

Computational modelling of Alzheimer's disease
RSMG 4 (progress report)

Mark Rowan
School of Computer Science
University of Birmingham
`m.s.rowan@cs.bham.ac.uk`

Supervisor:
Dr. John Bullinaria

Thesis group members:
Prof. Xin Yao (RSMG representative)
Dr. Jon Rowe

Additional advisor:
Prof. John Jefferys
(School of Neuroscience)

March 2011

1 Work done so far

1.1 Ruppin and Reggia Model

Since the last RSMG report work has progressed on my implementation of and experimentation within the Ruppin and Reggia (1995) network model of Alzheimer’s Disease. The model was implemented in Matlab and found to produce highly similar results to the initial results of Ruppin and Reggia (1995) under various experimental conditions.

The neural field-dependent synaptic compensatory algorithm of Horn et al. (1996) was then implemented in place of the original local, uniform compensatory mechanism. The purpose of the compensatory mechanism is to enable each neuron to effectively *gain-up* its measurement of the summed input as various input synapses are progressively lost. Without compensation, this effect would result in neurons very quickly failing to reach their firing thresholds, but by compensating for the decrease in input field strength the neuron can maintain for much longer a similar profile of firing behaviour (but at the expense of increased noise).

Rather than making use of some un-knowable “synaptic deletion value” for each neuron, the particular compensatory mechanism specified by Horn et al. (1996) relies only on measurements of the average input field strength of each neuron, comparing average signal activations (as obtained via recall of previously-stored memories) and noise activations (obtained as the network updates from a random initial state with no external cueing) with historical signal and noise data. Experimental support for such a biological mechanism is presented in Savioz et al. (2009).

The implementation of this field-dependent compensation mechanism was very difficult to achieve due to the rather obscure and unclear description of the algorithm given in the original paper. Eventually a mechanism resembling the one prescribed in Horn et al. (1996) was derived with helpful input from my supervisor and other colleagues, and it appeared to produce results in line with those predicted by Horn et al. (1996).

Experiments were then performed as follows:

Compensation using recent versus remote memories: It was found that the network is sensitive to the choice of which sets of memories (remotely stored, recently stored, or randomly selected from all previously stored) are used to calculate the signal term during synaptic compensation. Using only remote memories results in greater noise within the compensatory mechanism, and an earlier decline in performance as synapses are deleted (much closer to the 10 – 30% range seen in AD patients (Minati et al., 2009)). The implications for AD patients are shown in the context that initial retrieval of remote memories at early stages of damage is actually more reliable than with recent memories (Ruppin and Reggia, 1995): if the brain makes use of this effect and uses the more readily-available remote memories to calculate compensation, not only do the recently-stored

memories continue to become less reliable than the remote memories, but the noise in the system leads to earlier onset of catastrophic decline.

Effects of connectivity on network capacity and robustness: This experiment demonstrated that network capacity and resilience is related to the regularity of connections within the network. High small-world clustering coefficients (Watts and Strogatz, 1998) lead to redundancy within the network, meaning greater resilience to damage but at the expense of lower capacity, as well as longer pattern retrieval times. This is consistent with the findings of Supekar et al. (2008) who examined small-world functional networks in the brain and found a key correlation between loss of small-world connectivity and onset of AD symptoms.

Simulated tau lesioning: Lesioning with simulated tau rather than standard synaptic deletion was shown to create a very different profile of damage by allowing all neurons and synaptic connections to remain present (so output patterns are not artificially altered) and instead damping inter-neuronal transmission. Whilst initially offering a much more graceful decline in performance due to the persistence of synaptic connections and output units, the drop-off in performance when it finally occurs is much more severe with tau lesioning than with synaptic deletion despite some later compensatory recovery of performance, and may offer an alternative explanation of the sudden recall performance decline in AD.

These experiments were outlined and presented in a paper submitted to the *International Joint Conference on Neural Networks, 2011* (included with this report), to be held in August 2011 in San Jose, California. The date for notification of acceptance or rejection is expected to be on the 10th of April 2011.

1.2 Collation of biological data

Some preliminary work has been undertaken on the task of obtaining known biological constraints with which the models should comply. Such constraints include neuronal density, maximum number of synapses per neuron, tau phosphorylation rates, amyloid deposition rates, small-world clustering coefficients, and compensatory rates, although more constraints are likely to be identified as development of the models progresses.

Huttenlocher (1990) describes a study of human cerebral cortex development which includes data for area 17 of the striate cortex relating to total volume, neuronal density, and total number of neurons, from which an approximation of the number of synapses permitted per neuron can be drawn. These values were used to inform the default number of connections in the model described in section 1.1, although no fundamental differences in behaviour were actually experienced when using significantly more or fewer connections per neuron.

