NEW THOUGHTS AND APPROACHES IN PD PATHOGENESIS

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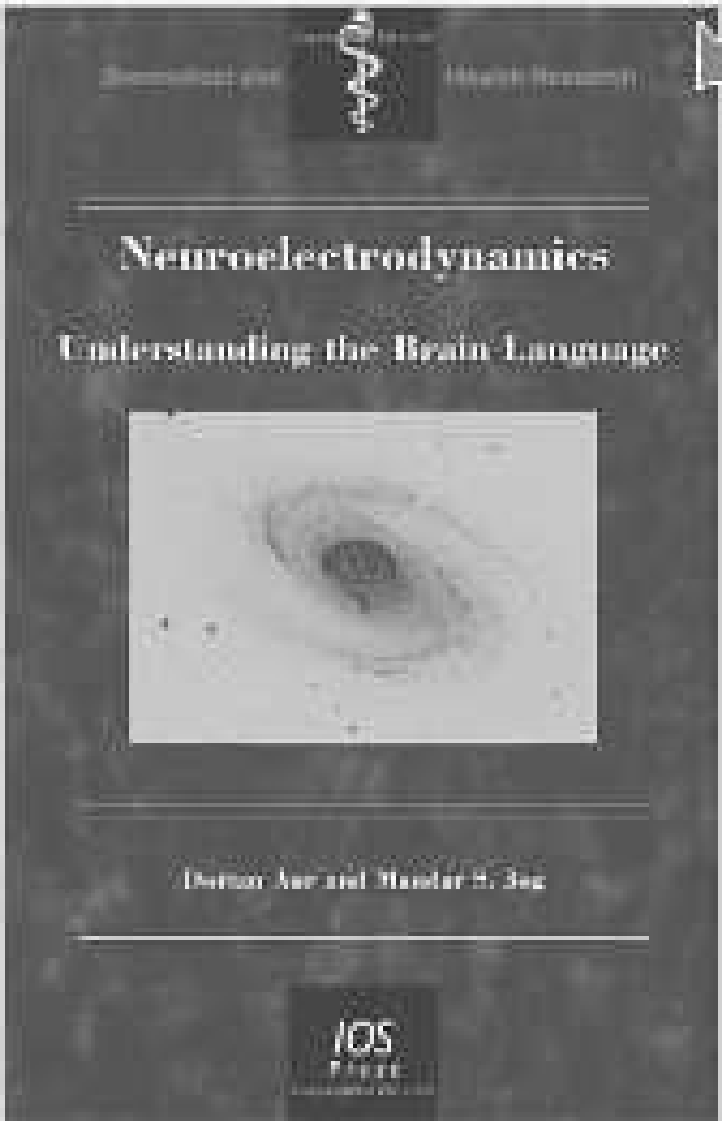


Many unresolved questions in PD

- As a degenerative disease, no pathogenic process has yet been identified as the reason for why neurons die – e.g. asymmetry
- In terms of the mechanisms, many fundamental observations have been made that point from "very far away" towards processes
- These processes share commonality with other degenerative disorders
- Currently, there is no consistent and robust common theme to these conditions

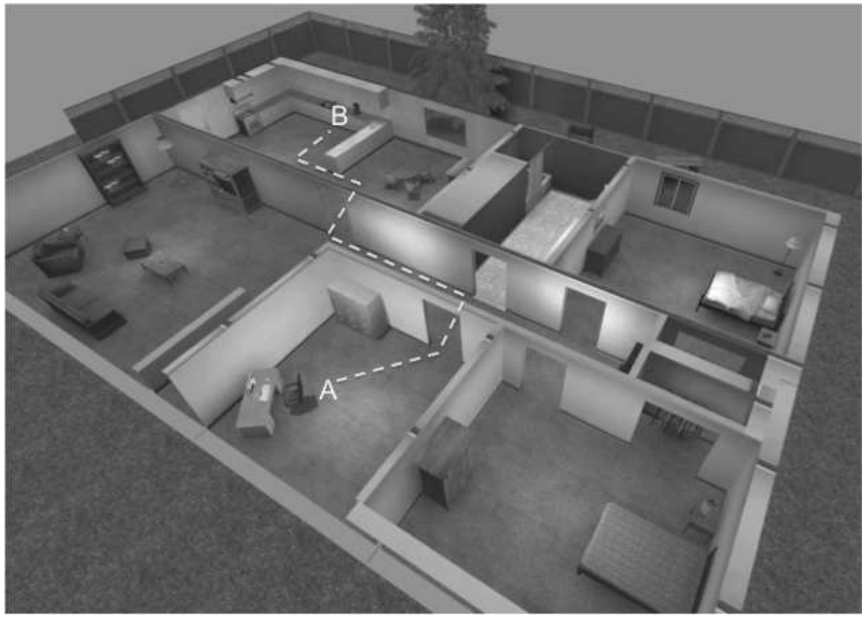
Too many features

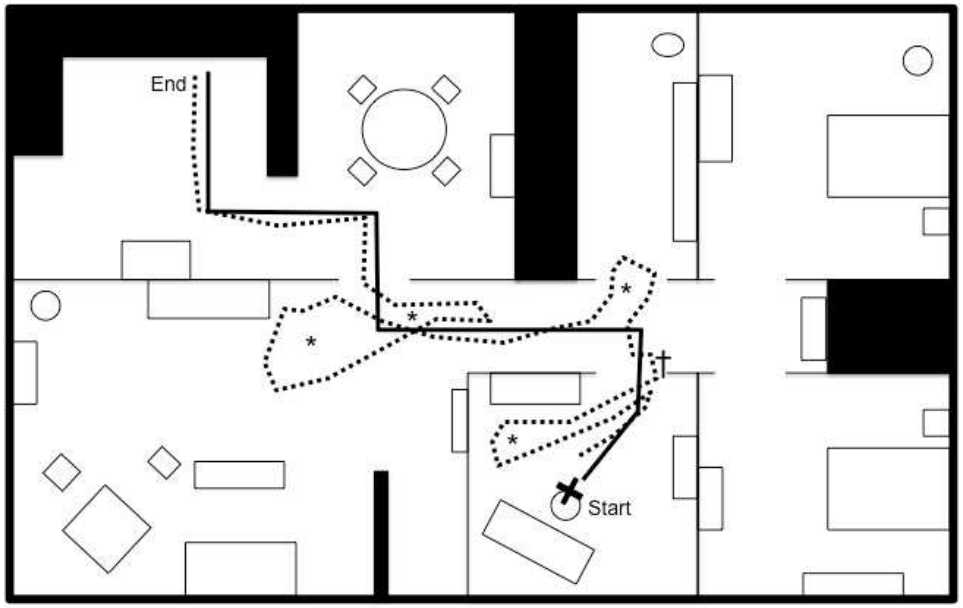
- Areas of vulnerability are diffuse
  - For example in PD, everything from SN to gastrointestinal splanchnic neurons are affected
- Large variability in the pathological features including
  - Protein accumulation
  - Architectural simplification – at all levels
  - Cellular connectivity disruption
  - Actual cell death
- And these are just a few variabilities….

