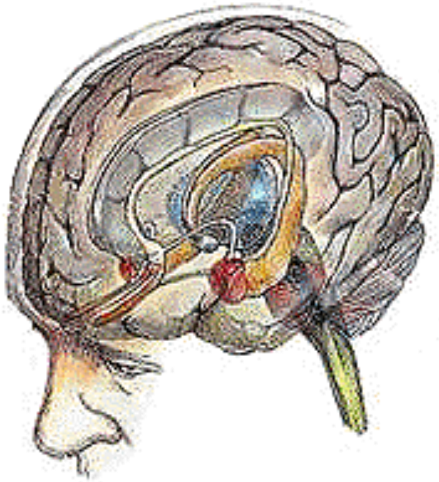
Applications of modelling clinically recorded datasets

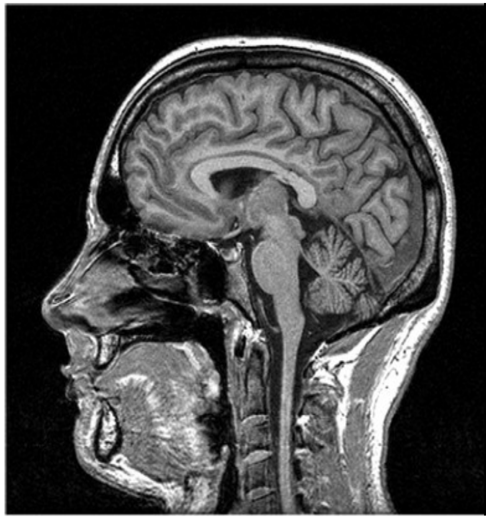
John R. Terry

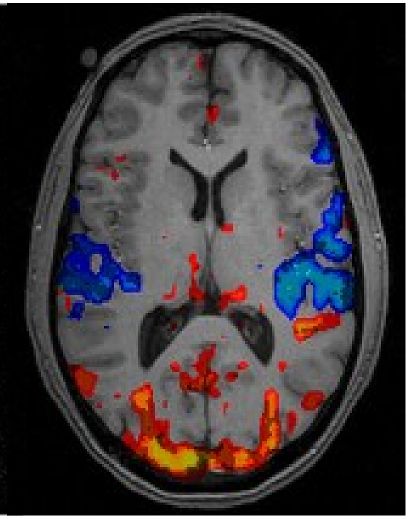


Outline

- Introduce different clinical techniques for recording neural activity
- Explore relationship between cognitive state and neural activity
- Describe transitions in data associated with epilepsy
- Absence seizures
- Clinical challenges in diagnosis
- Describe models of EEG recordings
- Explore use in the clinical environment
- General Anesthetic Agents
- Use of models to enhance understanding

fMRI





- Measures blood oxygenation/flow (The BOLD response)
- Higher oxygen consumption implies higher neural activity
- Believed to be due to changes in synaptic activity rather than increased neural firing
- Convolution models of the haemodynamic response (balloon model, Windkessel model)

Stephan *et al*. Cur. Opinion Neurobiology **14** 629-635 (2004)

Advantages: Non-invasive, simple to measure, good spatial resolution

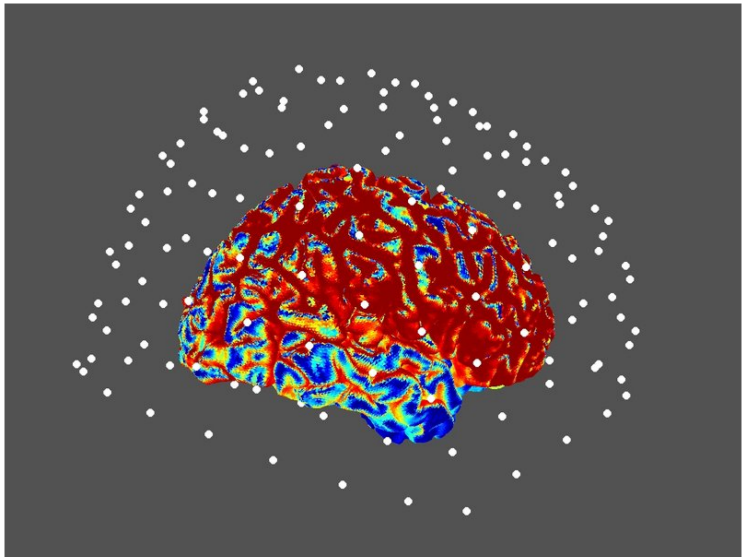
Disadvantages: Slow response time - poor temporal resolution, cost

MEG

- Records magnetic activity
- Fields are produced by same electrical changes that give rise to EEG - post-synaptic current flow across pyramidal neurons
- Magnetic fields ‘unaffected’ by conductivity of tissues within the head

Advantages: Excellent temporal resolution, better spatial resolution than EEG

Disadvantages: Cost, fMRI has better spatial resolution



EEG

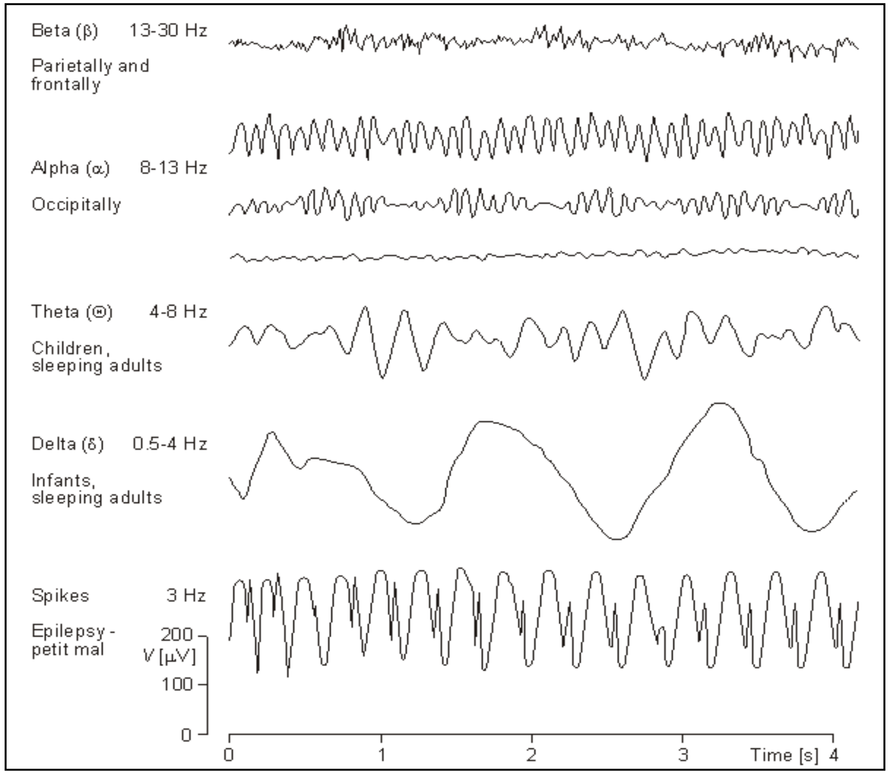
- Richard Caton made the first report of the electrical activity of the brain in Edinburgh! (1875)
- Hans Berger credited with first performing EEG in humans (1924)

EEG from Berger's 6yr old!

10Hz sine wave

Electroencephalography:
Basic Principles and Clinical Applications
Niedermeyer and Lopes da Silva

EEG



- These early studies demonstrated a link between EEG activity and brain state:

- "*When any part of the grey matter is in a state of functional activity, its electric current usually exhibits negative variation*" Caton (1875)

- "*There were found distinct variations in current that increased during sleep and with the onset of death strengthened, and after death became weaker and then completely disappeared*" Berger (1929)

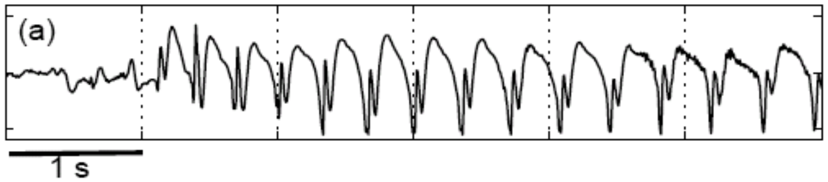
Epilepsy

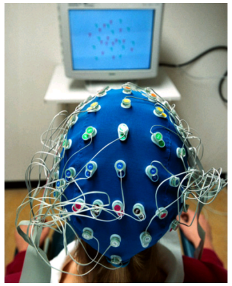
- The tendency to have repeated seizures

- Seizures are "*transient periods due to abnormal, excessive hyper-synchronous neuronal activity*" (Fisher *et al. 2005)*

- Around 40 different subtypes - classified as general or partial, complex or simple

