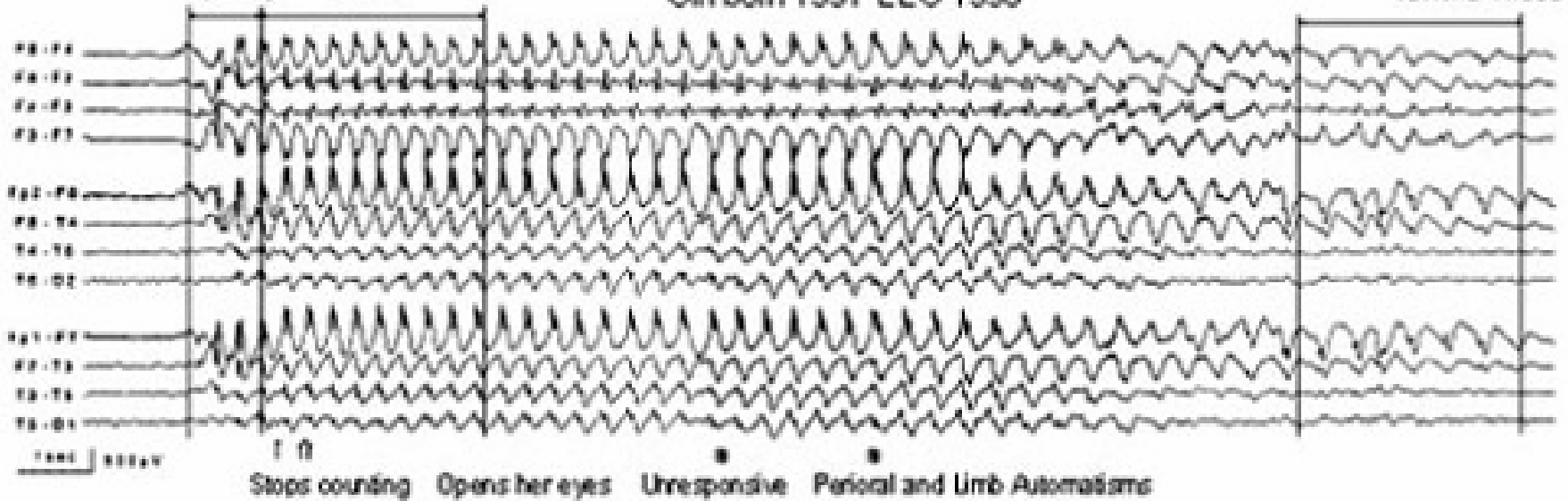
Girl born 1991 EEG 1998

terminal phase

Opening - Initial

Girl born 1991 EEG 1998

Terminal Phase



Stops counting      opens her eyes      unresponsive      limb automatisms

[http://professionals.epilepsy.com/page/generalized\\_absence.html](http://professionals.epilepsy.com/page/generalized_absence.html)

Adapted from: Holmes GL. Classification of seizures and the epilepsies. In: Schachter SC, Schomer DL, eds. The comprehensive evaluation and treatment of epilepsy. San Diego, CA: Academic Press; 1997. p. 1-36.