At the other end

- At the other end, specific physical manifestations of disease are clearly seen
  - In PD, many symptoms with immense variability within them are indeed the hallmark of disease
- Well learnt and established tasks fail, not simple movements but goal directed and functionally relevant movements
- This implies that whatever is happening at the pathological level, the system fails in its ability to process information adequately.
- The resultant is task failure.

What I mean by task failure





Pathology and phenotype NOT linked

- It seems clear then that the measurement of all of these variabilities, from the level of the gene to the phenotype may be a very difficult
- Indeed we may never be able to understand, by experimental measurement of pathology in the system, what and why goes wrong in the system
- Finally, phenotypic observations are probably not related directly in any way to the underlying pathological processes –
  - degeneracy and multifunctionality makes this happen

Bottom up, not top down…..

- Which tells me that a top down approach, whether it is electrophysiological , immunochemical or otherwise will always be by itself inadequate in understanding the brain language
- A synthesizing bottom-up approach does exist and is being applied to a small extent within neuroscience – small amount of modeling work
- This approach takes into consideration the basic fundamentals of biological systems – thermodynamics, multi-stability and finally Neuroelectrodymanics

The Thermodynamic brain

- Survival being the basic instinct, all systems are expected to obey the laws of thermodynamics and especially the second law
- The biological systems, and in our case of interest, the nervous system is may be able to break the requirement of the second law
- As such, the system is able to import and export entropy at a cost
- This cost is fuelled by metabolism of substrate

The Thermodynamic brain

- In order to utilize this concept, all components of the nervous system at all levels become locally efficient
- Vascular flow and branching, delivery of molecules including glucose and oxygen species follow this
- In essence, the system builds itself as a multitude of fuel efficient attractors from the lowest level to the highest, i.e. from genotype to phenotype and indeed behavior

The Thermodynamic brain

- In evolution, this hierarchical, locally maximized systems have come together to form a dynamical and complex system
  - This is the concept of local synergies that the nervous system is especially good at
  - Local synergies are at all levels membrane proteins, dendritic branching, gene transcription among the many others
  - This means that perturbations within the system are compensated by even remote effects that may not be visible directly e.g. at secondary and tertiary dendrites

Multi-stability and Non-equilibrium

- These thermodynamically synergistic states result in two very important features, vital to the nervous system
  - Multistability at every level
  - Non equilibrium states with phase transitions
- Both these features allow the nervous system to form spatial and temporal patterns at successively complex levels
- The multistability state

Multi-stability and Non-equilibrium

- These patterns are thermodynamically neutral or more efficient
  - This is the concept of self-organized criticality (Chialvo *Nat Physics 2010)*
  - The self organization may occur in the form of phase transitions that are multi-dimensional, multistable and sudden
  - Such transitions may represent tipping points or instabilities
  - As such at every level, from charge (faster, microscopic) to macroscopic attractors may form

Multi-stability and Non-equilibrium

- The rule of energy minimization persists within this system
  - This intrinsically leads to self-organization since each level reaches a particular point of complexity
  - It is then enslaved by the next level and so on
- The "switch" from one system to another occurs as a process of dynamic, and unstable phase transitions
  - Once the transition occurs from state A to State B, a collective of attractors builds within the self organizing structure
  - Inherent non-linearity and fluctuations within this system makes more and more likely that new constructs are built

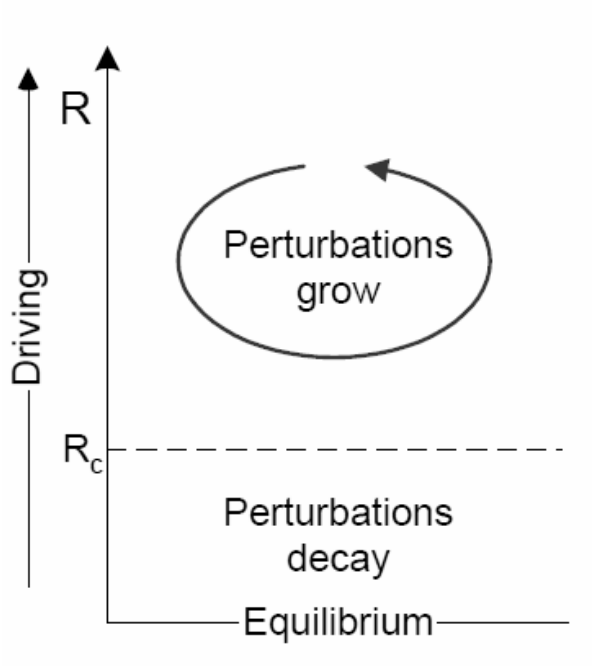
So what are the contributors?

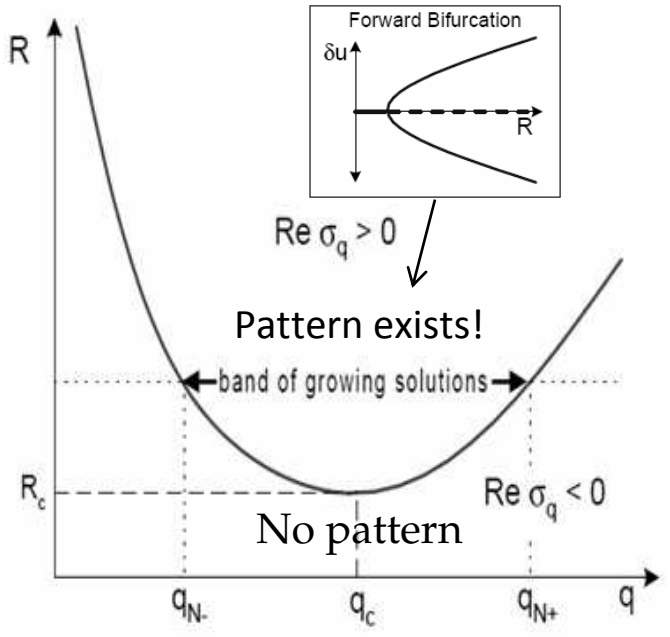
- This is an extremely difficult question to answer….
- At an anatomical level the ultra-structure of the neuron itself is dependent on these very rules
  - Dendritic branching, axonal arborization, transport ultrastructure, synaptic ultrastructure , neurotransmitters, ions, channels….to name a few

Self-organization and pattern formation

Self-organization: A mechanism that nature uses to form spatial and temporal patterns in its collective order and opens local interactions to exchange energy, matter and information with environment. Many systems self-organize towards a state which is barely stable.

