Computational modelling of Alzheimer's disease
RSMG 5 (progress report)

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1 Work done so far

1.1 IJCNN 2011 paper published

The experiments outlined in RSMG4 (different connectivities, differing sets of patterns used for compensation, and tau lesioning) were presented in a paper at the *International Joint Conference on Neural Networks, 2011* in August in San Jose, California and published in the IEEE conference proceedings (Rowan, 2011).

My attendance at the conference also enabled me to meet several researchers within the general field of computational neuroscience, and to examine some of the many and varied approaches currently being taken in research in this area. My specific findings will be reported later in this section.

1.2 Scale-free connectivity

It was suggested at the last thesis group meeting that scale-free ("hub-like") connectivity should also be examined alongside the small-world, Gaussian and flat-random connectivities examined in the IJCNN paper. This method of connectivity was implemented within the Ruppin and Reggia model, but the results were disappointing: under the existing paradigm of using the measure of *overlap* between stored and retrieved patterns to determine the performance of the network as it is lesioned, the network was never able to achieve anything close to 100% overlap even when only one pattern was stored.

A literature search revealed that this effect is both known and understood (McGraw and Menzinger, 2003; Lu et al., 2006; Torres et al., 2004). Scale-free networks consisting of 'hubs' and 'leaves' are good partial pattern recognisers at the regions close to the hubs with highest connectivity, but poor at retrieving whole patterns. McGraw and Menzinger (2003) explain that "the hubs are able to distinguish clearly among a large number of patterns even if the pattern reconstruction is incomplete i.e., limited to the hubs. The lower rate of errors among the hubs is not surprising in view of the fact that their input comes from a larger number of nodes". The authors also consider the implications for biological brain networks.

Before such a topology could be used in the Ruppin and Reggia model framework, changes would have to be made to the measures by which network performance during lesioning is recorded. McGraw and Menzinger (2003) provide a *partial overlap* measure which could be applied both to scale-free and more regular networks to give a suitably unified measure of performance. This could make an interesting extension to the findings in an Alzheimer's disease-like context reported upon in the IJCNN paper, but the amount of work required for a small pay-off in terms of expected results is relatively large, and particularly when considering that previous research has already analysed the effects, and that small-world networks (already analysed in the IJCNN paper) are generally accepted as a good model for brain connectivity, it was not considered worthwhile for inclusion in a paper at this point. This decision may yet be revisited

to provide additional results for the thesis, however.

1.3 Frontiers journal paper published

Much of the time since the last Thesis Group meeting has been spent preparing a paper for the open access journal *Frontiers in Computational Neuroscience* entitled "Information-Selectivity of Beta-Amyloid Pathology in an Associative Memory Model" (Rowan, 2012), in which I investigate the theory of Small (2008) that synaptic compensation drives the progression of beta-amyloid (Aβ) pathology in Alzheimer's disease. The theory suggests that (in accordance with the mechanism of synaptic compensation previously discussed in my IJCNN paper), neurons which lose connectivity due to the death of neighbouring neurons must increase their activity levels in order to compensate for this. This increased activity, according to Small, then makes the neuron more susceptible to Aβ: "An Aβ-induced decrease in synaptic signalling should cause a compensatory increase (scaling) in the excitability of adjacent healthy neurons. The increase in excitability would, in turn, be expected to raise intracellular calcium levels in the healthy neurons that are connected within the same network. Because calcium is a key mediator of Aβ neurotoxicity, an increase in cytosolic calcium could increase the vulnerability of the healthy neurons to Aβ toxicity" (Small, 2008).

The hypothesis presented in the *Frontiers* paper is that, as those neurons which are least strongly-connected to others suffer the greatest proportional drop in average activation when a neighbouring neuron dies, and that weak and/or diffuse connectivity in neural networks tends to imply a lack of significance of that particular neuron, there may be evidence to suggest that neurons with low overall contribution of information to the network will be the first to succumb to Aβ pathology.

The results, as presented in the paper using an information theoretic approach, show that in the Ruppin and Reggia model the simulated beta-amyloid pathology initially selectively targets neurons with low informational contribution to the overall performance of the network, but that it targets neurons with increasingly higher significance to the network as the pathology progresses. The arguments in the paper have been generalised to other types of networks, to show that it is not limited to just the Ruppin and Reggia model. The results additionally provide a possible explanation for the apparent low correlation between amyloid plaque density and cognitive decline in the early stages of Alzheimer's disease, which is a major issue of concern to neuroscientists investigating the "amyloid hypothesis" of Alzheimer's disease (Hardy and Selkoe, 2002; Savioz et al., 2009; Minati et al., 2009).