# 3-4 Hz generalized discharges

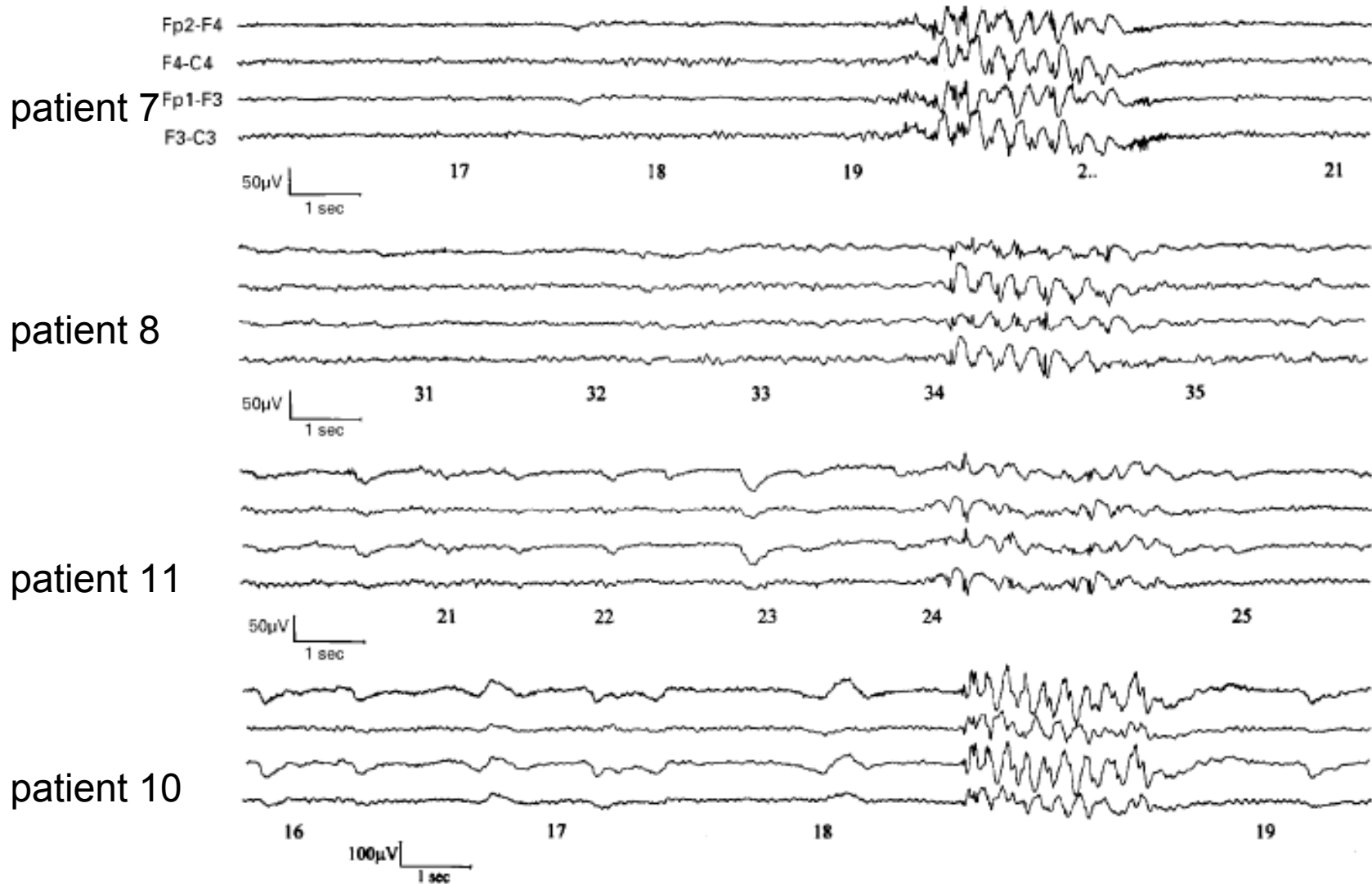


Figure 2 Video-EEG of patients 7, 8, 11, and 10 (consecutively from top down). Generalised discharges of 3-4 Hz spike/multiple spikes and slow waves are associated with ictal delay in pronouncing the next sequential numbers during breath counting (numbers annotated). Only 4 EEG channels are shown.

# Electrographic seizure activity

- Key elements:
  - change in observable behavior;
  - diminished adaptive response to environmental input;
  - abnormal EEG activity from cortex.
- Combination of these symptoms allows for differential diagnosis.

# Ictogenesis

- Ictal period: electrographic paroxysmal activity related to the seizure (clinical seizure not always coincides with the EEG seizure).
- Detecting ictogenesis = anticipation.
- Quantifying and interpreting preictal states = prediction.
- (in Bin He's book: prediction = anticipation)

# Why would you want to predict seizures?

- Because currently there's no cure for epilepsy.
- Drugs are based on GABA agonists (inhibitory neurotransmitter): daily intake. And they not always work.
- AED (anti-epileptic drug) examples: Carbamazepine, phenobarbital, phenytoin (Dilantin™), and valproic acid.
- Surgery sometimes indicated (in intractable epilepsy cases). “Split-brain” subjects.

# Methods of prediction

- Signal: usually EEG recordings (why? Can you list the reasons?)
- Linear and non-linear methods have been proposed – **none** has worked **well** so far.
- Problem: variety of disease personalities;
- Our current engineering approach is not optimized for variety of personalities.

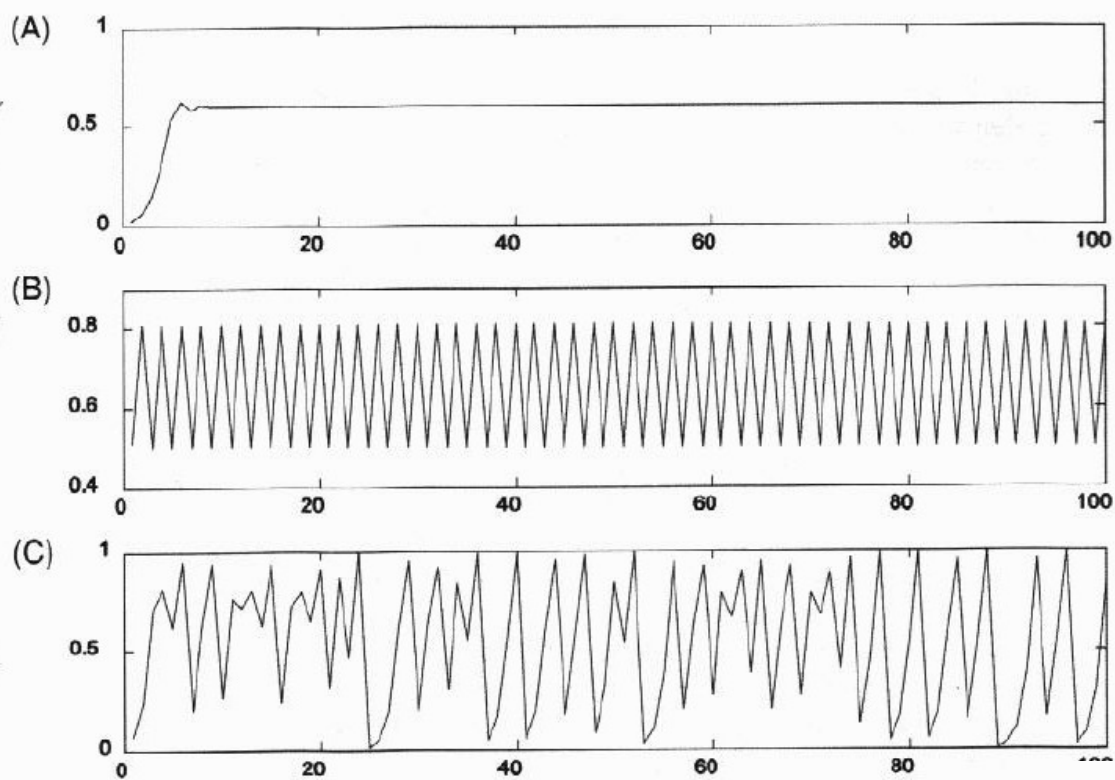
# Process predictability

Simple and deterministic processes can exhibit (a) stable; (b) oscillatory; (c) very poorly predictable behavior.