Pattern formation: A spatially organized structure in systems that are driven and dissipative , which occurs in the region of the growing perturbation i.e., far from equilibrium (modes with nonzero wave vector).

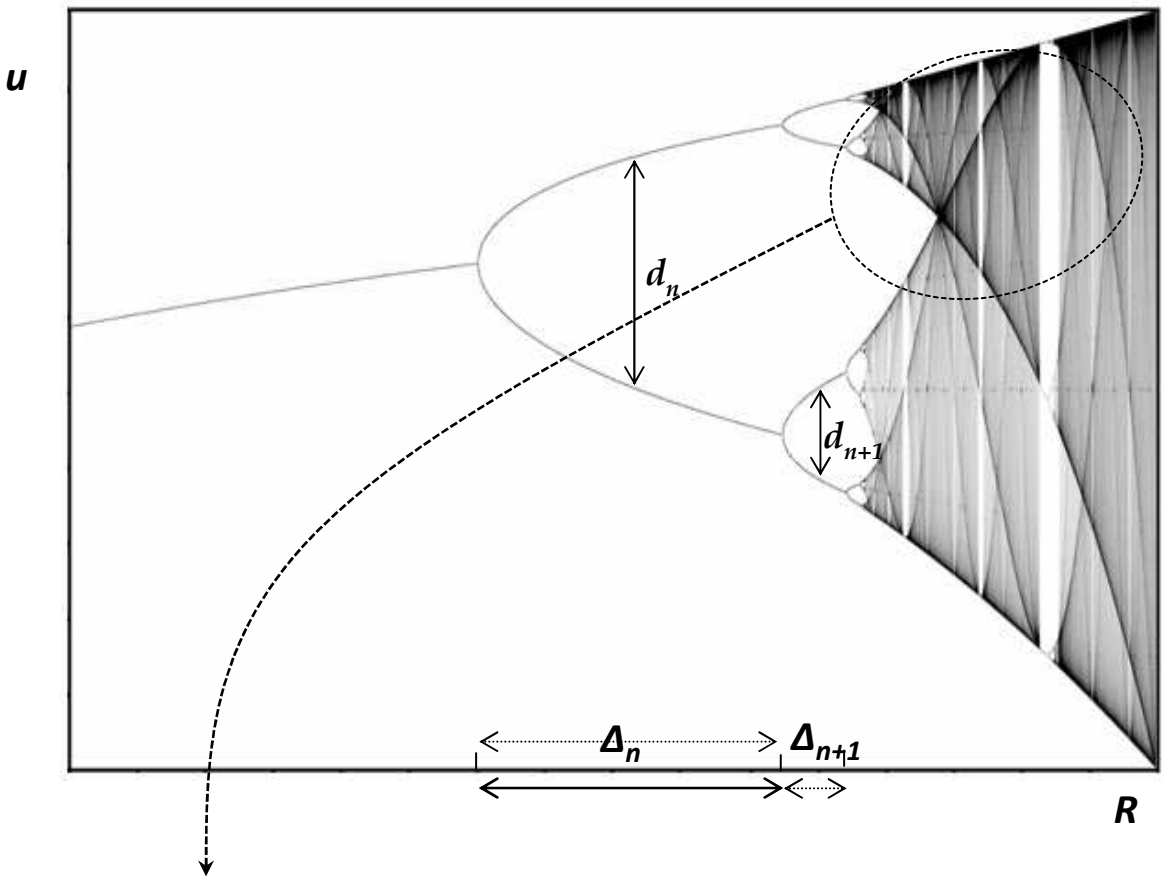




What do these do?

- Taking synchronization into account, dynamic attractors formation in spatiotemporal domain may be a way to code information in response to any input.
- Maximal number of attractors at criticality outcomes maximal information storage capacity.
  - At the finest level and therefore the fastest these include charges that are ubiquitous yet non-equally distributed in the nervous system

A complex form of bifurcations→ Route to Chaos



$$\delta = \underset{n\to\infty}{\mathrm{Lt}} \frac{\Delta_n}{\Delta_{n+1}}$$

$$= 4.669201609103\ldots$$

$$\alpha = \underset{n\to\infty}{\mathrm{Lt}} \frac{d_n}{d_{n+1}}$$

$$= 2.5029078750957\ldots$$

Degeneracy, hysteresis, dynamic instabilities, etc. .. related to the chaotic mode can also be extracted in order to quantify the phase transition
– Require to apply **Synchronization** in order to characterize the dynamic states.

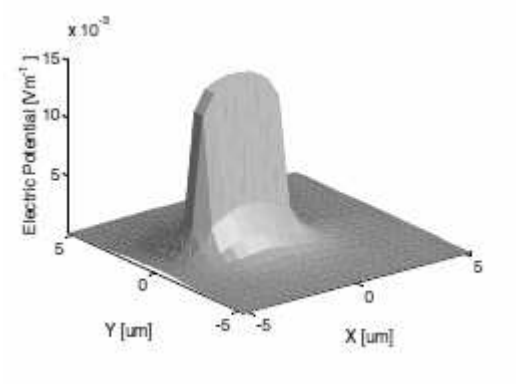
Feigenbaum *et. al.* (*Journal of Statistical Physics* 1978)

The transitions

- In this construct of multi-stability and non-equilibrium, we have tried to use this lowest level of assembly, charge, to investigate transition to and from multistable states
- In this construct we used the movement of a charge during action potentials as representing the carrier that is used for information
- This charge flux is then used to demonstrate how state changes can occur within the system

- Charges in motion generate an electric potential that is simplistically modeled as