1.4 Pyschological testing of models

The Ruppin and Reggia model, so far, has only been used to examine the performance on pattern retrieval during lesioning, as an analogy to memory loss in Alzheimer's disease. Whilst memory retrieval deficits are a key symptom of

Alzheimer's disease, they can also be observed in many other disorders, so this symptom alone is not an identifier for AD. Because of this problem, the previous Thesis Group meeting saw discussion of submitting more computationally powerful network models, such as reservoir networks (possibly analogous to cortex layer 5 pyramidal neurons, which have a designated "output layer" with internal-only neural reservoirs for "processing") to some of the clincal tests commonly used to diagnose Alzheimer's disease. Such tests include the Mini Mental-State Examination, and the Cambridge Neuropsychological Test Automated Battery (CANTAB).

1.4.1 Mini-mental state examination

The MMSE is the standard clinical test for Alzheimer's disease (Folstein et al., 1975). From the RSMG3 thesis proposal:

"It is a basic question-and-answer pyschological test designed to evaluate the cognitive performance of patients over a number of types of tasks. Some of the questions in the MMSE require advanced reasoning capabilities and knowledge within a global context ("what is the current month?" or "in which street are we?"), which are likely to be beyond the capabilities of even an advanced neural model for the purposes of this work. Other similarly 'hard' questions are those requiring the patient to name a given object when pointed at, or drawing a clock face with the hands pointing to a particular time. [...] Although the MMSE correlates well with the presence of dementia, it is not specifically a test for Alzheimer's disease as this depends on the underlying pathology. However, performance of the models in a manner showing similar cognitive decline to AD patients could be a good indicator of the validity of the models on the symptomatic level."

1.4.2 CANTAB

The *Cambridge Neuropsychological Test Automated Battery* (CANTAB) is a language-independent computer-administered series of cognitive tests for a range of disorders, and has been shown to be more specific to the underlying pathology of various disorders including Parkinson's and Alzheimer's disease than the MMSE, due to the objectivity built into the testing system in contrast with the MMSE's reliance on a clinician's subjective opinion (Sahakian et al., 1988). The automated nature of the tests may additionally make them more suitable to an artificial neural network model-based testing scenario.

Relevant tests Each of these tests has been shown in the literature to be sensitive to Alzheimer's disease.

PAL Paired Associates Learning is one of the CANTAB tests specifically used to test for Alzheimer's disease and other dementias. In Paired Associates Learning, "boxes are displayed on the screen and are opened in a randomised order. One or more of them will contain a pattern. The patterns

are then displayed in the middle of the screen, one at a time, and the participant must touch the box where the pattern was originally located. If the participant makes an error, the patterns are re-presented to remind the participant of their locations." PAL tests visual memory and new learning, both of which are affected in AD. [1]

To implement PAL computationally, an associative network (e.g. Ruppin and Reggia) could be trained on abstract binary patterns. A linear readout layer of six neurons, each representing one of the six possible spatial locations of the patterns, could then be trained to produce the correct 'box' location for each pattern. Clearly, when learning patterns, both the associative network and the readout layer must be trained simultaneously. This architecture has some parallels with the concept of a reservoir network, in which a randomly connected and untrained population of neurons projects inputs into a high-dimensional space, and then feeds into a linear readout layer. In the case of PAL, the 'reservoir' would be trained, but only inasmuch as it is able to provide known activation patterns for given input cues, just as in a reservoir network.

An interesting extension could be to present patterns which were not seen at all, and for the network to either recall a 'no pattern' response, or to correctly identify that the pattern was not displayed (e.g. via activation of a seventh neuron in the readout layer).

MSVS Match to Sample Visual Search can help to differentiate between Parkinson's disease and Alzheimer's disease, and also between Lewy Body dementia and Alzheimer's disease[2]. In this test, a complex target pattern (which varies in dimensions of colour and shape, and is deliberately abstract to prevent possible associative named-object learning) is presented to the patient along with one identical and a varying number of other similar stimulus patterns. The patient is then required to select the identical stimulus pattern to the target pattern, discarding those other patterns which were similar but not identical.

DMS In Delayed Matching to Sample, a target pattern is presented briefly and then removed before a number of similar (and one identical) stimulus patterns are presented, with a varying level of delay between the two presentations. This test includes the recognition aspect of working memory: in AD patients, the memory trace fades more quickly than in Parkinson's patients, and DMS "tests for damage in the medial temporal lobe area, with some input from the frontal lobes" [3].