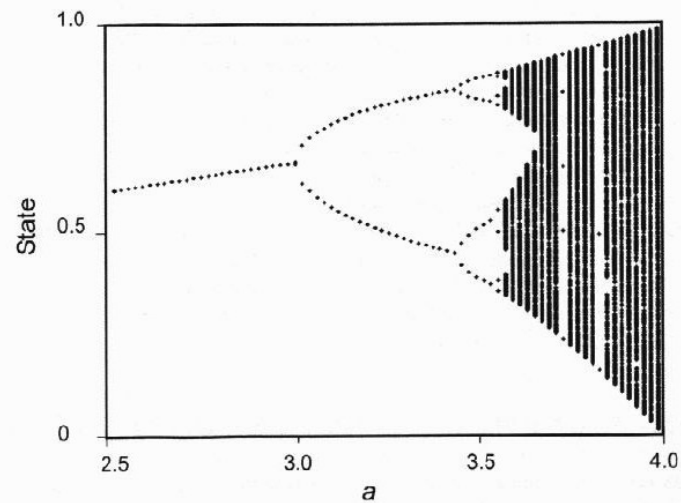
- Example: logistic equation

$$x_t = a(1-x_{t-1})x_{t-1}$$

- Solution to this equation converges to a single value if  $a < 3$ ,
- There is a stable periodic behavior for  $a$  between 3 and 3.4495;
- Chaotic behavior for  $a > 3.569$ .



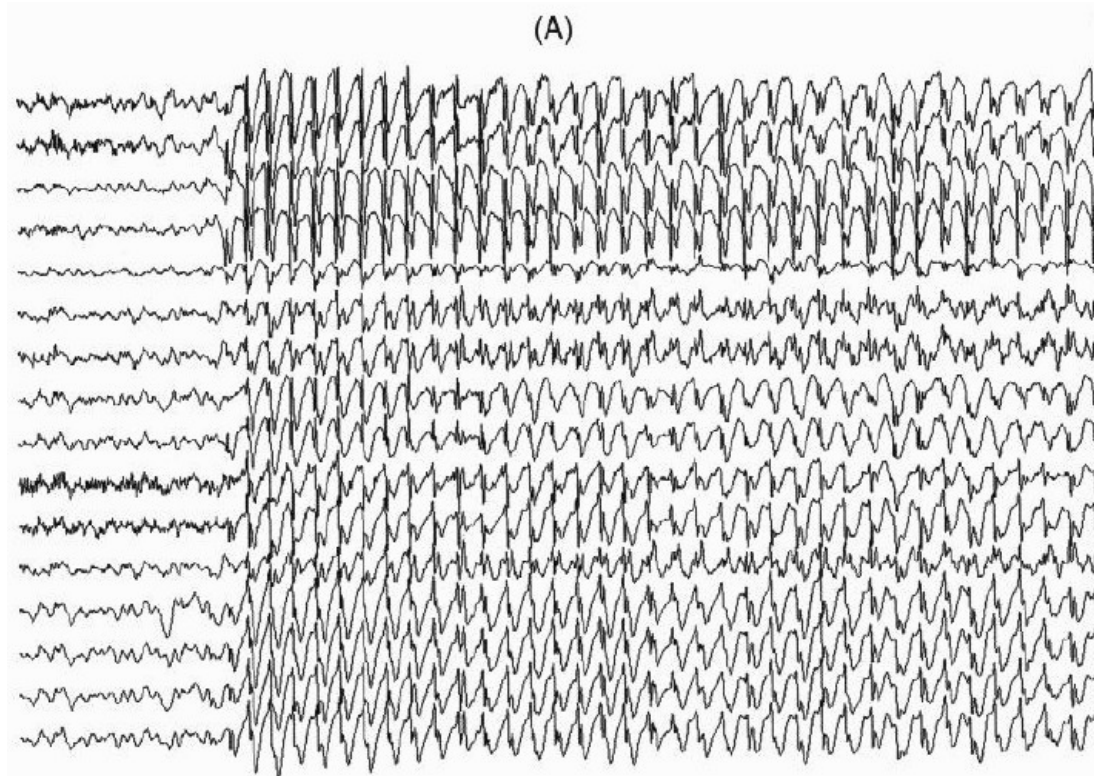
**FIGURE 12.1.** Three examples of a time series created with the logistic equation (Eq. (12.1)): (A) the series converges to a single value for  $a = 2.50$ ; (B) for  $a = 3.24$  there is oscillatory behavior between two (C) chaos at  $a = 4$ .



**FIGURE 12.2.** One of the icons of chaos: the final state diagram showing the period-doubling route to chaos. Final states plotted against the value of  $a$  in the logistic equation (Eq. (12.1)). The logistic equation (a quadratic iterator) transitions to oscillatory behavior at the bifurcation  $a = 3$ . For  $a > 3.569 \dots$  the system transitions to chaotic behavior. Interestingly Feigenbaum (1983) discovered that the ratio of two successive ranges over which the period doubles, is a constant universally encountered in the period-doubling route to chaos (Feigenbaum's number:  $4.6692 \dots$ ). A Matlab script to create the final state diagram can be found in Appendix 2.