Supekar et al. (2008) provides analysis of mean path lengths and small-world clustering coefficients in normal brains as well as AD brains which, whilst not

directly utilised during construction and analysis of the model, will be useful when further exploring the relation between network behaviour and small-world connectivity effects.

With regards to synaptic compensation rates, Horn et al. (1996) discuss the likely effects and differences in behaviour when choosing large values equating to full synaptic plasticity in young brains and small values equating to reduced synaptic plasticity in aged brains. However, actual biological data are not referenced, and are still to be located in the literature.

2 New problems encountered

In addition to the continuing requirement to locate further definitive biological data with which the models should comply, it still remains unclear precisely how and where the model fits in with known theories of learning, i.e. hippocampal versus neocortical organisation. Papers such as O'Reilly and Rudy (2000) and McClelland et al. (1995) still need to be fully read and understood, and lessons learned from them applied to the modelling process.

Hopfield-style models, due to their single input-output-processing layer, suffer from the downfall that neuronal deletion alters the output patterns by definition, without necessarily having any effect on the actual function of the network. Reservoir networks, a relatively recent class of neural network model also incorporating recurrent dynamics in the connections between units (Lukosevicius and Jaeger, 2009), provide a decoupling between the 'processing' and 'output' of the model, allowing us to circumvent this problem. Unlike traditional Hopfield-style associative networks, reservoir networks rely on an *untrained* (and usually random) recurrent "reservoir" of neurons which projects the input into high-dimensional space, feeding into a linear readout layer which is trained on the input data. Besides greatly simplifying the training process, reservoir networks allow greater computational flexibility than associative networks, displaying capabilities such as time-series prediction and function regression, and have even been shown to act as useful motor controllers (Steil, 2004).

It is already known that reservoir networks such as Echo State machines can operate efficiently with sparse connectivity (Reinhart and Steil, 2009; Lukosevicius and Jaeger, 2009) as found in the brain (Bassett and Bullmore, 2006), unlike Hopfield-class networks such as the Ruppin and Reggia model which generally display low memory capacity with sparse connectivity strategies. Additionally, analyses by Schiller and Steil (2005) and Dominey et al. (2006) show the similarities between the way in which traditional feed-forward networks and the brain both chiefly alter just the output weights (which are the only weights which can be altered in reservoir networks). Therefore, two important questions which must be answered are as follows:

- Can reservoir networks be shown to be better models than, or at least as accurate as, Hopfield-style associative networks such as the Ruppin and Reggia model (i.e. can it be shown that they are biologically and evolutionarily preferable)? What are the differences in behaviour?

- Which other symptoms of AD can be represented in a reservoir network, other than just failure to accurately recall a stored pattern? As the computational power is much greater, could a basic model of degradation of language or motor skills or some other feature be implemented?

Finally, following the release of OGER (see section 3), some time will need to be spent analysing this software and assessing its applicability to the research, particularly any trade-off which may occur between speed of model construction versus potential loss of modelling fidelity (i.e. the ability to finely control the neuronal-level behaviour of the model). If OGER becomes important to the research it is likely some time will have to be invested into learning to use the Python programming language and the *NumPy* Matlab-like toolbox, however this is not expected to be a particularly large overhead.

3 New developments elsewhere

Since the Thesis Proposal was written, an announcement was made by Verstraeten et al. from University of Ghent, Belgium, regarding the first release of their *OrGanic Environment for Reservoir Computing* (OGER) software¹. This is a free Python toolkit which enables rapid construction of various types of reservoir network systems and easy training on a range of problem types, and includes an interface to spiking neural network simulators compatible with *PyNN* to allow for increased biological realism. One supplied tutorial example models biological place-cells for robotic controllers, implying that the simulator can be used for at least basic biological modelling. Another tutorial example demonstrates learning of an artificial grammar, which could be useful when attempting to simulate more complex AD symptomatic behaviours than simple pattern storage and retrieval.

Other newly-encountered software which may be of use during the development of the models includes the *Spiking neurons toolkit*² from Dalhousie University, Canada (written in MATLAB). This toolkit provides graphical representation of simulations of various types of spiking neurons, which may aid understanding of the principles of Hodgkin-Huxley, Wilson, Izhikevich, and Integrate-and-fire neurons. Another potentially useful and recent software package which warrants further examination is the *BRIAN simulator*³ (Goodman and Brette, 2009), which is a Python library designed to reduce the time required to implement various spiking neural network simulations. Some work could even be done to try to combine its functionality with that of OGER, to create a powerful connectionist modelling system which may be of use to other researchers.