DMS could be implemented in a basic associative network such as the Ruppin and Reggia model Ruppin and Reggia (1995) as a simple analogy to working memory. The network holds the learned target pattern,

[1] http://www.cantab.com/cantab-tests-paired-associates-learning.asp
[2] http://www.cantab.com/cantab-tests-Match-to-Sample-Visual-Search.asp
[3] http://www.cantab.com/cantab-tests-delayed-matching-to-sample.asp

but over a relatively short period of time the learned pattern becomes corrupted and cannot be recalled correctly.

The target pattern is presented to the network via the external inputs, as in the standard Ruppin and Reggia model, but when repeatedly representing the training pattern for subsequent learning iterations, the training pattern could be altered slightly on each iteration by cumulatively adding increasing amounts of noise to it each time. The delay between target and stimulus presentation in the test could then be modelled by extending the period of this "noisy" learning by a proportional number of iterations.

After the appropriate length of time (i.e. the number of iterations during which the working memory network updates with ever-noiser versions of the target pattern), a set of three similar (e.g. $\Delta < 0.25$) and one identical pattern can be presented to the network in random order, and the network allowed to converge if the pattern is found, or update until a timeout is reached to indicate a negative response.

Performance on the "number correct" and "percentage correct" measures can be obtained easily, whilst the "response time" performance could be measured by summing the average number of total retrieval update iterations over a number of trials – as the stimulus patterns are presented in a random sequence, on average the total number of retrieval iterations will reflect the performance of the network.

Reliability The various CANTAB tests have been validated numerous times for the efficacy of their role in diagnosing specific cognitive disorders, including Alzheimer's disease Bartók et al. (2001); Kim et al. (2009) and schizophrenia Levaux et al. (2007).

Lowe and Rabbitt (1998) showed that some elements of CANTAB are subject to task-learning practice effects, such that repeated taking of the test over a period of several weeks by normal age-matched subjects led to observed variance in task performance after the first iteration, particularly when an optimal strategy was discovered by patients taking the test on subsequent occasions.

Paired Associates Learning, which was developed for CANTAB by Morris et al. (1987) as a specific test for AD in contrast to Parkinson's disease, was one of only a few CANTAB tests found by Lowe and Rabbitt (1998) to have a test/re-test correlation at acceptable levels when considering "average number of trials to success", meaning that it is fairly robust to practice effects over multiple trials.

1.5 Visual category boundaries

It was also suggested in the last Thesis Group meeting that work by Mayhew et al. (2010) on the shaping of the representation of visual category boundaries through learning in aging, using a perceptual categorisation task involving concentric vs. radial dot patterns, could be relevant. However, although this

particular test could be suitable as a general task for a neural network to undertake as it is lesioned, direct relevance to possible diagnoses of Alzheimer's disease (as opposed to loss of plasticity in general aging) has proven hard to ascertain.

2 New problems encountered

2.1 Problems with abstract connectionist modelling

Feedback at IJCNN and from the reviewers of the Frontiers paper has indicated that abstract connectionist modelling in the ways explored so far is generally perceived by neuroscientists to be too far removed from biological processes to be a useful model of Alzheimer's disease (although clearly some useful observations have already been made in a generalistic way in the IJCNN and Frontiers papers in the context of "associative memory" and "Alzheimer's-like lesions").

If implementing pyschological testing such as the Paired Associates Learning test from CANTAB, it is vital that the possibility of a negative hypothesis can be supported in addition to the "pathology" hypothesis. For example, although a model could be created which degrades in an AD-like way on the PAL test, this does not mean that it is a model of AD if it also degrades in the same way on tests with specificity for different disorders such as Parkinson's disease or schizophrenic psychosis. In this case, the model would have failed to accurately represent the symptoms of AD: the model must be able demonstrate poor performance on PAL but good performance at similar levels of damage on tests such as Spatial Working Memory (which tests for prepsychosis)[4].

Each CANATB test is designed to look for damage to specific brain regions. The problem with such psychological testing is that it relies on accurate represention of whole regions of the brain and the subsequent breakdown in interactions between them. Without a comprehensive and reliable model of all of the regions implicated, accurate representation of biological processes is impossible. A form of modular architecture could be created to include all of the regions implicated in, for example, both PAL and Spatial Working Memory (SWM), but if Alzheimer's disease is simulated in this model by lesioning the areas specifically examined in the PAL test and sparing those areas tested by SWM, then even though the model could be shown loosely to demonstrate AD symptoms, nothing new is learned about the disease process as this strategy just becomes a simplistic exercise in computational implementation of known brain pathology in an abstract, low-resolution model.