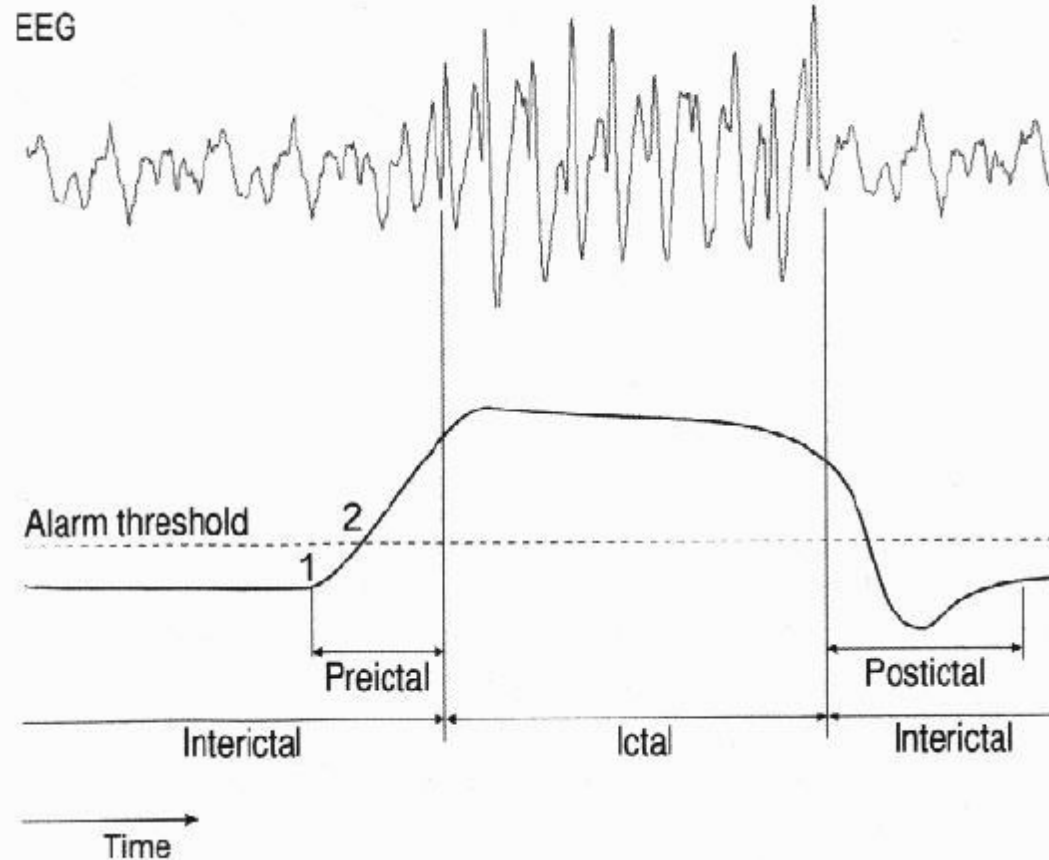


# Generalized seizure: straightforward detection



**FIGURE 12.3.** Examples of 15-s EEG/ECOG epochs around seizure onset. (A), (B) Two generalized seizures recorded from the scalp. Both (A) and (B) are from the same patient to show the stereotypical aspect of the sudden seizure onset. (C) Seizure onset from a patient with a mixed seizure disorder. Data was recorded from the surface of the cortex. Only few channels show involvement in seizure activity. (D) An example of a complex partial seizure recorded from the cortical surface. Initially the seizure activity can be observed in few electrodes; subsequently it propagates to a wider area.

# Marker for detection of phases



**FIGURE 12.4.** Schematic representation of the different stages involved in seizure anticipation and detection. The upper trace is the EEG and the lower trace depicts an idealized time series of an extracted metric. The interval between seizures is interictal. The preictal state is the hypothetical state in which processes leading to the seizure onset start (1). The anticipation epoch starts where the metric exceeds the alarm threshold (2). The epochs during the seizure and the recovery after the event are indicated by the ictal and post-ictal epochs respectively.

# Methods for seizure prediction

- Linear
  - Power, variance, linear decomposition.
- Nonlinear
  - Attractor dissimilarity; Lyapunov exponent, correlation dimension, complexity loss.
- Multichannel
  - Cross-correlation; phase synchrony; adaptive seizure prediction.

# Linear methods: example

- Total power: sum of squares of sampled points ( $x_i$ ) in a window (divided by  $N$ )

$$P_o = \frac{1}{N} \sum_{i=1}^N x_i^2$$

- Results: increased episodes of power were found several hours prior to seizure onset. In children: successful in 2 out of 5 (Litt, 2001).
- Bottom line: method not robust.