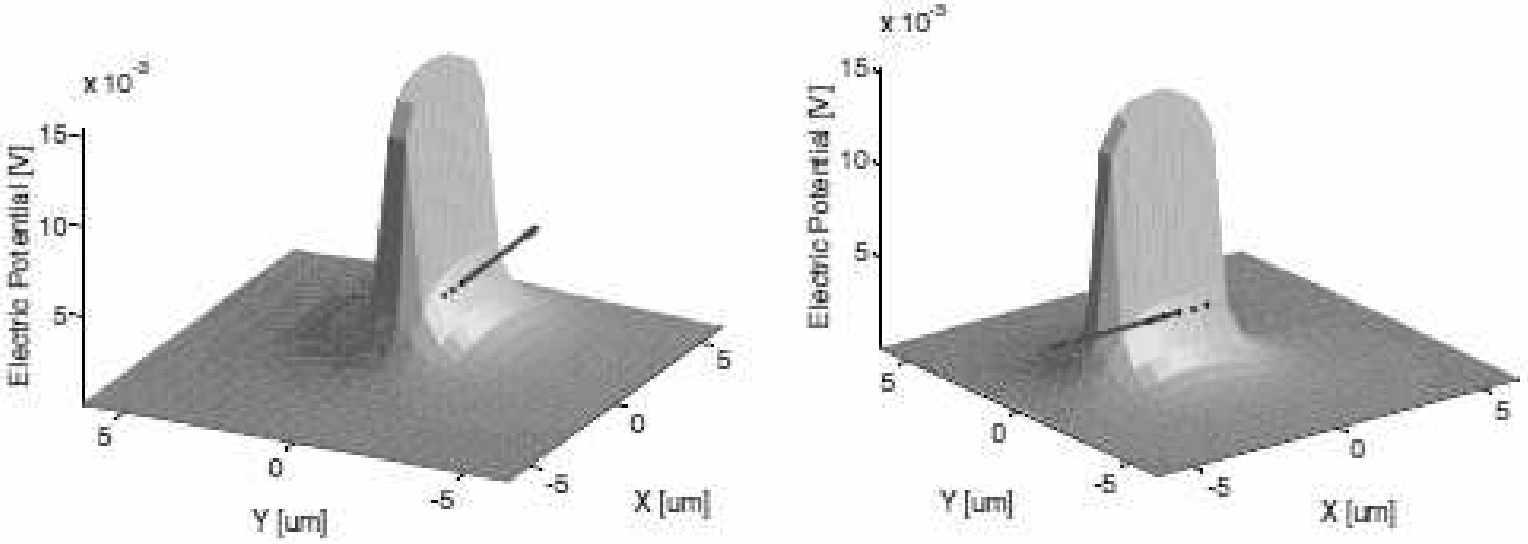
$$V_{\sum} = \sum_i \frac{q_i}{4\pi\varepsilon r_i}$$



- However, this set of charges distribute in the local space under the influence of the such dynamic fields

Directionality of charge flux

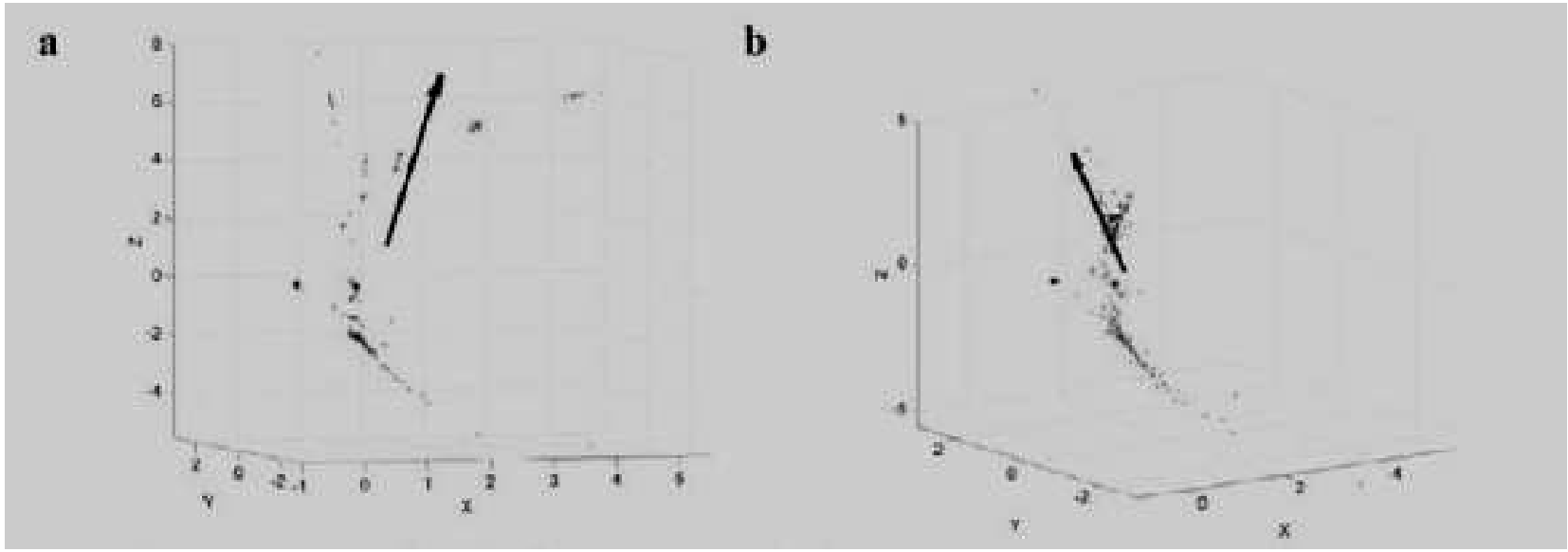
- Charge dissipation can then be studied in terms of the construct of multistate and non-equilibrium conditions as having the property of directionality of propagation



The paradigm

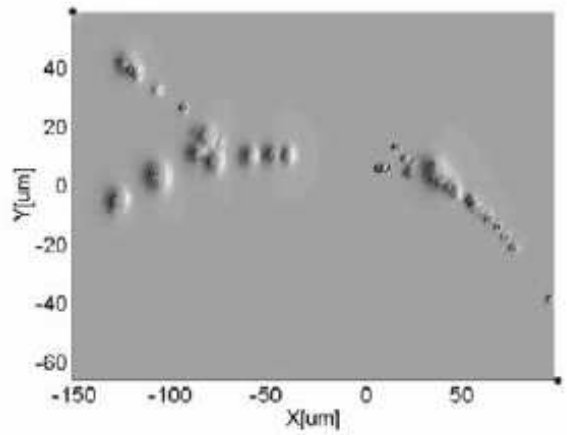
- Using ensemble tetrode recording
  - We recorded from the dorso-lateral striatum in rodents
  - Animals were performing a learning task on a T-maze
  - Data were filtered and gathered continuously while multiple trials of data were acquired
  - All data was in the spike domain
  - Data was analysed using standard spike sorting and analysis methods

- We then applied this analysis of spike directivity to every spike recorded during this behavioral task during learning



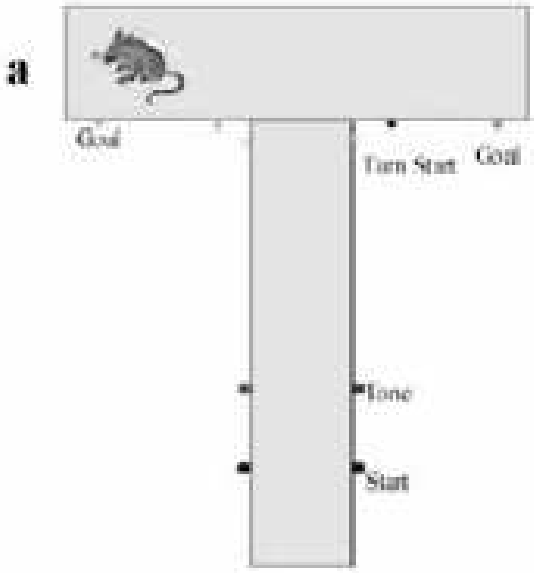
- A charge density map for every spike can be computed using a variety of techniques for each spike