In contrast, much current computational neuroscience research, such as the work presented by Damien Coyle at IJCNN 2011 (Bhattacharya et al., 2011), examines biophysical effects underlying known pathology, such as the slowing of alpha rhythms in highly detailed realistic neural network models, whilst other research in computational neuroscience such as Still (2009) focuses on information-theoretic analyses of neural networks and individual neurons. It is currently

[4] `http://www.cantab.com/cantab-tests-Spatial-Working-Memory.asp`

unclear to me how an abstract connectionist model, as used in the IJCNN and Frontiers papers, would be able to contribute significant new knowledge to the field without making use of detailed biophysical models of wider brain function, or delving into the intricacies of spiking neural models.

2.2 Utilisation of associative capacity in the brain

During the review process for the Frontiers paper, one reviewer commented that the "predictions require the networks in the brain to operate at a low loading level: Synapses that are not encoding a lot anyway are removed and thus the performance initially only drops little. I think the author has to be more critical concerning the fact that the predictions break down at high loading levels [when more than approximately 50% of the total usable capacity of the network has been utilised]. It is not enough to just state that these may be unphysiological because of noise. In fact the opposite may be true: because of the noise the capacity limit is reached much earlier and thus the real brain networks are close to the capacity limit!".

"Usable capacity" is defined here as the maximum number of patterns which can be stored before the network totally fails to retrieve patterns using a partial input cue. However, even at this 50% loading level, there is significant noise during the retrieval process. Depending on the permissible noise levels within the brain, this may infer that the "workable capacity" has already been reached.

Unfortunately, it is not easy to say at what level of loading the brain actually operates, or whether different parts of the brain operate at different loading levels. Leibold and Kempter (2006) demonstrate in a computational framework how actual information content per synapse may actually be far below theoretical optimality in the brain, but the crucial factor for the validity of my predictions in the Frontiers paper is whether information is uniformly distributed across all synapses (which would likely be the case when each synapse is operating at the maximum available capacity), or whether the distribution is varied. If there is significant variance in the distribution, then it is still plausible that beta-amyloid pathology targets the synapses with the weakest connectivity and hence, as implied, the lowest information contribution. To test this theory, however, a more detailed and biologically-realistic model than the abstract Tsodyks-Feigel'man network will be required.

2.3 Testing of information selectivity hypothesis in biologically realistic networks

It would be of interest to be able to provide a mechanism for testing the hypothesis in the Frontiers paper regarding information-selectivity of amyloid pathology in biologically-realistic computational models. Potential suitable candidate models in which the principles can be tested already appear to exist in the form of peer-reviewed journal publications with full source code available from Yale

University's ModelDB[5].

Some time will need to be spent attempting to identify the best models of appropriate brain regions and neuron types from ModelDB which can then be extended to model synaptic compensation and lesioning according to Small (2008), but if this search proves unsuccessful, an alternative approach may be to create a model from scratch in an environment such as PyNN[6] (see next paragraph). Such a model could follow the principles of work such as Bhattacharya et al. (2011), in which a set of biologically-realistic neurons connected randomly (but according to biological constraints) is stimulated by random input, and the flows of subsequent activation are analysed. Although this type of model does not perform any specific task, as evidenced by the randomly weighted connections and random stimulation, they can nonetheless provide biologically accurate simulations of the underlying neural processes.

PyNN, mentioned earlier, is a simulator-independent language for building neuronal network models which can run on a number of supported biological spiking neural simulators (e.g. NEURON[7] and Brian[8]), allowing a high degree of control over the model whilst also mitigating some of the more complex issues regarding implementation of simulated biological neurons. A further simulation environment which could be useful in this context was recently published by Richert et al. (2011), which uses a PyNN-like API and offers the added benefit of Izhikivech neurons, which are "very popular among the computational neuroscience community for being efficient, with only a few open parameters, yet supporting a wide-range of biophysically accurate dynamics" (Richert et al., 2011). Izhikevich (2004) provides a concise description of which models to use for cortical spking neurons.