Petit-Mal (or Childhood Absence Epilepsy)

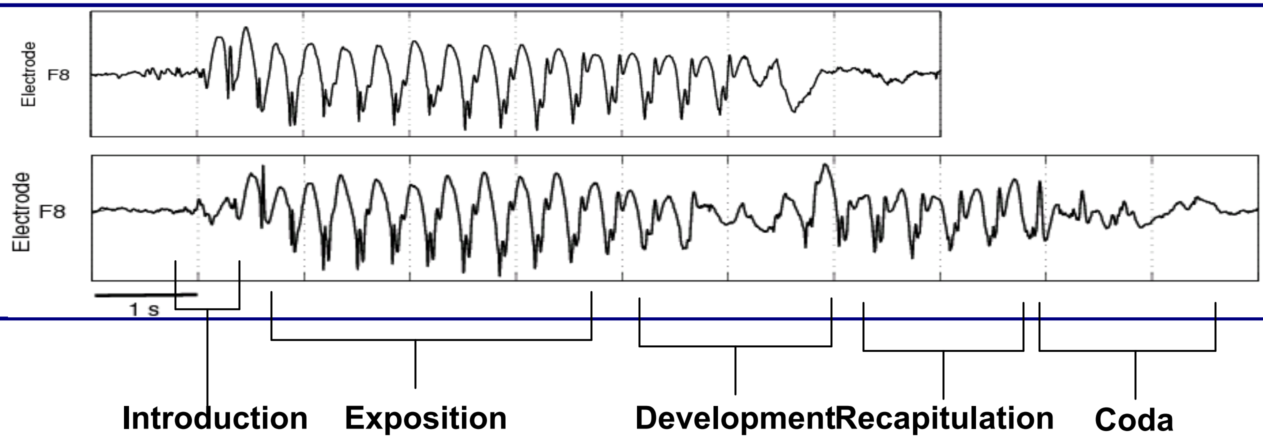




2-4Hz Spike-Wave Discharge - “textbook” rhythm

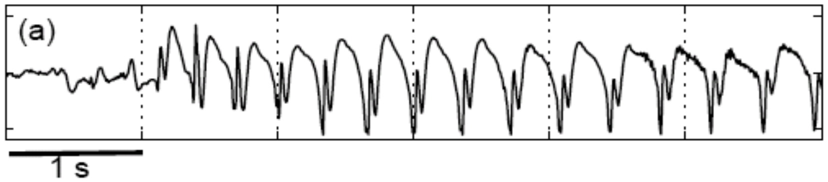
Electroencephalography:
Basic Principles and Clinical Applications
Niedermeyer and Lopes da Silva

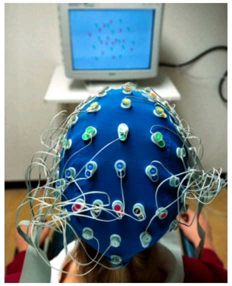
Patient 1



Petit-Mal Sonata: Predominant EEG seizure patterns in CAE
Sogawa, Mosche *et al.*

Petit-Mal (or Childhood Absence Epilepsy)





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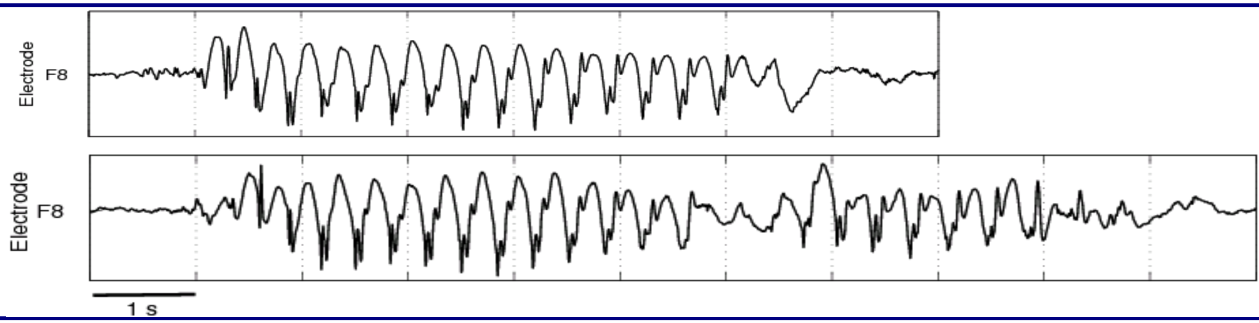
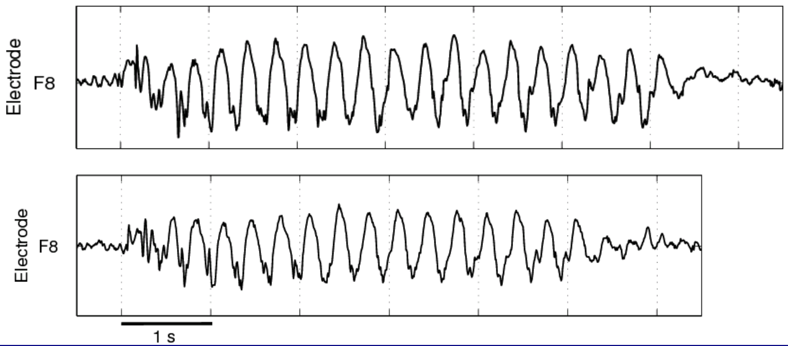


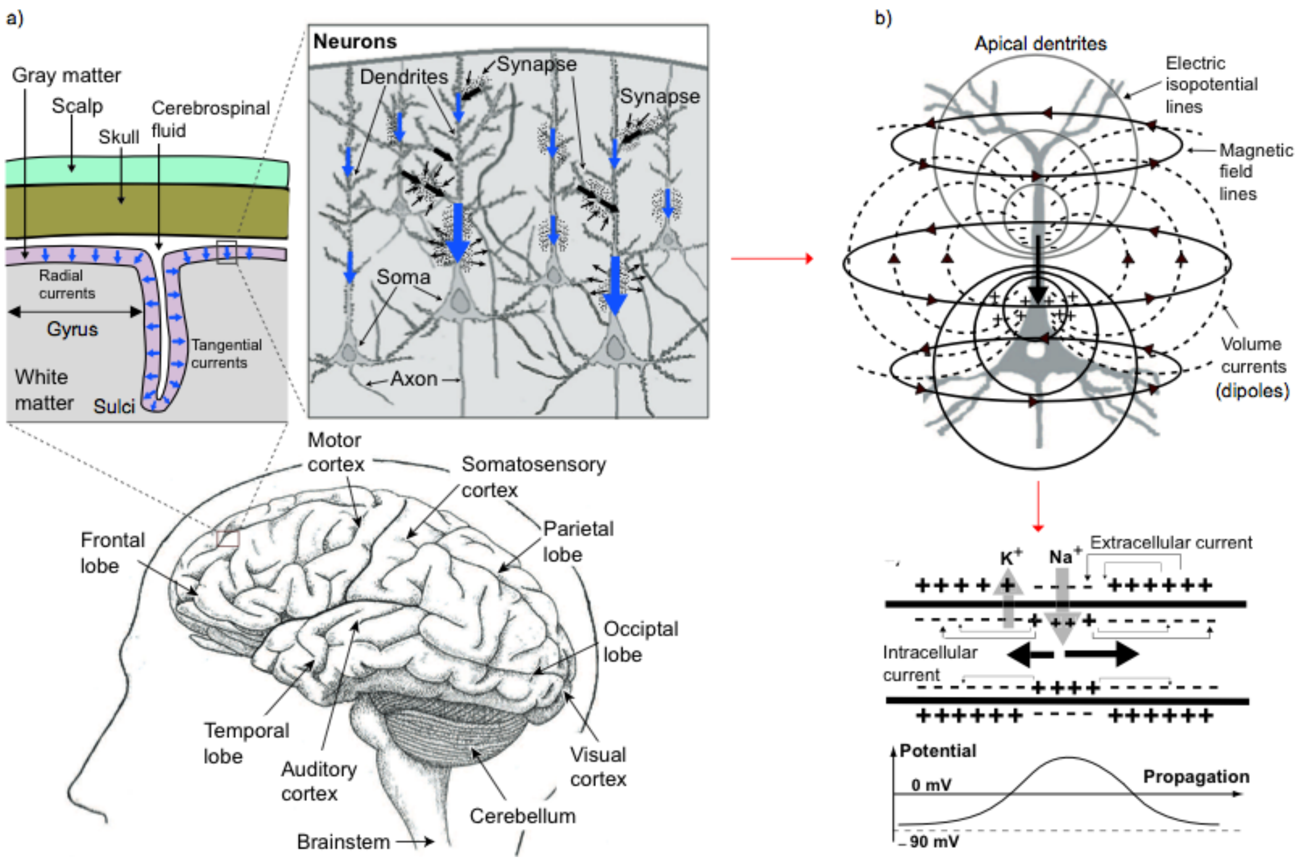
Patient 2



Petit-Mal Sonata: Predominant EEG seizure patterns in CAE
Sogawa, Mosche *et al.*

Modelling EEG

- Modelling neural data recordings has a long history
- To build a specific model of EEG data we should first consider:
  - What does EEG represent?
  - What are the underlying contributors to this?