# Nonlinear methods

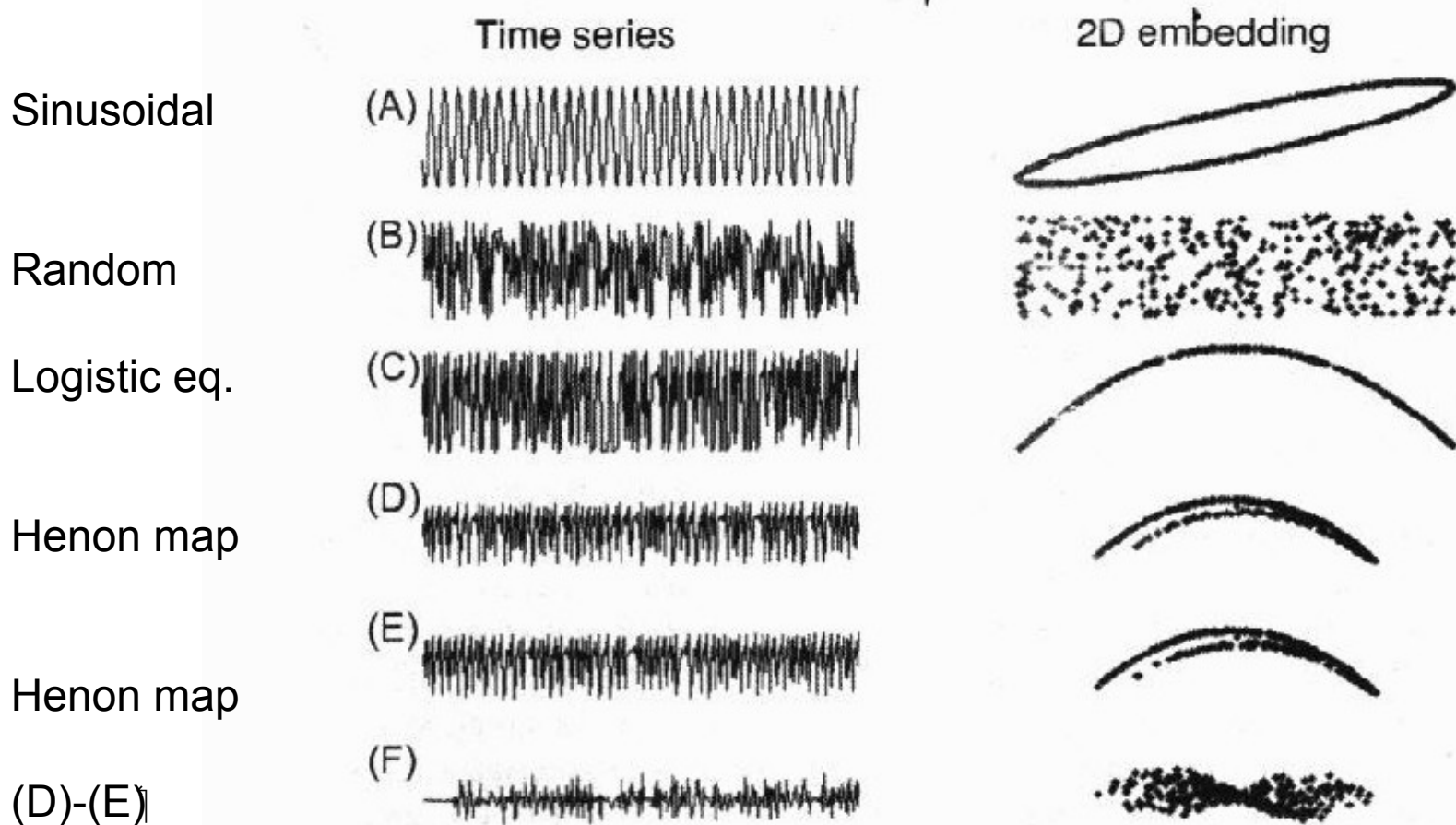
- Embedding

- Consider the time series:  $x_t(x_i, x_{i+1}, x_{i+2}, \dots, x_n)$
- We will create a set of vectors such that:

$$X_i = \left[ x_i, x_{i+\Delta}, x_{i+2\Delta}, x_{i+3\Delta}, \dots, x_{i+(m-1)\Delta} \right]$$

- Where  $\Delta$  is the delay in number of samples and  $m$  the dimension of the vector.
- System evolution can be shown as a phase space plot.
- Attractors can be spotted (when present, and if of lower dimension than the embedding)

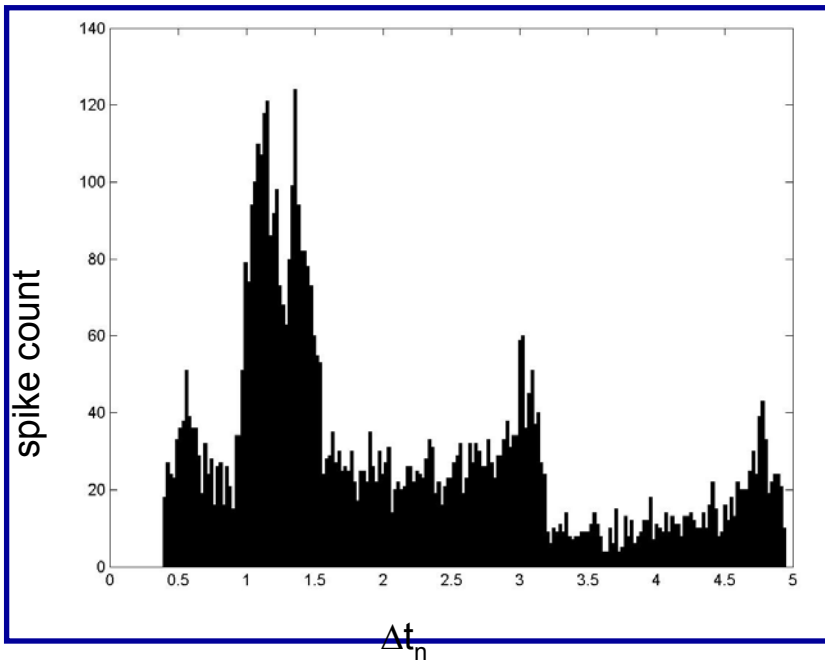
# Examples of 2D embedding



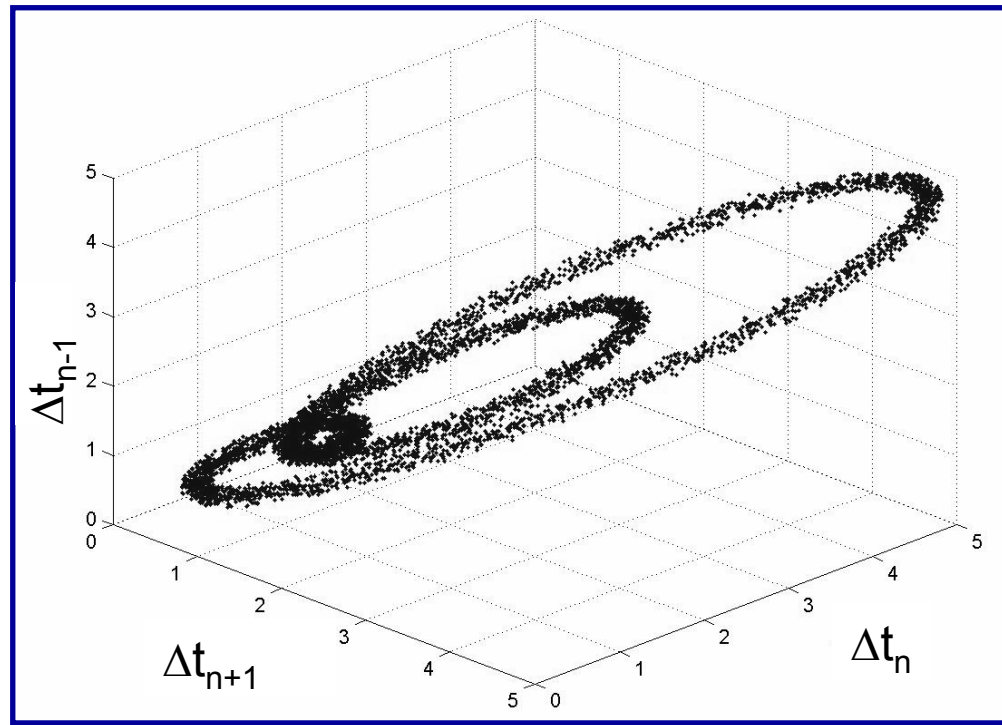
**FIGURE 12.5.** Examples of time series (left column) and embedding in two dimensions (right column). (A) sinusoidal signal; (B) random signal; (C) time series determined by the logistic equation ( $x_t = 4x_{t-1}[1 - x_{t-1}]$ ;  $x_0 = 0.397$ ); (D, E) two examples of a Henon map ( $x_t = y_{t-1} + 1 - ax_{t-1}^2$ ;  $y_t = bx_{t-1}$ ,  $a = 1.4$ ,  $b = 0.3$ ). The initial conditions differ between (D) and (E):  $x_0 = 0$ ,  $y_0 = 0$  and  $x_0 = 10^{-5}$ ,  $y_0 = 0$ , respectively; (F) the difference between (D) and (E) shows that initially both time series develop in a similar fashion (difference  $\rightarrow 0$ ). However, after 25 iterations the difference in initial condition causes a different evolution in each time series. A Matlab script to create this figure can be found in Appendix 2.