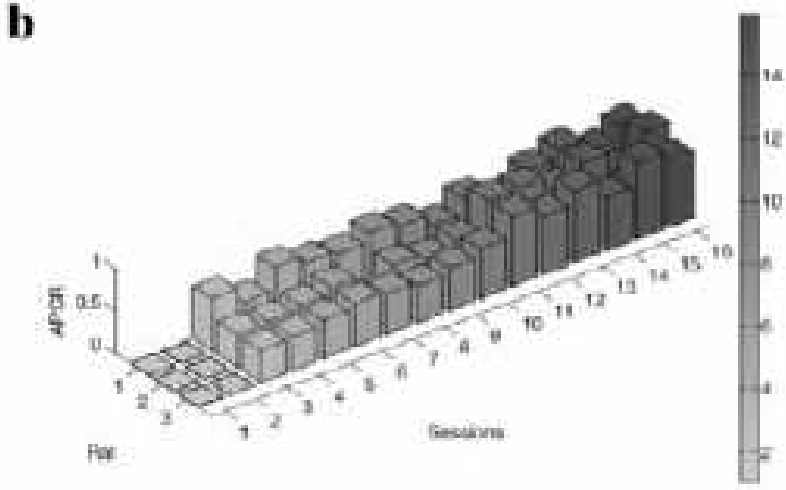
a) Perform the ICA algorithm for all four channels
b) Construct the transformation T_1, as the law of cosines $u_i=T_1(s)$.
d) Compute the position p_k of electrical sources.
e) De-bending by constructing a symmetric plot.



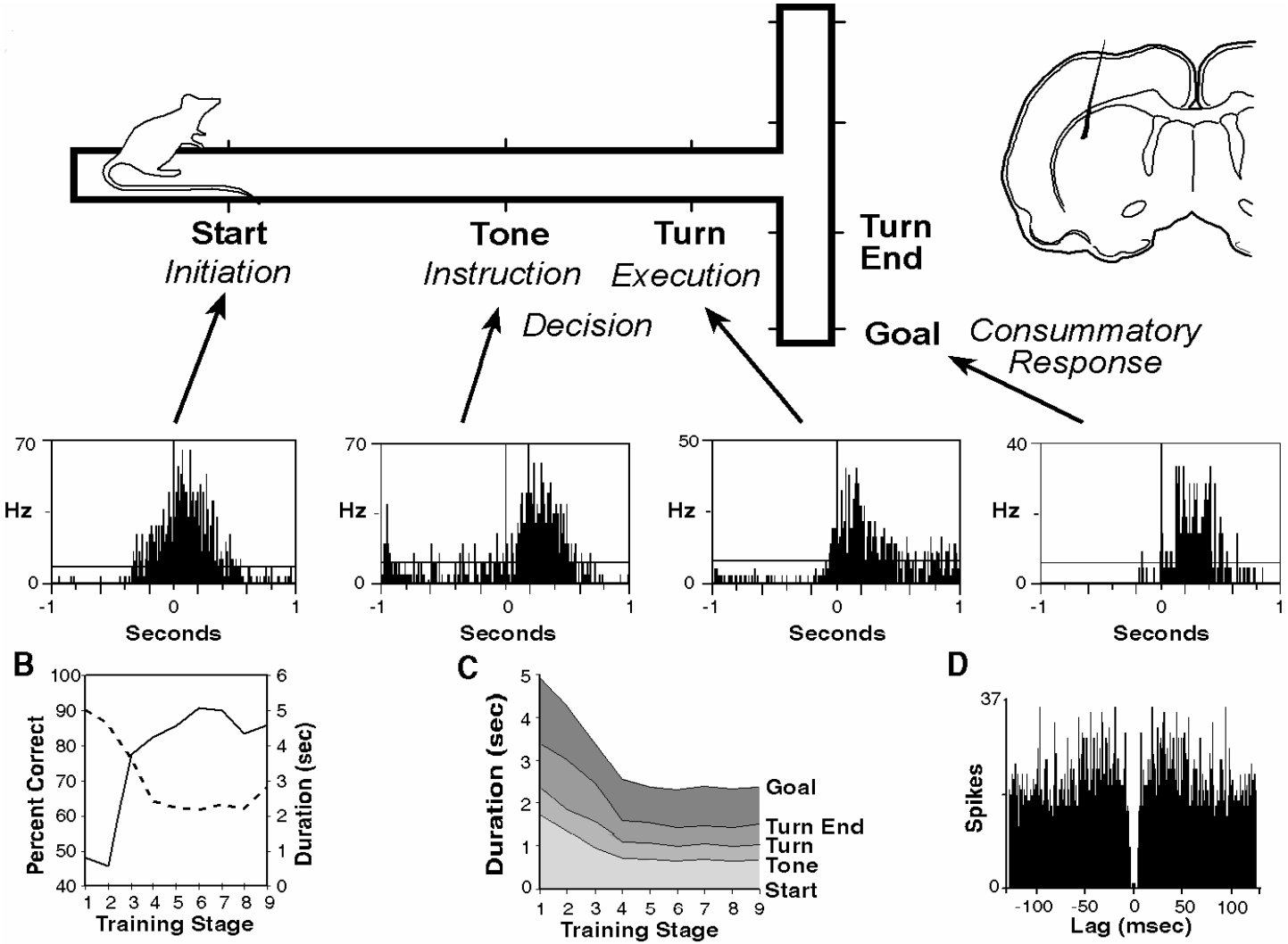
Application to the learning task

- T maze task with task acquisition over time
- Approximately 10 days of learning





Striatal "clumps"