Modelling EEG

- Modelling neural data recordings has a long history

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  - What does EEG represent?
  - What are the underlying contributors to this?

Challenges

- Consideration of 10^{12} neurons or even 10^4 macrocolumns

- Localisation of distribution of electrical activation

- Understand how local synaptic interactions mediate synchrony responsible for underlying field potentials that form EEG

- Do observed rhythms originate from neuronal pacemakers?

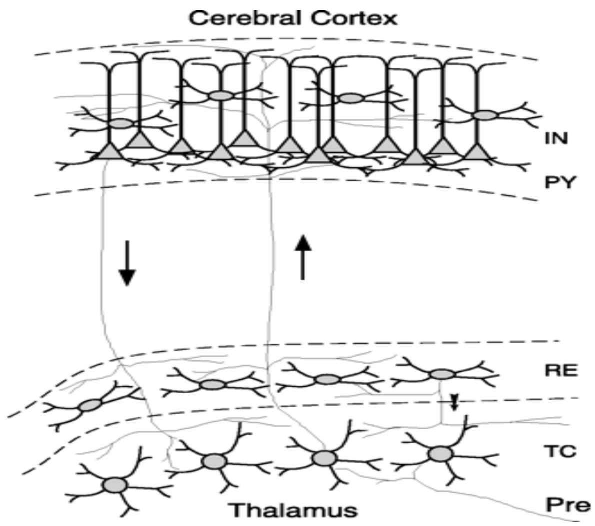
- Are macroscopic dynamics an *emergent* property not apparent at the neuronal level?

Thalamocortical Networks

- Some EEG rhythms can be explained by ensembles of neurons projecting their activity into the cortex

- In particular thalamic neurons which are able to display intrinsic oscillatory behaviour (even when synaptic transmission is blocked)

- These properties are suggestive of a fundamental role in sleep spindle and absence seizure activity



Destexhe & Sejnowski
Thalamocortical Assemblies

Oscillating Circuits

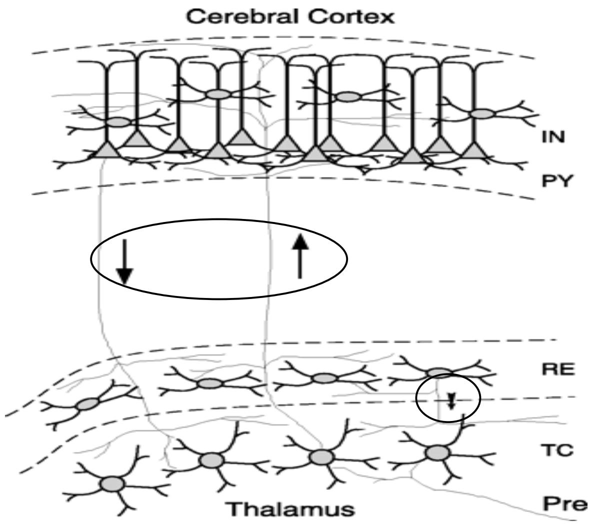
Dynamical equations

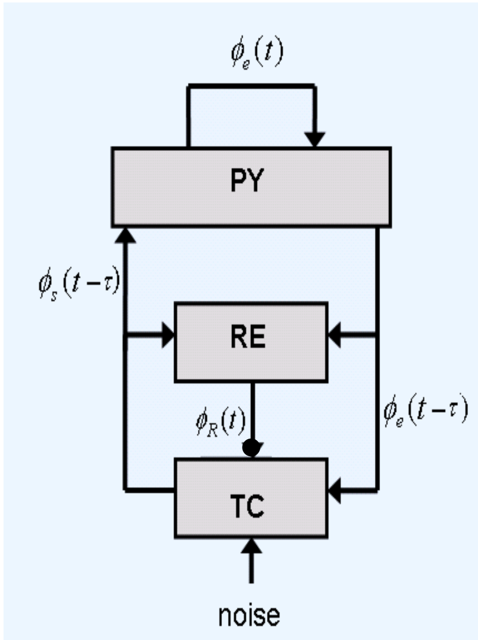
Positive and negative feedback

τ

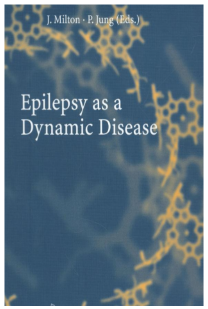
Time Delays

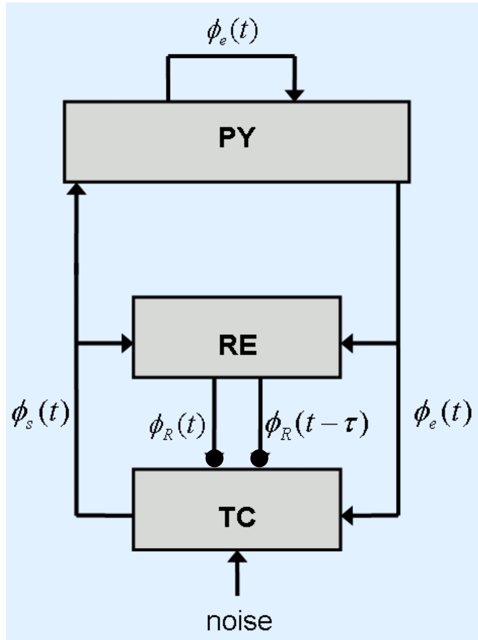
Q. What is the minimal circuit required for oscillation?



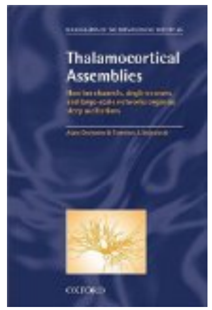


Milton (2003)





Destexhe & Sejnowski (2001)



Building an EEG model

- Aim is to build a macroscopic model, whose state variables can be mapped onto EEG recordings

- Partially circumvents the need to model all physiological details

- We will build a *mean-field model* that describes aggregated activity of the implicated neuronal populations

Deco *et al.* PLOS CB **4**, 1000092 (2008)
Jirsa Neuroinformatics **2**, 183 (2004)
Liley *et al.* Network: Comp Neural Sys **13**, 67 (2002)

- The specific model we will focus on is described in

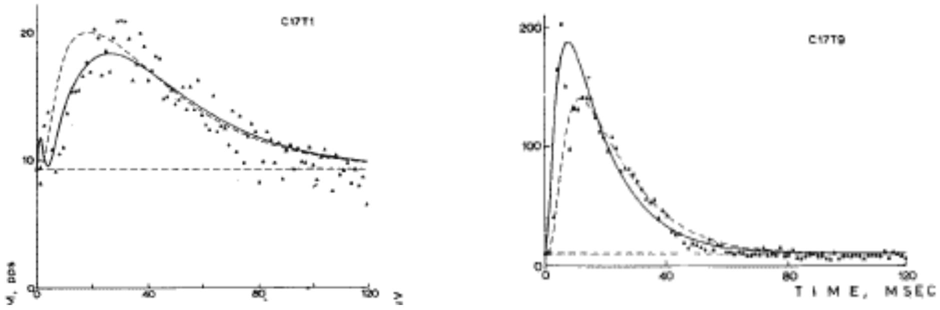
Marten *et al*. Phys Rev E **79**, 021911 (2009)
Marten *et al.* Phil Trans Roy Soc A **367**, 1145-1161 (2009)

- This model is adapted from

Robinson *et al.* Phys Rev E **65**, 041924 (2002)

Building an EEG model

- Freeman in the 1970s explored the response of a neural mass to an electrical input



Freeman Mass Action in the Nervous System (1975)
Lopes da Silva *et al*. Kybernetik **15**, 27 (1974)

- This biexponential response may be modelled using a 2nd order ODE:

$$\left(\frac{1}{\alpha\beta}\frac{d^2}{dt^2}+\left(\frac{1}{\alpha}+\frac{1}{\beta}\right)\frac{d}{dt}+1\right)V(t)=I_{ext}$$