# 3d embedding: tracking patterns

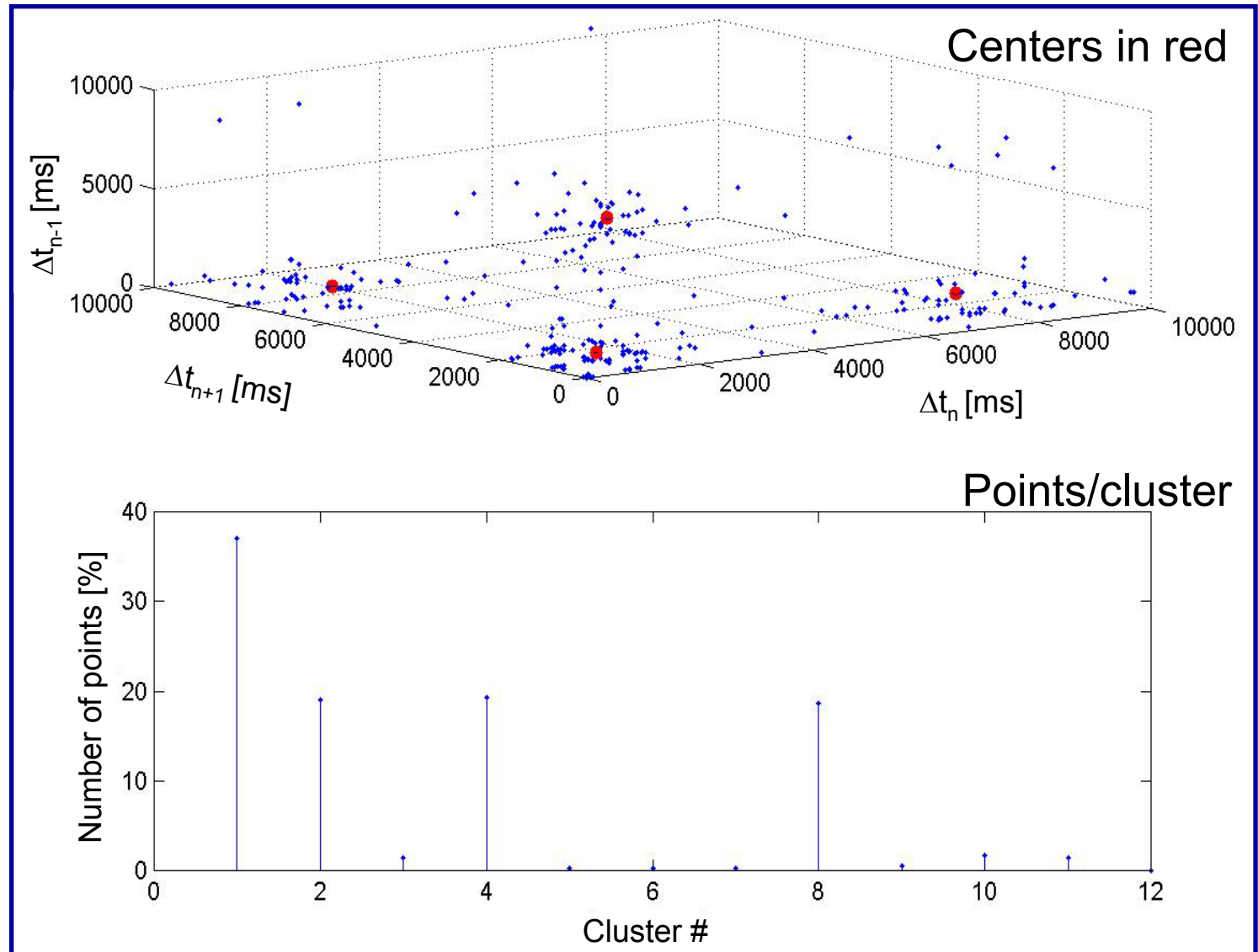
$$y = \sin(x) + \sin(2x) + \sin(3x + 30) + 2 + k(x);$$
$$k(x) \in (0.2; 0.3) \text{ (random numbers)}$$