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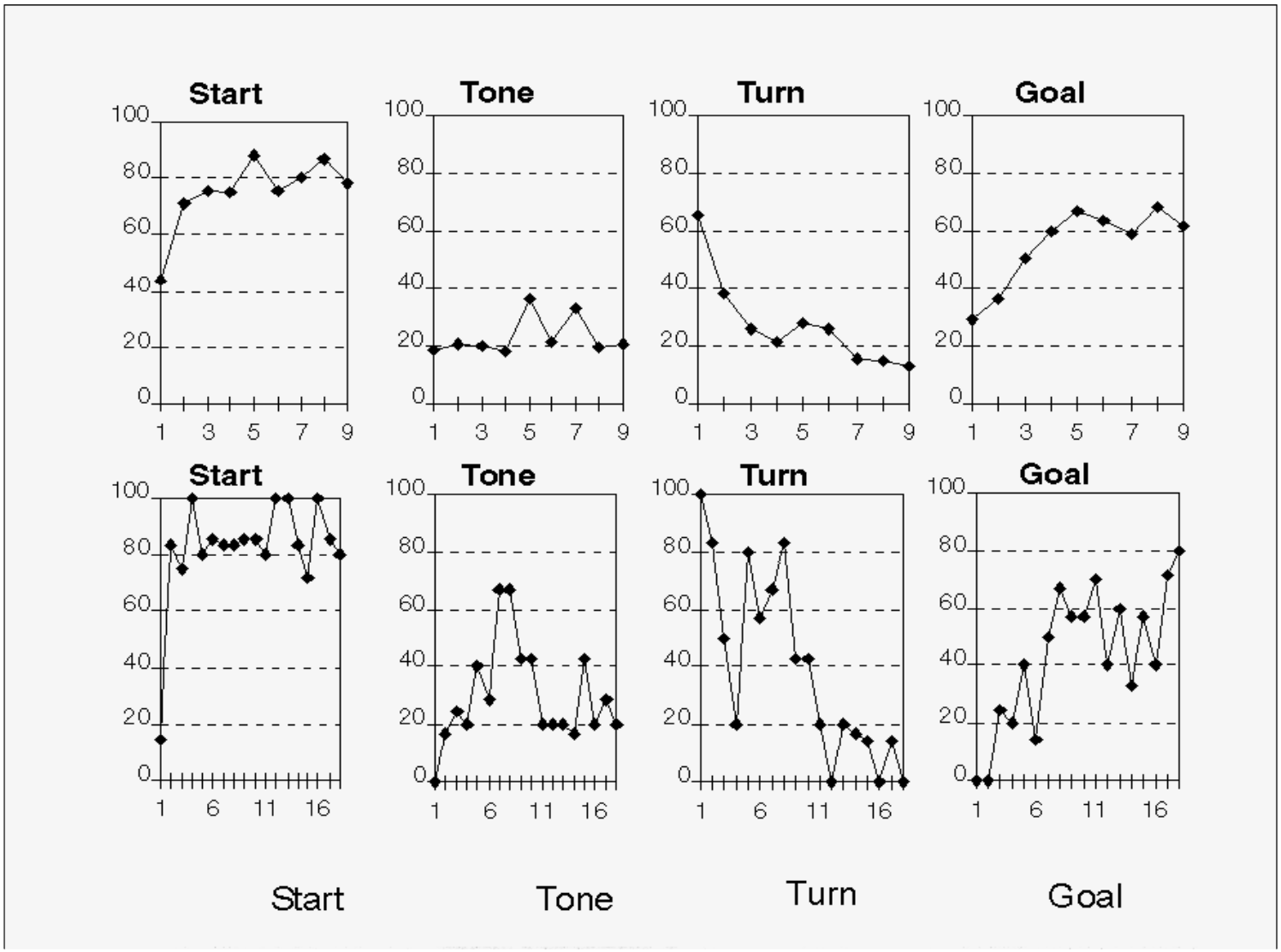
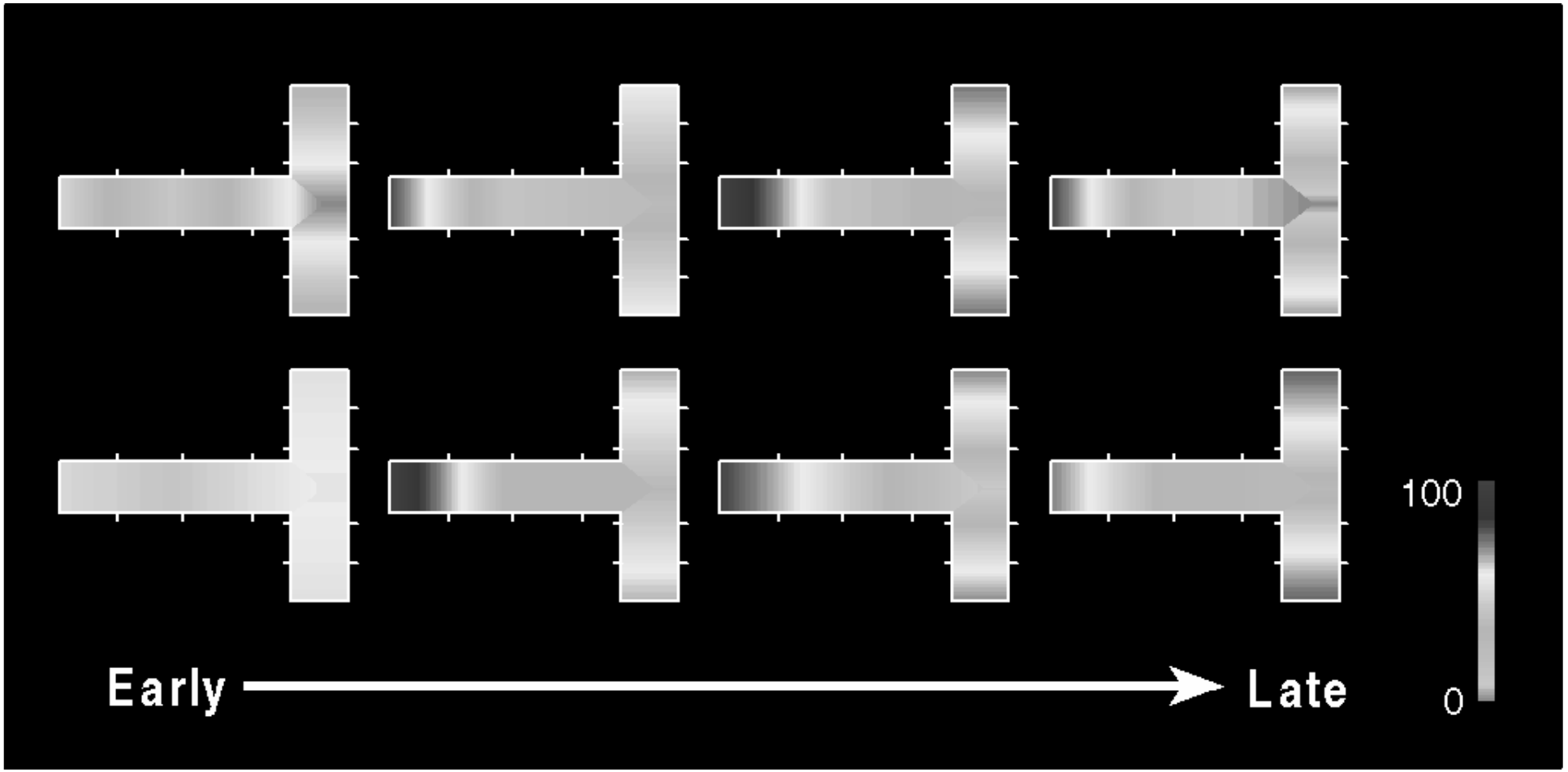
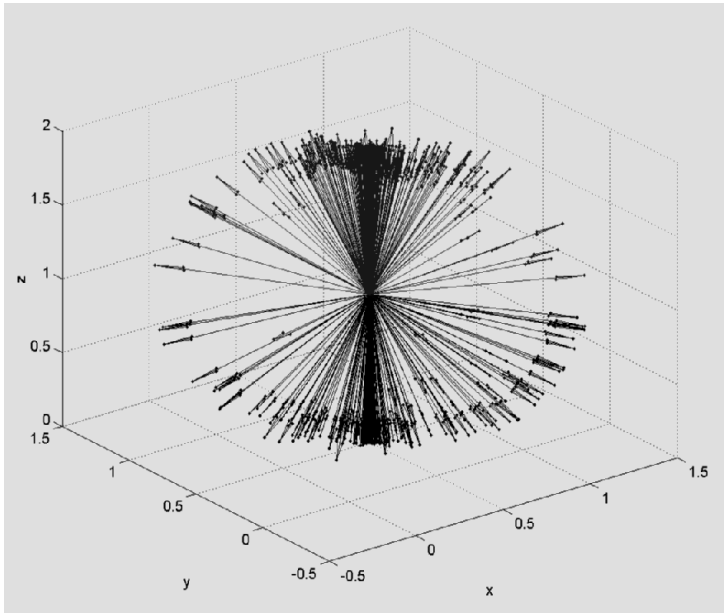
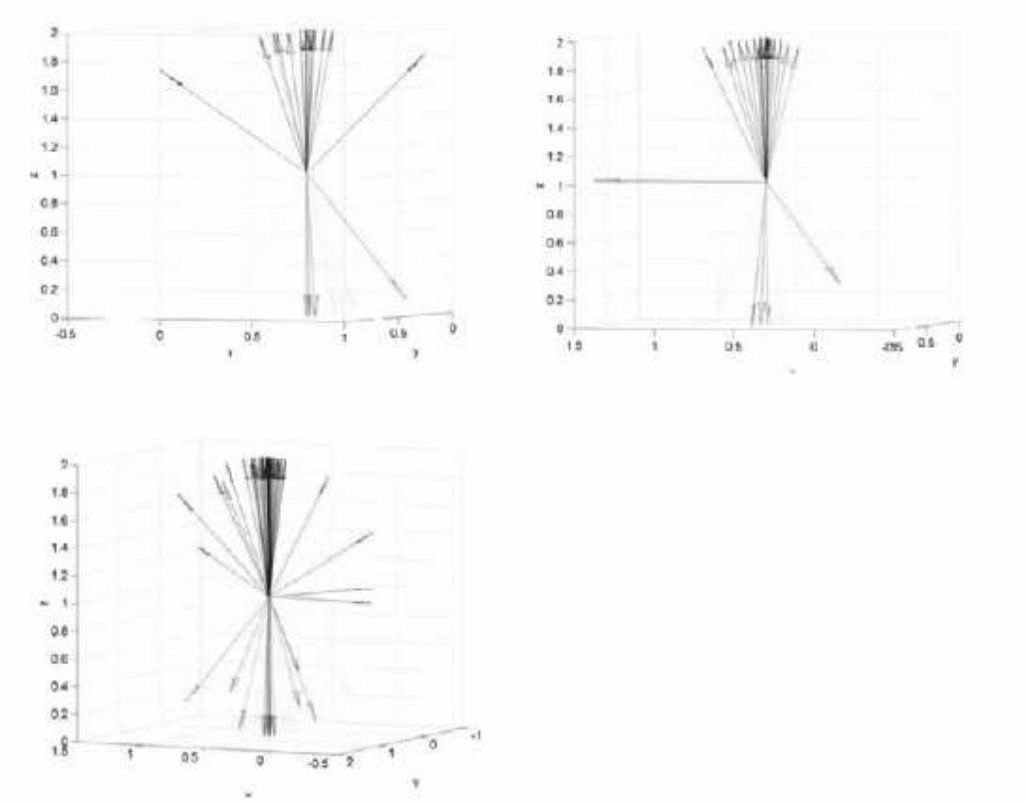