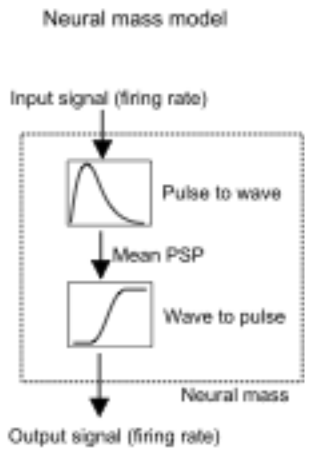
- By assuming the rise time to be infinitely fast, a 1st order equation is used in some models instead

Wilson & Cowan, Biophys. J. **12**, 1 (1972)
Liley *et al.* Network: Comp Neural Sys **13**, 67 (2002)

Building an EEG model

➢ Jirsa and Haken described a wave to pulse and a pulse to wave converter to account for incoming/outgoing fields of activity for an average neuronal population

Jirsa & Haken Phys Rev Lett **77**, 960-963 (1996)



➢ Based upon these assumptions we may build a population level model

Building an EEG model

- Each neural mass (PY, RE, TC) is described by four dynamical laws:

1) Mean soma membrane potential

$$\left[\frac{1}{\alpha\beta}\frac{\partial^2}{\partial t^2}+\left(\frac{1}{\alpha}+\frac{1}{\beta}\right)\frac{\partial}{\partial t}+1\right]V_a(t)=P_a(t)$$

2) Mean firing rate

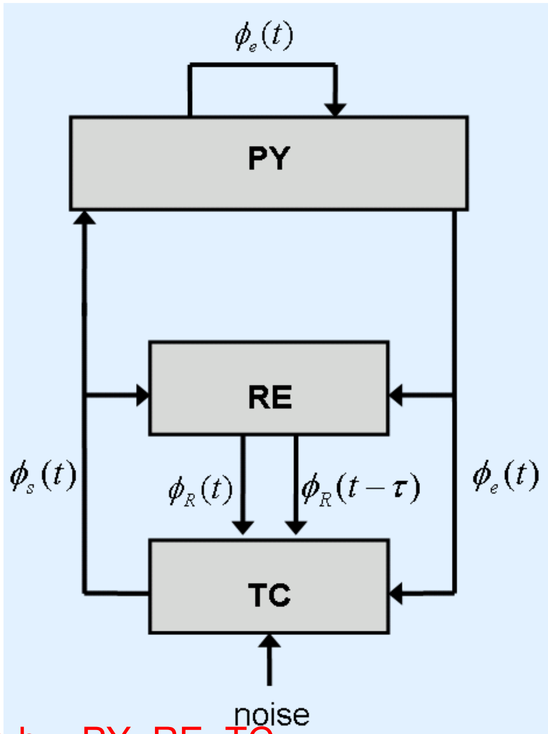
$$\zeta_a(t)=\frac{Q_a^{\max}}{1+\exp\left[-\frac{\pi}{\sqrt{3}}\left(\frac{V_a(t)-\theta}{\sigma}\right)\right]}$$

3) Field equation

$$\frac{1}{\gamma_a^2}\left[\frac{\partial^2}{\partial t^2}+2\gamma_a\frac{\partial}{\partial t}+\gamma_a^2\right]\phi_a(t)=\gamma_a^2\zeta_a(t)$$

4) Post-synaptic input

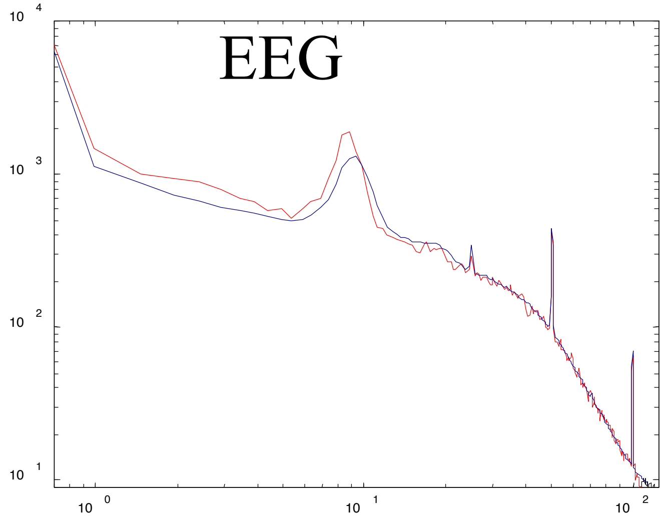
$$P_a(t)=\sum_b \nu_b\phi_b(t)$$

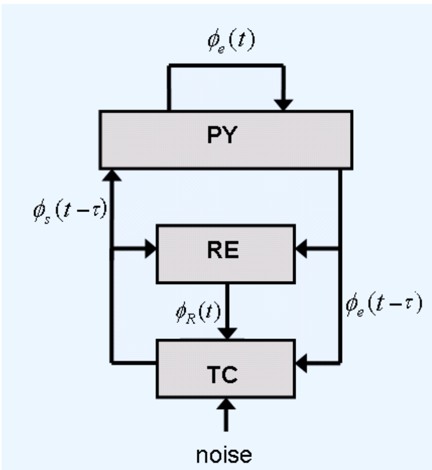


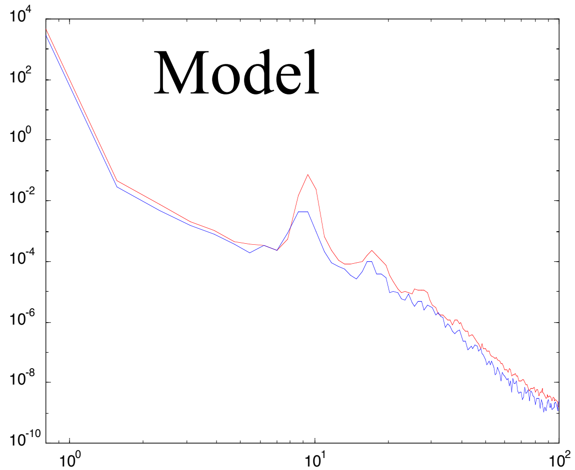
a,b = PY, RE, TC

Numerical Simulation

Breakspear *et al* Cereb Cortex **16**, 1296 (2006)







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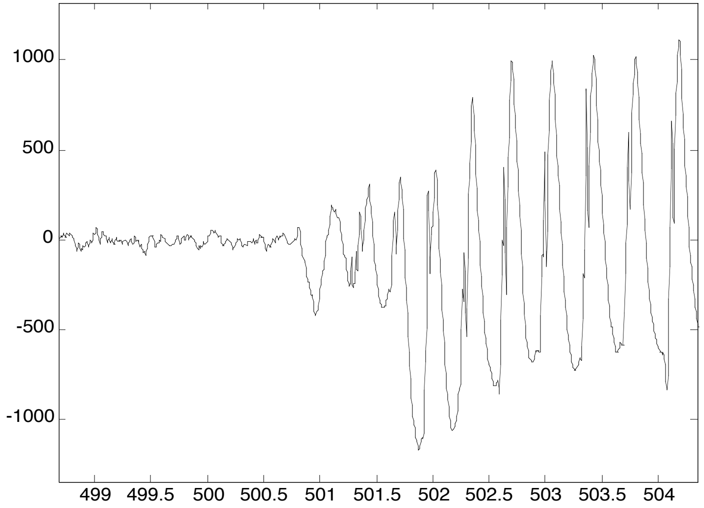