Once a suitable candidate model has been identified, or implemented in PyNN or the Richert et al. (2011) environment, synaptic compensation could be implemented either artificially (by manually recording neurons' mean field activations and adjusting them as they vary over time), or in a biologically-realistic manner according to the literature (Savioz et al., 2009). It should then be possible to lesion neurons according to the beta-amyloid pathology as predicted by Small (2008) and Small (2009), and from there to investigate the information-selectivity predictions made in the Frontiers paper.

Providing there is sufficient biophysical detail, it may also be possible produce biologically-testable predictions from this model which could be used to confirm the information-selectivity hypothesis in real brains, if such an experiment were ever to be possible. This level of prediction from the model would ideally be undertaken in collaboration with a neuroscientist (from here in Birmingham or through the Universitas 21 scheme[9]) in order to gain the maximum benefit. I have recently been invited to present my research to the Neuronal Networks group in the School of Neuroscience at the University of Birming-

[5] `http://senselab.med.yale.edu/modeldb/`
[6] `http://neuralensemble.org/trac/PyNN`
[7] `http://www.neuron.yale.edu/neuron/`
[8] `http://www.briansimulator.org/`
[9] `http://www.international.bham.ac.uk/partnerships/u21/fundingstudents.shtml`

ham in February 2012, which may provide an ideal opportunity to solicit such collaborations.

3 Changes to the plan of research

Clearly, much has changed in the research plan since the RSMG4 report in April 2011. For the reasons demonstrated, abstract connectionist modelling in basic associative or reservoir networks appears to be insufficiently detailed to really be able to provide much insight into the neurological disorders within Alzheimer's disease. For similar reasons, psychological testing of symptoms within such a basic network is likely to contribute little additional knowledge to the field, as a biologically realistic model of multiple whole brain regions would be required before any true predictions could be made.

It appears that the most productive path for research during the remainder of the PhD lies in making biologically-testable predictions regarding the information-selectivity hypothesis through experimenting on biologically realistic neural models, either from ModelDB or created from scratch using a simulation environment such as PyNN or the environment of Richert et al. (2011).

3.1 Predicted final contributions to knowledge

According to the current plan of work, the following is a list of contributions to knowledge which should be present in the thesis.

- Confirmation of results of Ruppin and Reggia (1995) (*IJCNN 2011*).
- Clearer description of local field-dependent compensation rule of Horn et al. (1996) (*IJCNN 2011*).
- Effects of using recent versus remote memories during compensation (*IJCNN 2011*).
- Effects of connectivity density and strategy (e.g. small-world) on network capacity and robustness (*IJCNN 2011*).
- Lesioning strategy representing tau pathology (*IJCNN 2011 paper*).
- Lesioning strategy representing amyloid pathology (*Frontiers paper*).
- Model of Small's theory of compensation-driven progression of Aβ pathology in an abstract associative network (*Frontiers paper*).
- Information-selectivity of beta-amyloid pathology in Small's theory of Aβ progression, possibly explaining the poor correlation between amyloid plaque levels and cognitive decline in early AD (*Frontiers paper*).
- Biologically realistic simulation of synaptic compensation.

- Biologically realistic simulation of Small's theory of compensation-driven beta-amyloid progression.
- Initial confirmation or contradiction of information-selectivity hypothesis in a biologically realistic simulation.
- Potential biologically testable predictions for the information-selectivity hypothesis which could be used to look for evidence of this effect in real brains.

4 Timetable for remainder of the research

Date	*Tasks*
January 2012	Attempt to identify recent candidate models from the ModelDB which could be extended to incorporate synaptic compensation and targeted deletion according to compensation rates.
29th Feb 2012	*Present research to Neuronal Networks group in School of Neuroscience and solicit potential collaborations for research into biological predictions of information selectivity hypothesis.*
Feb – Jun 2012	[If no suitable candidate models found, implement an appropriate network in a simulation environment such as PyNN]. Implement synaptic compensation and subsequent targeted deletion in a biologically realistic model (either created from scratch or taken from ModelDB).
Jul 2012	*Teaching preparation for Intelligent Robotics module.*
Aug – Sep 2012	Obtain preliminary results from the model, and potential biologically-testable predictions in collaboration with a neuroscientist if possible.
26th Sep 2012	*RSMG6 report due.*
Autumn 2012	Write a conference or journal paper with collaborator, demonstrating findings and outlining biological predictions.
Winter 2012	Begin writing-up thesis.
Spring 2013	Submit thesis.

Table 1: Proposed timetable of specific aims until the next Thesis Group meeting in September 2012, followed by a more general timetable to thesis completion.

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