Poincare section, phase space plot



# Neuronal activity: response to stimulation



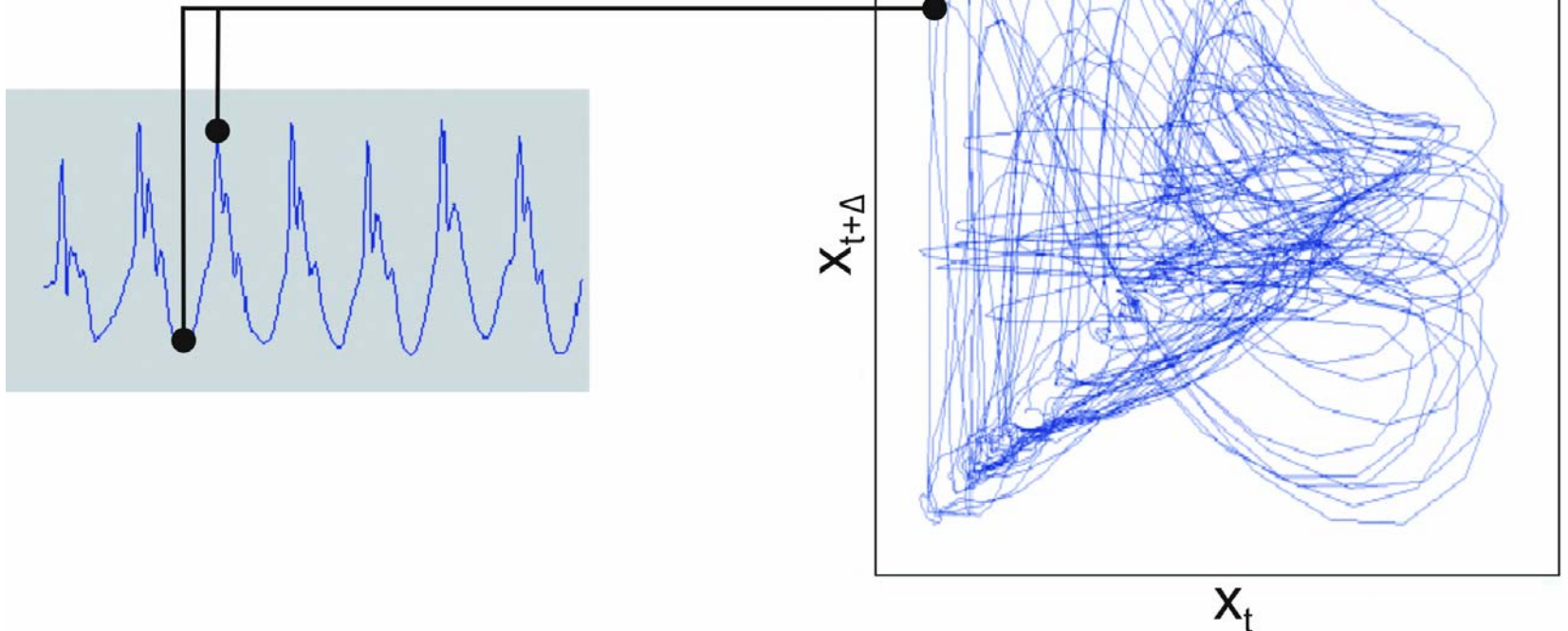


# Sensitivity to small perturbations

$10^{-5}$  difference in initial condition grows disproportionately to the evolution of the system. (bottom line: poor predictability!)

# Lyapunov exponents (LE)

- LE ( $\lambda_i$ ) describe attraction (convergence) or divergence of trajectories in each dimension of the attractor.  $\lambda_i$  is the rate with which the distance between two trajectories gets closer or further apart.
- The main objective of nonlinear methods for EEG and ECoG time series analysis: find the largest Lyapunov exponent.
- This LE determines the sensitivity of the system to the initial conditions!
- Controversial results in the community.
- Bottom line: this (nonlinear method) hasn't been proven to work as a reliable seizure predictor either.

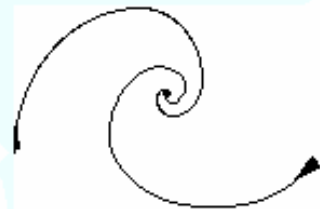


# Lyapunov exponents ( $\lambda$ )

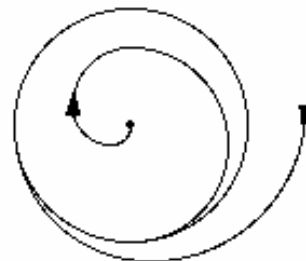
$$\lambda = \lim_{\substack{t \rightarrow \infty \\ |\Delta x_0| \rightarrow 0}} \frac{1}{t} \ln \frac{|\Delta x(X_0, t)|}{|\Delta x_0|}$$

This number, called the Lyapunov exponent " $\lambda$ " [lambda], is useful for distinguishing among the various types of orbits. It works for discrete as well as continuous systems.

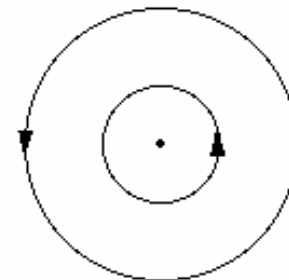
## Some Orbits with their Lyapunov Exponents