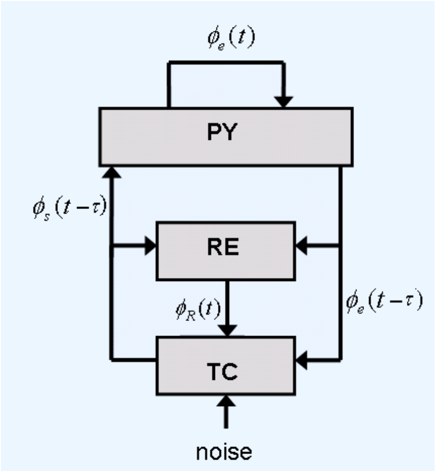

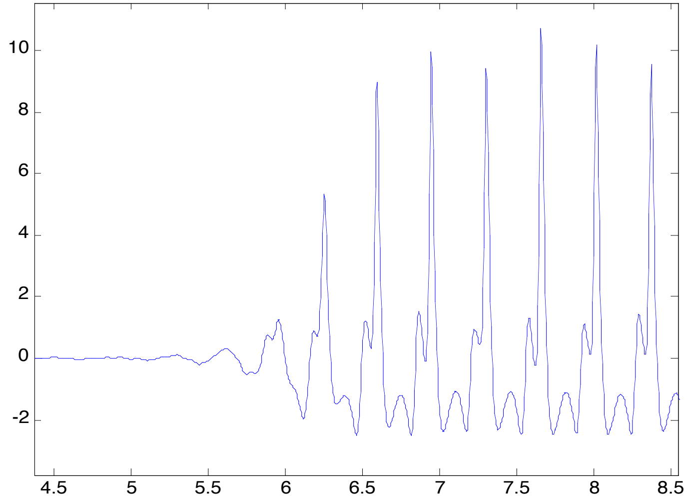

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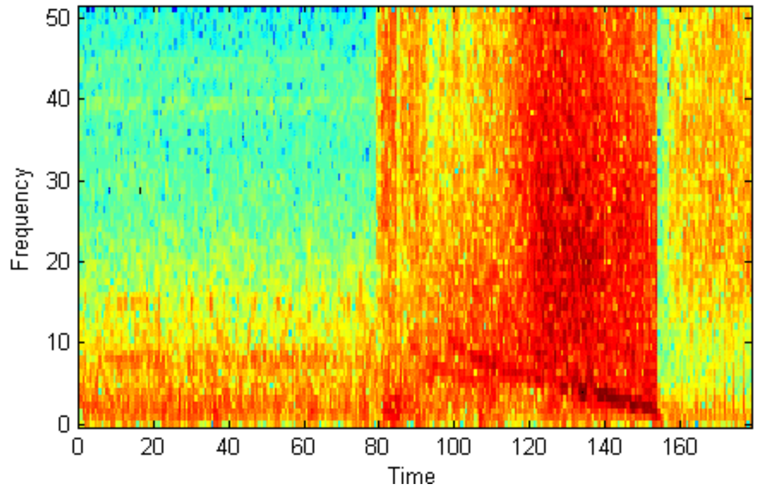
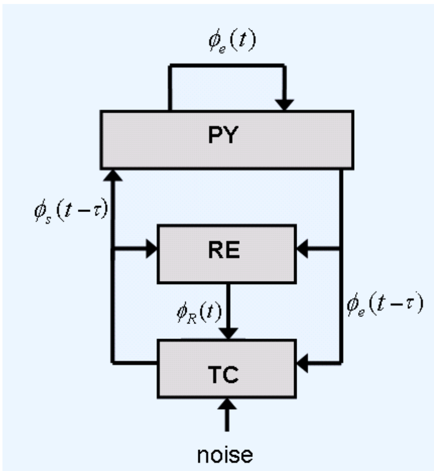
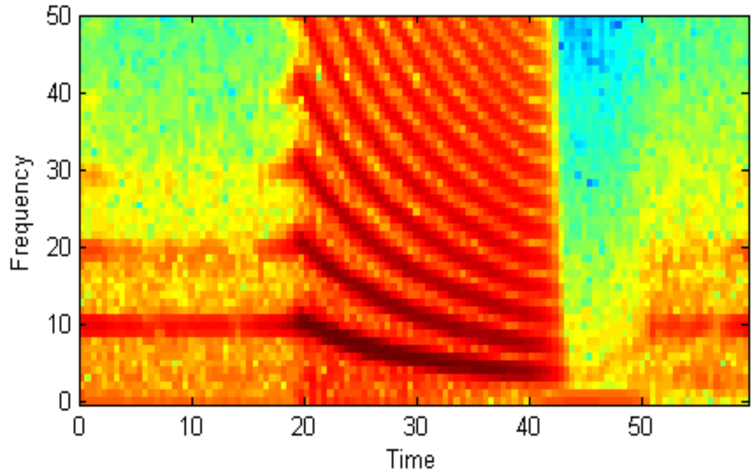




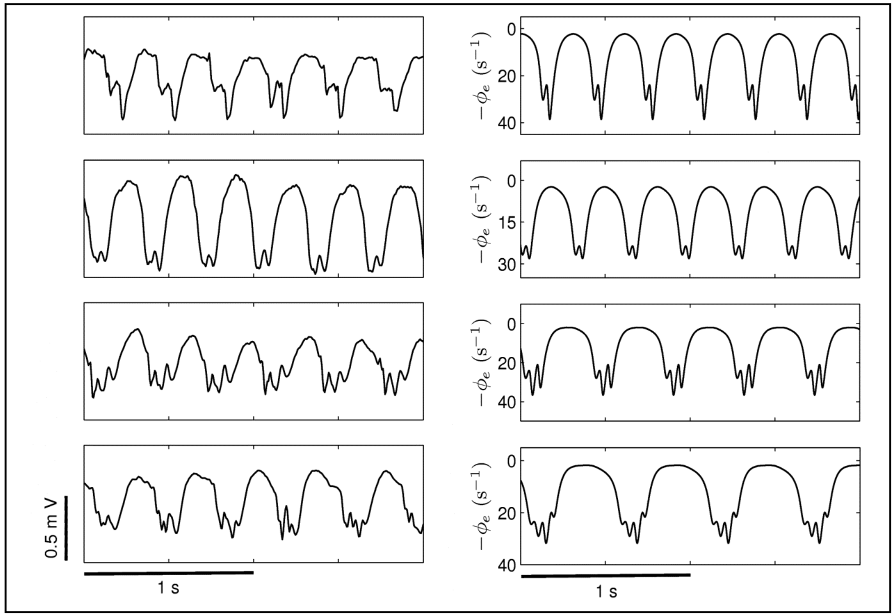


Numerical Simulation

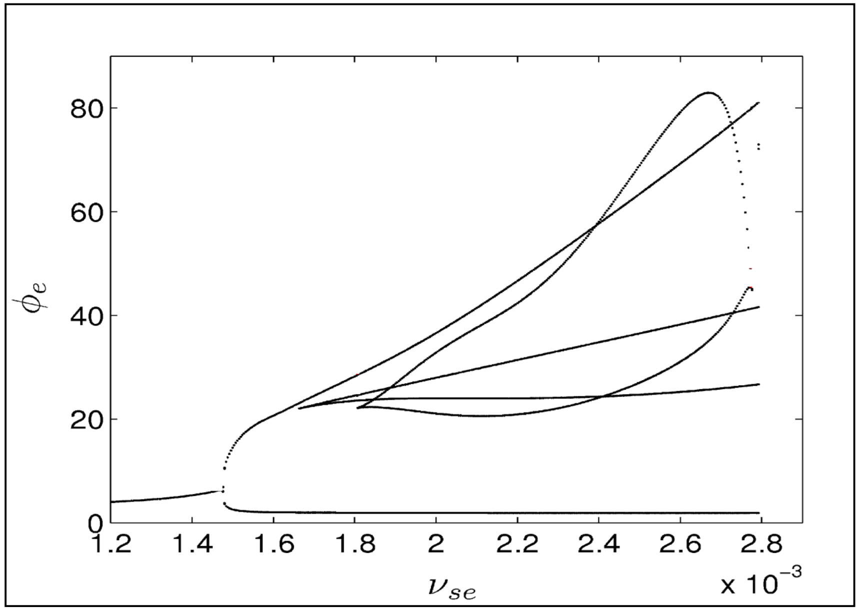
Marten *et al* Phil Trans Royal Soc A **367**, 1145 (2009)

Numerical exploration demonstrates a qualitative agreement between model and clinical data

Patient EEG **Model**

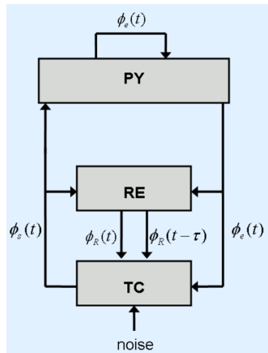


Numerical Bifurcation Plot



corticothalamic weight and time delay corresponding to $GABA_B$ process were natural parameters to vary

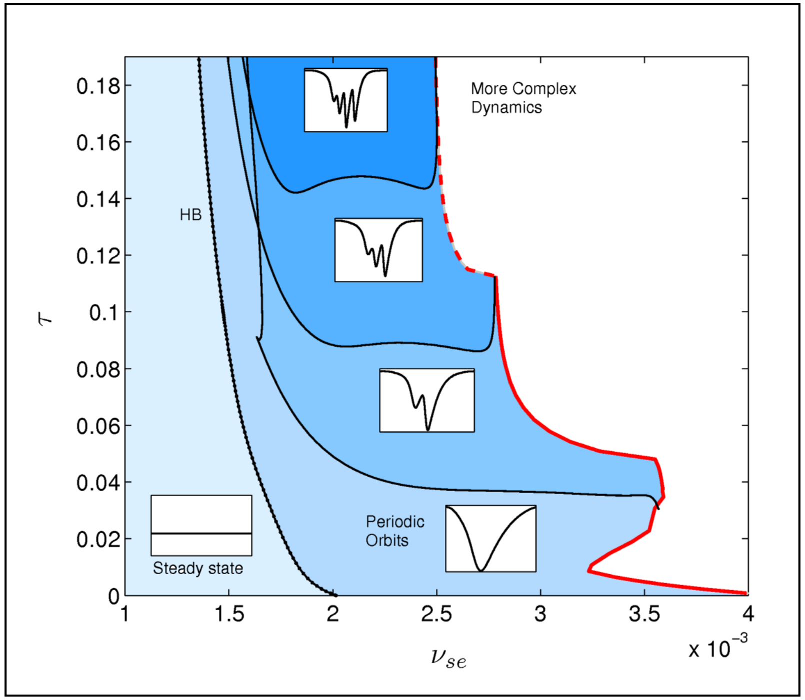
Breakspear *et al* Cereb Cortex **16**, 1296 (2006)
Rodrigues *et al* Phys Lett A **355**, 352 (2006)