A recent paper by Papon et al. (2011) investigates a potential contributory link between anaesthesia and AD through three mechanisms: increased amyloid-beta production (which is then deposited in amyloid plaques and contributes

¹<http://organic.elis.ugent.be/oger>

²<http://web.cs.dal.ca/~tt/fundamentals/programs/MatlabGUIs/>

³<http://www.briansimulator.org/>

to cognitive decline), directly enhanced phosphorylation of tau via kinase activation, and indirect tau phosphorylation via phosphatase inhibition as a result of induced hypothermia during anaesthesia. It is likely that these findings will further inform the model's implementation of tau and amyloid pathology simulations.

Further findings relating to the spread of amyloid pathology in AD are presented by Small (2008), who shows that synaptic scaling, or compensation as it is termed elsewhere, can play an important role in the progressive spreading of beta-amyloid. The mechanism described indicates that "an $A\beta$ -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 $A\beta$ neurotoxicity, an increase in cytosolic calcium could increase the vulnerability of the healthy neurons to $A\beta$ toxicity" (Small, 2008).

4 Changes to the plan of research

Currently the proposal to design an evolutionary framework for the Ruppin and Reggia model has not been implemented, as the range of parameters for this model is relatively small and useful default values were given in the original paper. However the intention remains to implement such a framework for the next part of the research, as this will likely be very useful for finding optimal parameters for the currently under-explored field of reservoir networks.

It is also likely that the original proposal to carry out similar experiments to those performed on the Ruppin and Reggia model in an alternative network model such as LEABRA (O'Reilly, 1996) will be dropped as it is not clear that this will greatly contribute to knowledge at a level above that which can be achieved in the Ruppin and Reggia model whereas reservoir networks, by comparison, offer a totally different neural simulation framework with which to experiment and explore, and it is anticipated that the majority of the remaining research will be undertaken in this area.

Dropping this proposal will potentially allow more time for further work on the Ruppin and Reggia model, depending on feedback received from IJCNN 2011. This work could include designing experiments to explore the previously-reported effects (section 1.1) further and in greater detail as outlined in the "Further Work" section of the paper, such as incorporating amyloid pathology simulations (including the N-APP mechanism mentioned in the Thesis Proposal (Nikolaev et al., 2009)) alongside the simulated tau lesioning to enable both of these medical hypotheses to be tested in a 'basic' network before transferring to the more complex reservoir network.

Besides these changes, the remainder of the plan remains largely unchanged since the Thesis Proposal.

4.1 Predicted 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, the first group of which have already been completed or at least partially explored as part of the IJCNN 2011 paper.

4.1.1 Ruppin and Reggia model (partially explored)

- Confirmation of results of Ruppin and Reggia (1995).
- Clearer description of local field-dependent compensation rule of Horn et al. (1996)
- Effects of using recent versus remote memories during compensation.
- Effects of connectivity density and strategy (e.g. small-world) on network capacity and robustness.
- Lesioning strategies representing tau and amyloid pathology.

4.1.2 Reservoir network model

- Effects of small-world connectivity on behaviour versus random connectivity in the reservoir.
- A local field-dependent compensatory rule similar to Horn et al. (1996) but adapted to work in reservoir networks (normally, changing the parameters of the reservoir without re-training the output layer results in dramatically different dynamics so this must be undertaken carefully).
- Observation of the effects of lesioning connections within a reservoir network, and how the behaviour during lesioning compares with Hopfield-class networks.
- Specific differences in behaviour when lesioning according to simulated tau and/or amyloid pathology in comparison to the Ruppin and Reggia model.
- Indications, with biological justification regarding whether or not reservoir networks can be shown to make useful, accurate, and powerful models of the brain and the progress of Alzheimer's disease.
- Enhanced representation of AD symptoms such as effects on language or motor skills, taking advantage of the reservoir network's greater computational power.

4.1.3 General contributions to knowledge

- A corpus of data relating to biological constraints for computational neural network models.

5 Seminars and papers

In addition to the paper mentioned in section 1.1, I have attended two courses during this academic year. The first, the *8th Fall Course on Computational Neuroscience* at the Max Planck Institute in Göttingen, Germany⁴, was aimed at researchers in theoretical and computational methods in neuroscience, to acquaint them with recent developments and methods. A number of specialist papers in various areas of computational neuroscience were studied and group presentations were given. This course provided me with opportunities to deepen my knowledge of the field of computational neuroscience and to make potentially useful contacts for future collaboration.

The other course, at Universität Zürich, Switzerland, was a hands-on workshop in Reservoir Computing⁵, focussing on using the OGER toolbox (as mentioned in section 3). A number of example problems were given (such as classification of music or visual movement, or signal prediction) and attendees were then given the opportunity to create of various types of reservoir networks within the OGER framework to solve these problems. The OGER toolbox appears to be potentially useful for the next stage of my research as it could drastically reduce the time required to create working networks which can then be lesioned.