dissipative  
(attracting fixed point)  
 $\lambda < 0$

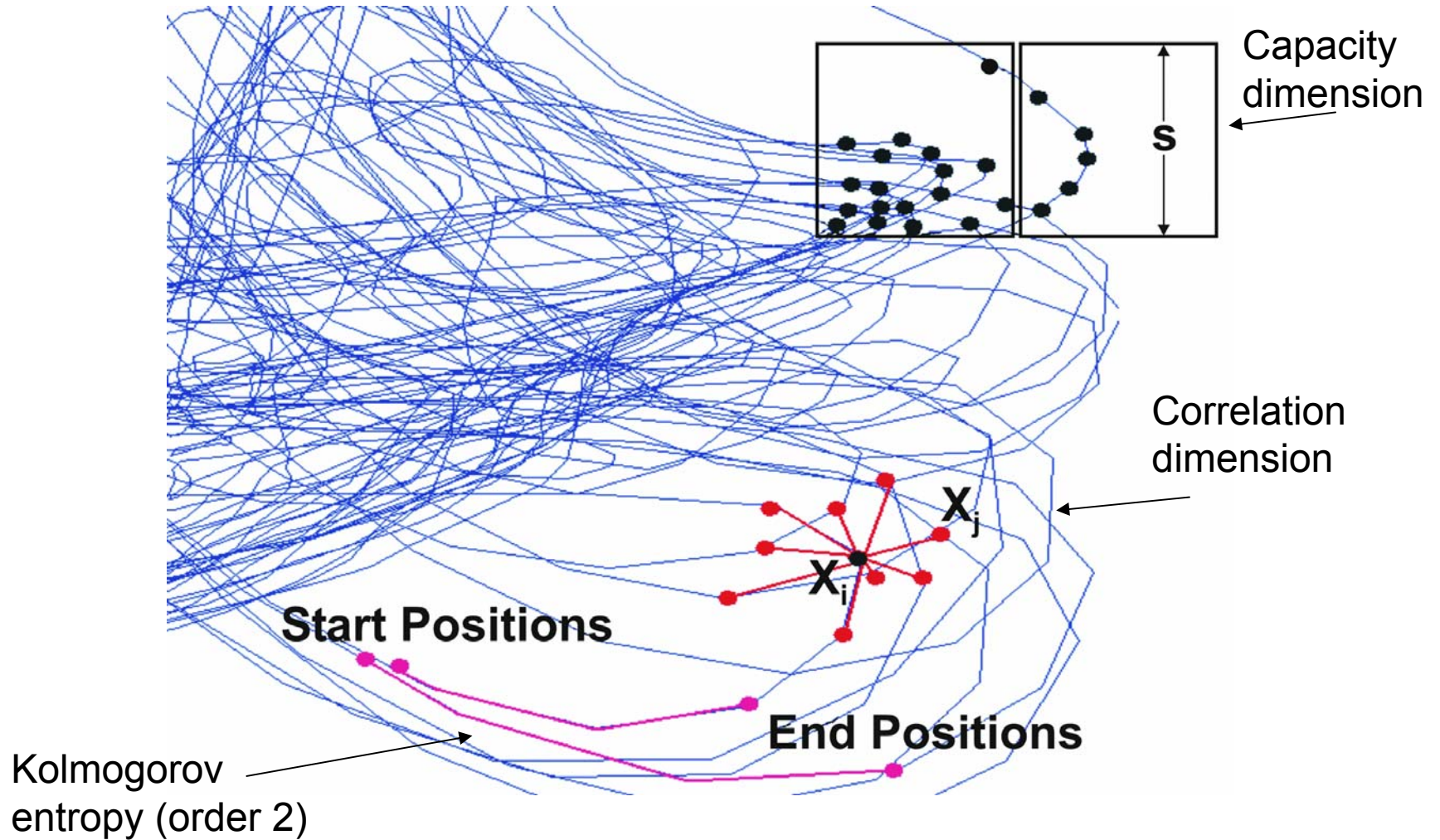


dissipative  
(attracting orbit)  
 $\lambda < 0$



conservative  
(neutral fixed point & orbits)  
 $\lambda = 0$

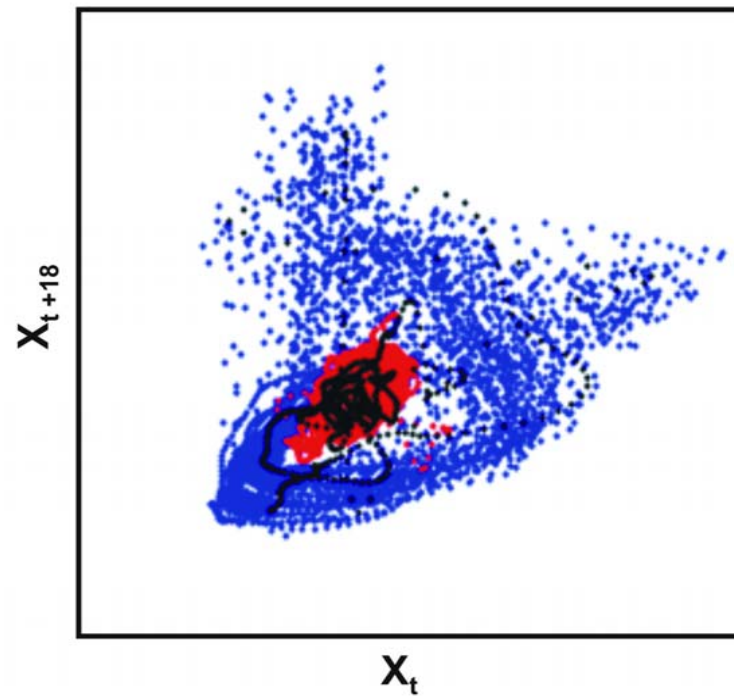
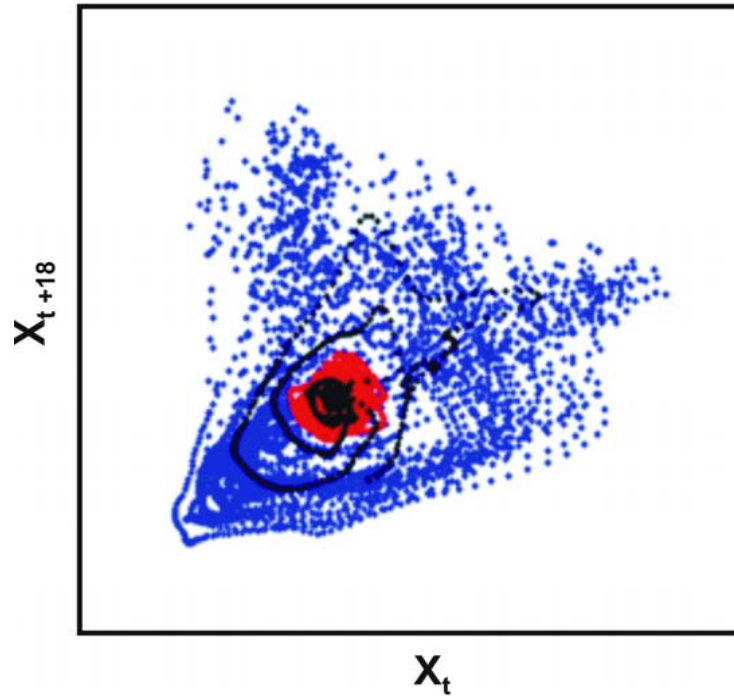
# Properties of an attractor



# Seizures can be divided in two (only two?) classes

Seizure 1

Seizure 2



Embedding (with  $t=18$  data points, corresponding to 45ms) of two seizures from one patient. Blue: seizure attractor; red: normal EEG. Black: transition from seizure to normal.