Numerical Continuation

➢ Technique for tracking branches of bifurcations as parameter(s) vary

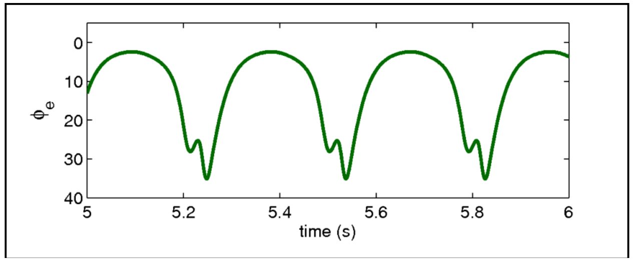
➢ Common packages include AUTO, XPPAUT, MATCONT, DDE-BIFTOOL
See Hinke Osinga's site http://www.enm.bris.ac.uk/anm/staff/hinke/dss/index.html

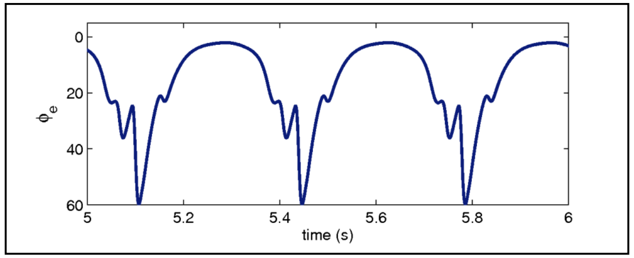


- Standard continuation methods only give us the "common" bifurcations (HB, PD, SL).

- However, from the time series we observe more complex solutions.

- New additional routine allows us to find inflection point branches.

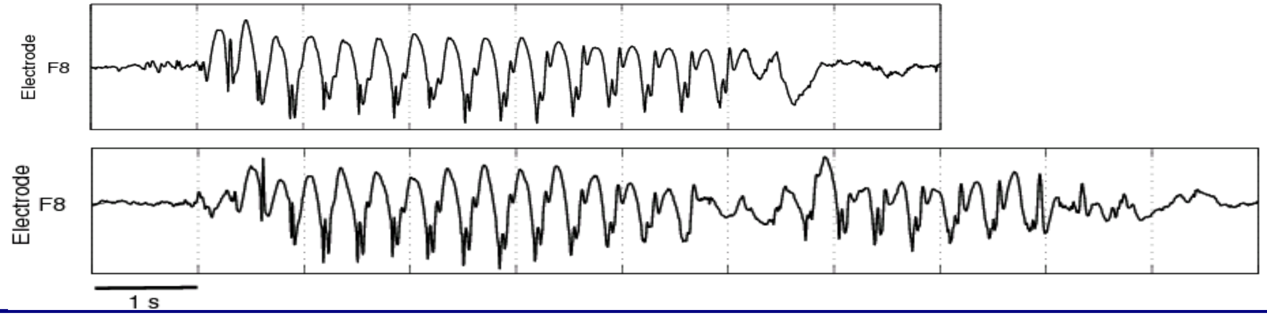




Characterising Seizure Evolution

- Could these results be applied to characterizing seizure evolution?

Patient 1

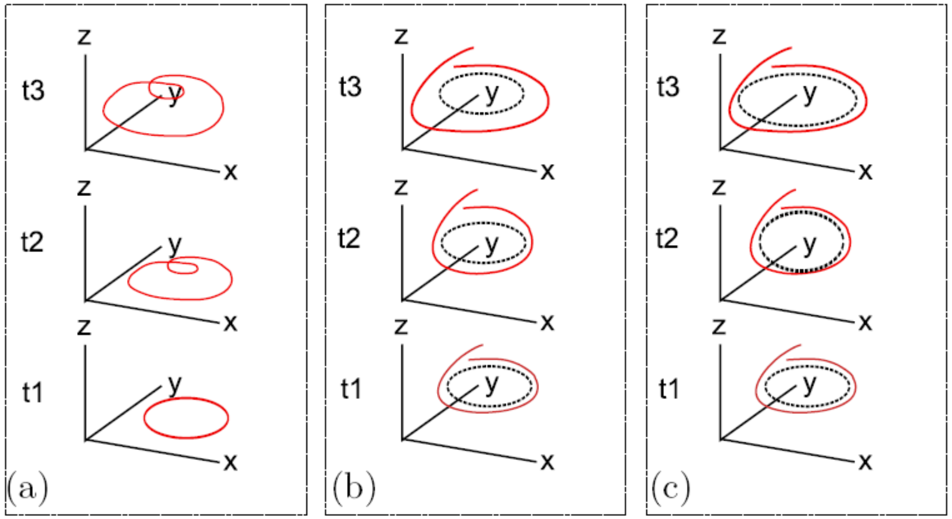


Q. How do we interpret seizure evolution?

a) Deforming attractor?

b) Transient solution towards a fixed attractor?

c) Transient solution towards a deforming attractor?