100
0
Early
Late

Multistable to Bistable transition





From charge to behavior

- The conjecture then is that even at the fundamental level, charge, which is a carrier of information shows organization
- This organization in terms of flux seems to follow a transient, bi-stable pattern a reflection of a local maxima.
- What drives is the demand for behavior which changes the system from non-equilibrium to transient “equilibrium” locally
- This state is thermodynamically expensive and is transformed into internal entropy H_i

- The transfer of these patterns into internal independent entropy dynamics is the representation of learning

- Can we see this learning in the behavioral world?

Learning in Three Phases

Early learning phase , learning begins low MI values

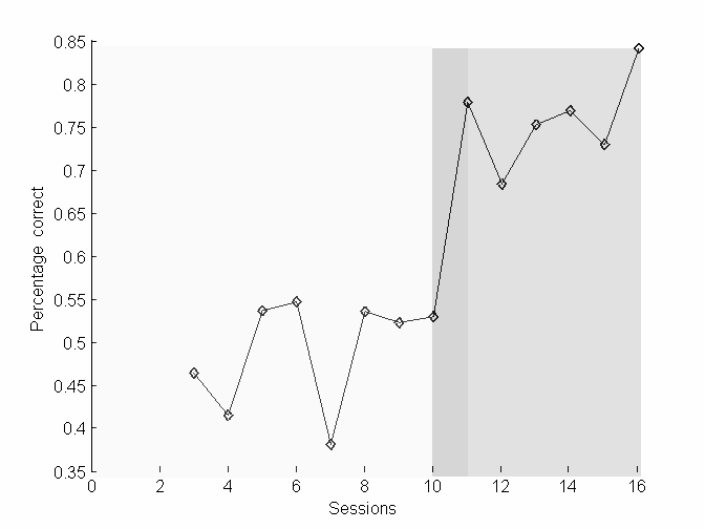
Task-acquisition phase -rapid increase in MI

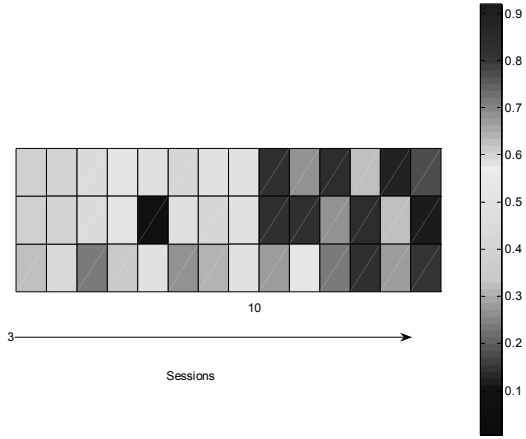
Over-training phase MI stabilization

From a behavioral perspective

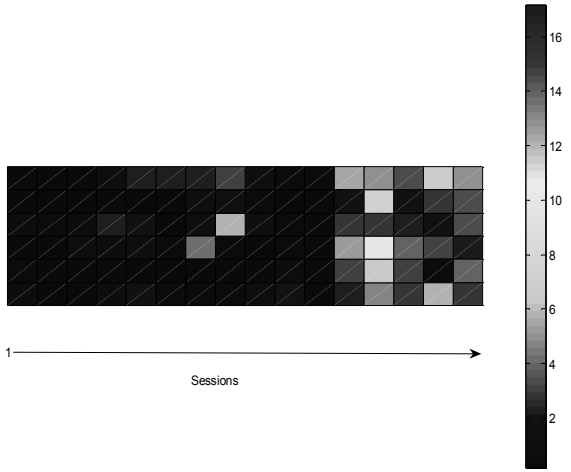
- The mean percentage correct before session 10 was 48%
- It is 76% after session 12.
- This is a 1.58 fold increase in the percentage correct behavioral responses between these two phases