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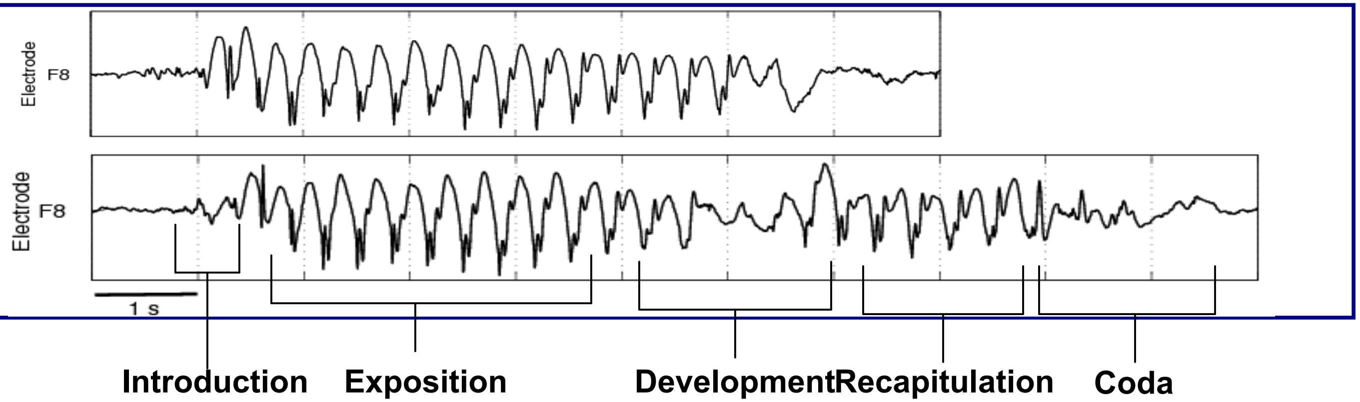
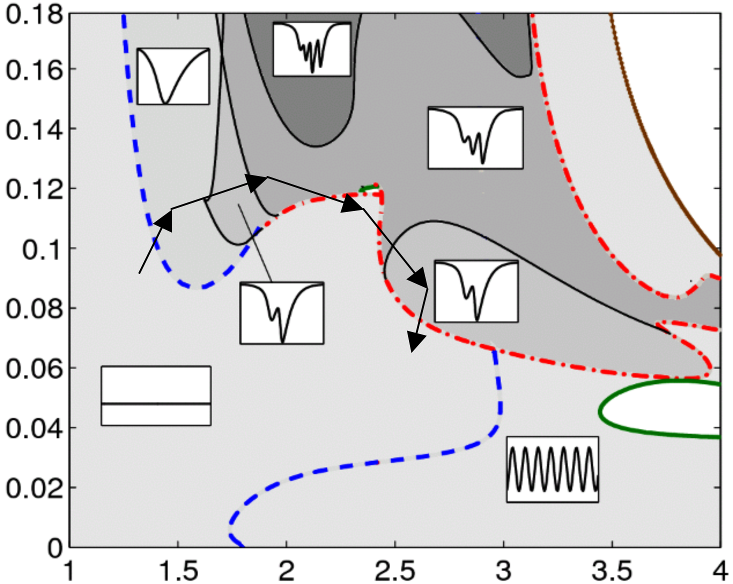
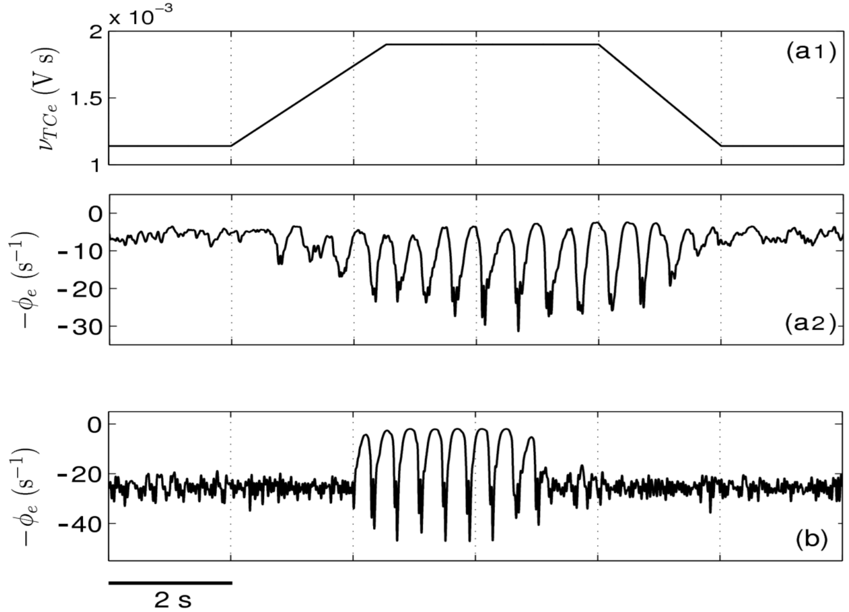
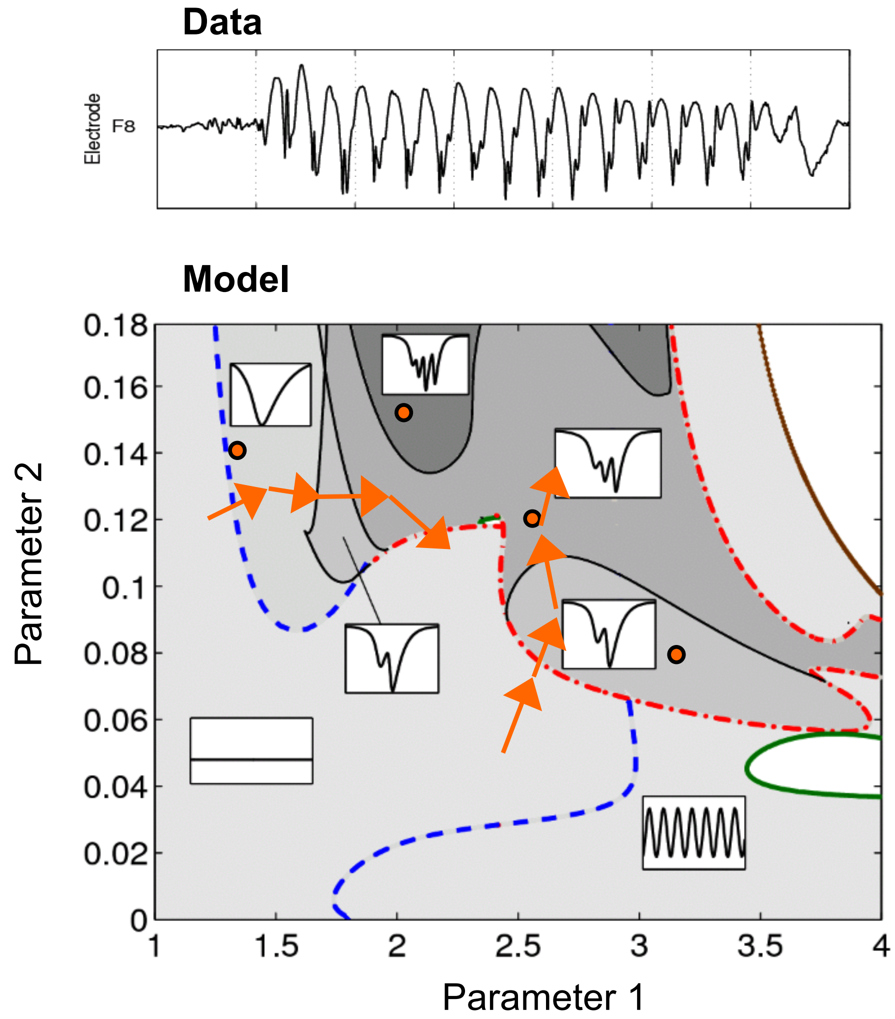






Characterising Seizure Evolution

- 1) To map out the progression of EEG during absence seizures in a low-dimensional parameter-space (say 2-3 parameters of interest).
- 2) From this: test if progress consists of random ‘jumps’ or a more ‘function-like’ relationship.
- 3) Group subjects according to how these parameters change. Could be used to classify subjects?
- 4) Investigate if some parameters vary in a similar manner between subjects, and perhaps use a more detailed model to investigate them.



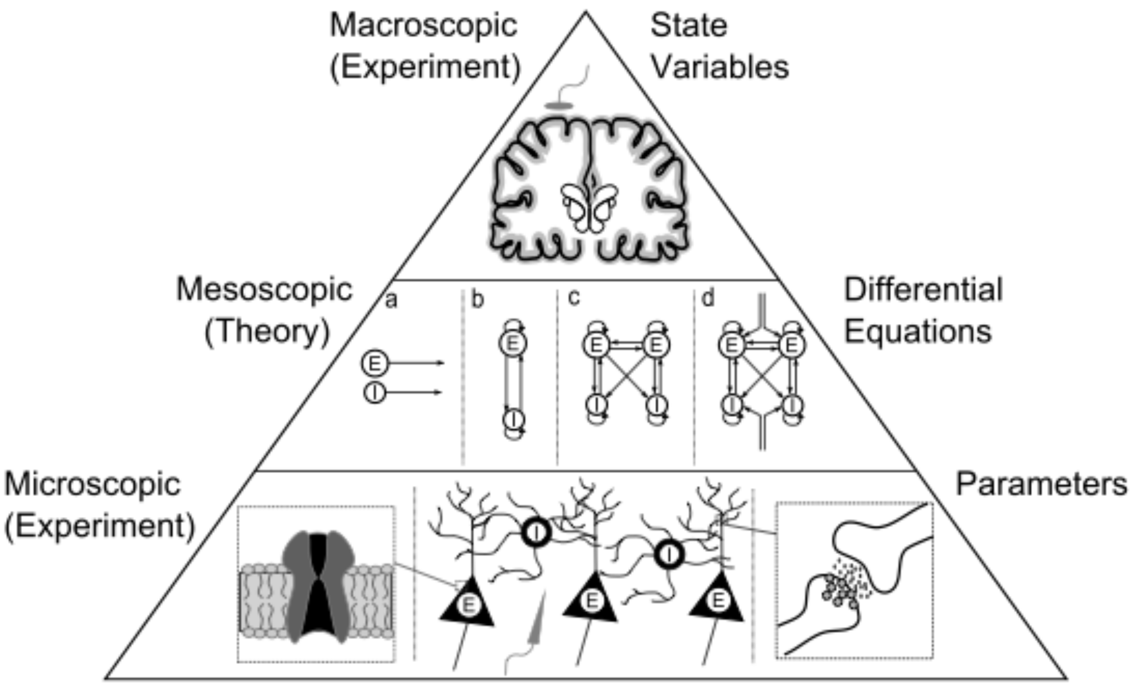
Characterising Anaesthesia

Liley & Bojak J. Clin. Neurophys. 22, 302 (2005)

- Cortical drug response is another area where mean-field models have been utilised successfully

- **Seems Challenging!**

- Mean-field models describe population response; psychoactive agents target individual molecules



Characterising Anaesthesia

- Predominant pharmaceutical action of a general anesthetic agent believed to be as a $GABA_A$ agonist.

- i.e. they potentiate amplitude / frequency of IPSPs via positive modulation **SOMEHOW!**

- $GABA_A$ contains a large subunit / subtype diversity

- Recent studies have shown specific drugs target specific subunits i.e. benzodiazepines may be sensitive to specific α and γ subtypes, whilst anaesthetics differ in affinity relative to β subtypes.

- Care must be taken when modelling these differences, as small changes in IPSP shape, can lead to big macroscopic differences

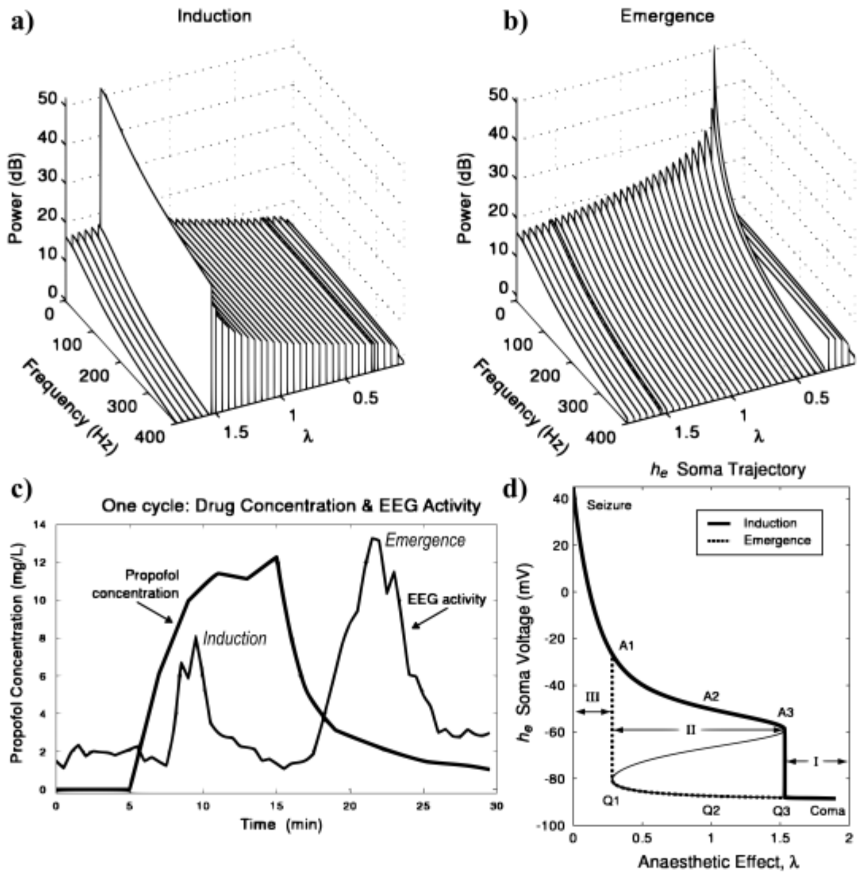
Foster *et al* Cognitive Neurodynamics **2**, 283 (2008)

Characterising Anaesthesia

➢ Steyn-Ross *et al* built a 1d cortex of linked neural masses to allow comparison of spatial inhomogeneities observed in EEG

➢ Concluded that transition to unconsciousness corresponded to a phase transition due to increases in inhibitory effects

Steyn-Ross *et al* Prog. Biophys. Mol. Biol. **85**, 369 (2004))

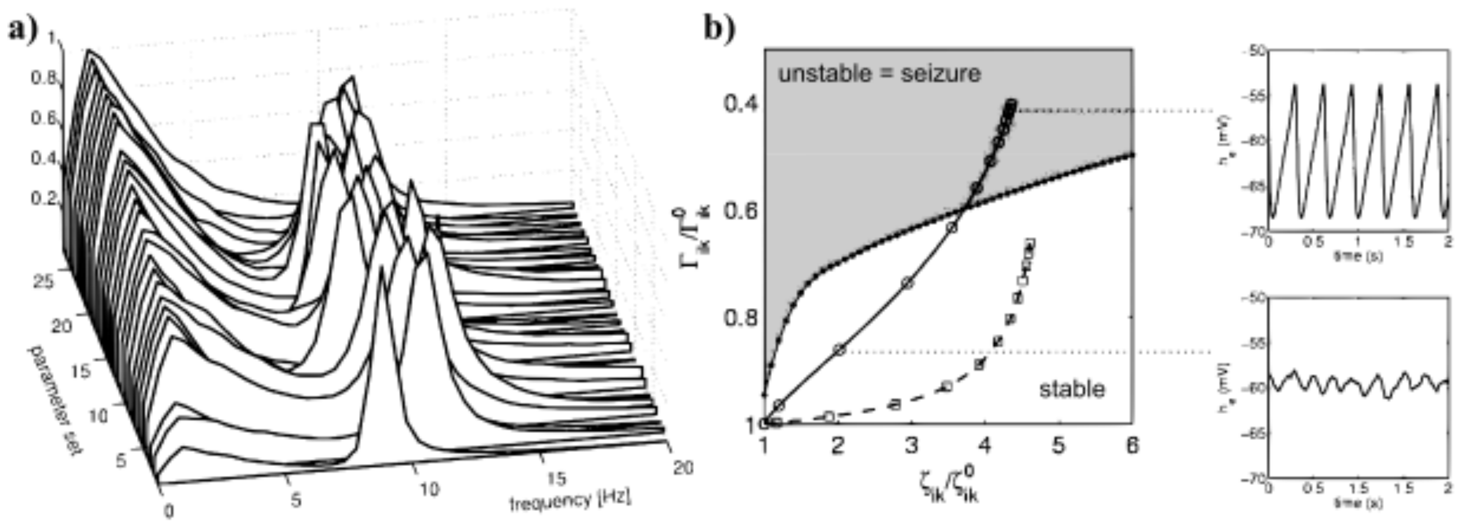


Characterising Anaesthesia

➢ Some agents have been shown to promote epileptiform acitivty

➢ Seemingly at odds with suppressive nature of compounds

➢ Liley & Bojak modelled this by fitting specific form of IPSP profile from in-vivo studies



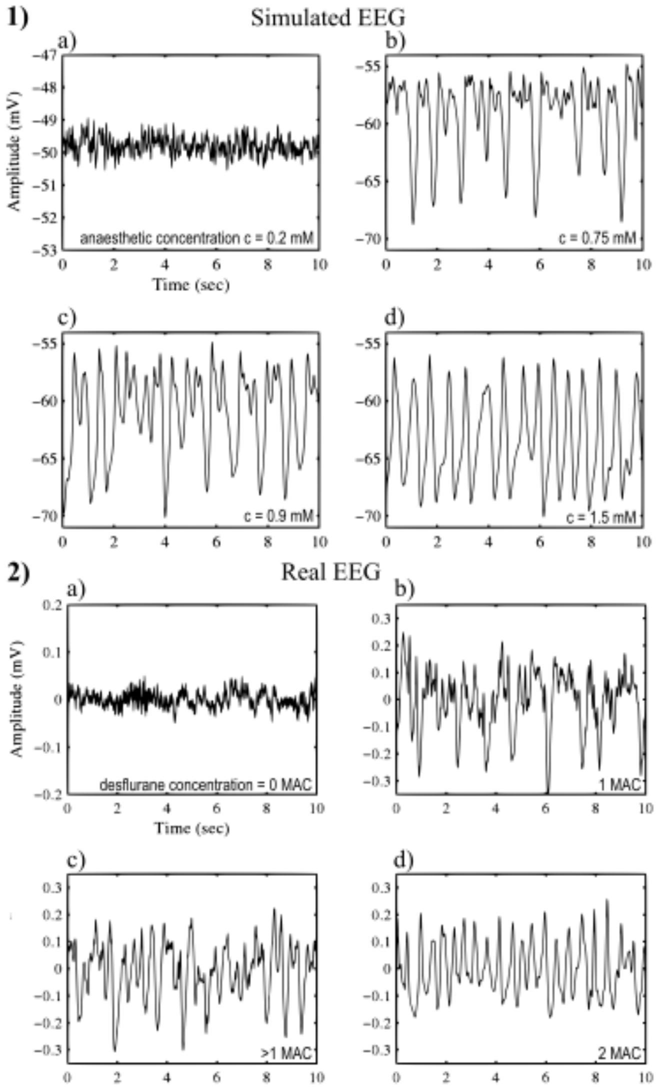
➢ Agents which acted to reduce amplitude of IPSP whilst increasing overall inhibition raised the risk of seizure activity

Liley & Bojak J. Clin. Neurophys. **22**, 300 (2005)

Characterising Anaesthesia

➢ More recently Molaee-Ardekani *et al* showed good qualitative agreement between model and EEG recordings when in addition to IPSP suppression, adaptation of the firing rate functions was included

Molaee-Ardekani *et al*
Phys Rev E **76** 041911
(2007)



Summary

- Many neurological disorders require novel approaches to develop new treatment strategies; both pharamacological and macroscale

- Mathematical and computational techniques can assist in interpreting clinical and experimental data

- Many clinically recorded neural data sets evolve dynamically; differential equation based modelling is an ideal framework

- Crucial to develop closer interactions between mathematicians and clinical / experimental neuroscientists - COMMON LANGUAGE!

- I have a folder of many of the early (1970s) and not so early material described in this talk, please see me with a memory stick if you'd like a copy!

Thanks!