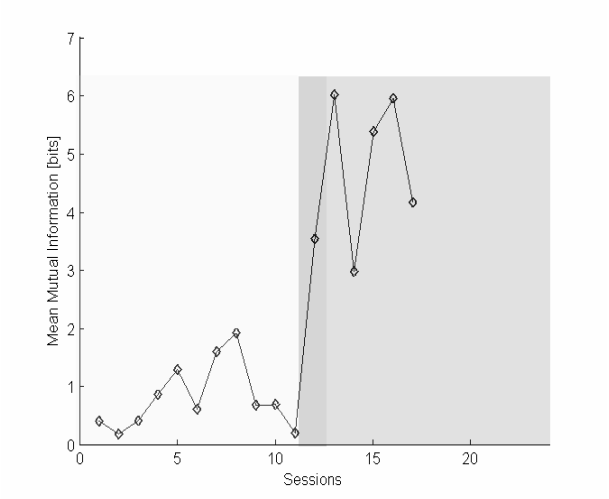
What do we see in behavior? – The "AHA" moment

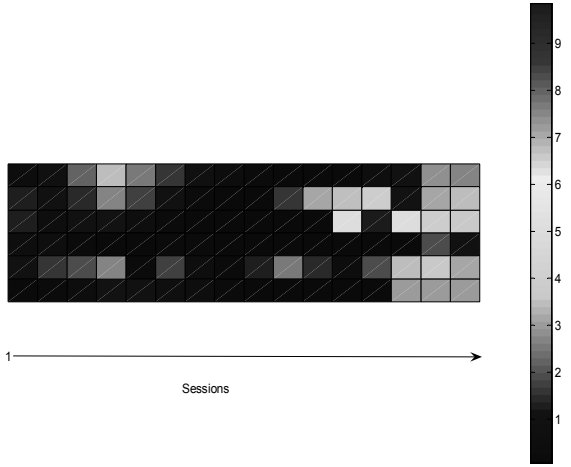


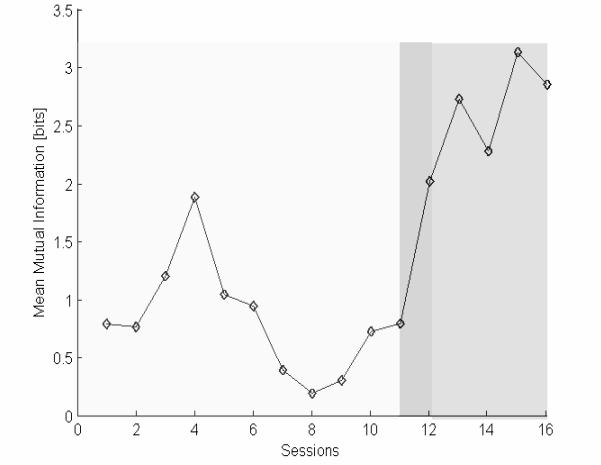


In terms of information within the network









Now computing the actual amount of information in bits

Pre-tipping	Post-tipping	Percent change
0.10±0.5	1.590±0.81	1481%
0.81±0.5	4.891±0.3	600%
0.820±0.49	2.59±0.44	313 %

And now to conjecture….

In this context, what happens in disease?

- Among the processes that are implicated, a form of metabolic damage has always been used as an important contributor
- This “oxidative stress”, resulting from many different species such as oxygen free radicals are felt to “cause” cell death
- Unfortunately, the steps before and after are missing and hence why and how this happens has remained a mystery

The thermodynamic concept

- One way of thinking this through is that the neurons metabolically produce abnormal toxins and destroy themselves, (genetic)
- Another is that an exogenous trigger that causes this to occur (environmental)
- However a common feature within this construct is the concept of thermodynamics of the system

In Parkinson and other degenerative diseases

- The system, and the constituent cells especially neurons start on a pathway of metabolic failure
- In this regard, the neuron faces a loss of multistability at multiple levels
- Whether in PD, this begins at the stage of the mitochondria or as in ALS, at the level of failure of the tubular transport systems, is an unknown
- However, the conjecture is that at least one or more system reaches equilibrium

In Parkinson and other degenerative diseases

- In order to attempt a return to multistable state, then requires energy expenditure.
- This comes at a cost to other systems within the cell
- Some of this may be translated to maintaining dendrite integrity, some to protein chemistry, membrane structure, and many other subsystems
- Some systems are more capable of handling this than others

In Parkinson and other degenerative diseases

- Which ones begin to themselves start reaching an "equilibrium" state then simply a matter of their constituent properties, local environment and for the lack of any other word…luck?
- Accumulation of protein is one such manifestation of poor clearing
- This then becomes an unstoppable process once a critical stage of equilibrium occurs
- The highly non-equilibrium multistate system is converted to an equilibrium state

In Parkinson and other degenerative diseases

- This is when we may start to see the epiphenomenon of synchrony at large levels internally and in EEG style recordings.
- Since the disease insult is relentless and continuous, the disease is progressive
- The system is unable to reach a state of multistate and so transitions become impossible
- Many aspects then become locked within the system

Many equilibria

- This state of many subcomponents of the system reaching equilibrium states is now fatal.
- The second law of thermodynamics, which only held locally now becomes global
- The boundary conditions are now limited and the system becomes gradually enslaved with reducing attractor states
- Solutions are limited and both biologically(thermodynamically) and otherwise there is failure

Thermodynamic collapse

- In an attempt to reduce the thermodynamic load, many compensations occur
  - The neuron reduces its load by dendritic simplification, others increase firing, some sequester material and accumulations result
  - Regional differences, local and remote effects occur and there is essentially a progressive thermodynamic failure
  - Phenotypic manifestations occur as disease

Summary

- The nervous system is organised based upon thermodynamic laws and those of nonequilibrium and multistate
- Transiently, at many levels, local maxima that result in a stable state exist but rapidly convert to internal entropy state
- This non-equilibrium and desynchronized state remains similar in aging, but will equilibrate with disease
- The progressive transform from non-equilibrium to equilibrium may be the underpinning of disease