6 Timetable for remainder of the research

As of January 2011 I have taken up a Teaching Assistant position, which means the timescale of the PhD will be extended by approximately seven months to account for the extra teaching time required. During the summer of 2011 it is likely that I will be occupied for up to a month full-time preparing material for a module.

<i>Date</i>	<i>Tasks</i>
<i>Ongoing</i>	Continue to collate definitive medical data against which my models should be compared, and lay out the way in which model can be shown to be a small part of the overall larger brain organisation (i.e. hippocampal vs neocortical organisation).
Mar – Jul 2011	Follow-up work on Ruppin and Reggia model taking into account feedback from IJCNN 2011 reviewers, and examining preferential attachment (hub) model of network generation and amyloid / N-APP lesioning experiments.
<i>Paper (Jun 2011)</i>	Submit results of extended network connectivity analysis and/or amyloid pathology to a neuroscience conference or journal, potentially in collaboration with a neuroscientist, if significant progress made.
<i>1st-7th Aug 2011</i>	<i>Present first paper at International Joint Conference on Neural Networks 2011 in San Jose, California.</i>

⁴<http://www.bccn-goettingen.de/events-1/cns-course>

⁵<http://reslab.elis.ugent.be/seminars/amarsi-workshop-reservoir-computing>

<i>Paper (Aug 2011)</i>	Submit an updated review of computational lesioning methods in neural networks including categorisation of tau and A β simulations, following on from Bullinaria (2003).
Aug – Sep 2011	Preparation work for Intelligent Robotics module.
Sep – Dec 2011	Begin work on implementation of a reservoir computing network which incorporates biologically plausible synaptic compensation (very important, as the reservoir network’s dynamics change dramatically with only slight changes in the internal reservoir).
<i>October 2011</i>	<i>Submit RSMG5 progress report.</i>
<i>Paper (Jan 2012)</i>	Submit a computational article on “biologically-inspired robust / self-adapting reservoir networks” to a journal such as <i>Neural Networks</i> .
Spring 2012	Examine behaviour of model under AD conditions in tau and amyloid simulations.
<i>Paper (mid 2012)</i>	Collate results of AD lesioning in compensatory reservoir networks and submit, potentially in collaboration with a neuroscientist, to a suitable conference or neuroscience journal.
Summer 2012	Implement advanced psychological testing of reservoir computing models (e.g. perceptual test in collaboration with Zoe Kourtzi in School of Neuroscience).
<i>Paper (late 2012)</i>	Submit computational neuroscience paper on psychological perceptual testing of neural network models.
Winter 2012	Begin writing-up thesis.
Spring 2013	Submit thesis.

Table 1: Proposed timetable of specific aims until the next Thesis Group meeting in October 2011, followed by a more general timetable to thesis completion.

References

- D.S. Bassett and E. Bullmore. Small-world brain networks. *The neuroscientist*, 12(6):512, 2006. ISSN 1073-8584.
- John A. Bullinaria. Lesioned networks as models of neuropsychological deficits. In A.M. Arbib, editor, *The Handbook of Brain Theory and Neural Networks*, pages 635–638. MIT Press, Cambridge, MA, second edition, 2003.
- P.F. Dominey, M. Hoen, and T. Inui. A neurolinguistic model of grammatical construction processing. *Journal of Cognitive Neuroscience*, 18(12):2088–2107, 2006.

- D.F.M. Goodman and R. Brette. The Brian simulator. *Frontiers in neuroscience*, 3(2):192, 2009.
- D. Horn, N. Levy, and E. Ruppin. Neuronal-based synaptic compensation: a computational study in Alzheimer’s disease. *Neural Computation*, 8(6):1227–1243, 1996.
- P.R. Huttenlocher. Morphometric study of human cerebral cortex development. *Neuropsychologia*, 28(6):517–527, 1990. ISSN 0028-3932.
- M. Lukosevicius and H. Jaeger. Reservoir computing approaches to recurrent neural network training. *Computer Science Review*, 3(3):127–149, 2009.
- J.L. McClelland, B.L. McNaughton, and R.C. O’Reilly. Why there are complementary learning systems in the hippocampus and neocortex: Insights from the successes and failures of connectionist models of learning and memory. *Psychological review*, 102(3):419–457, 1995.
- L. Minati, T. Edginton, M. Grazia Bruzzone, and G. Giaccone. Reviews: Current Concepts in Alzheimer’s Disease: A Multidisciplinary Review. *American Journal of Alzheimer’s Disease and Other Dementias*, 24(2):95, 2009.
- A. Nikolaev, T. McLaughlin, D. O’Leary, and M. Tessier-Lavigne. N-APP binds DR6 to cause axon pruning and neuron death via distinct caspases. *Nature*, 457(7232):981, 2009.
- R.C. O’Reilly. *The Leabra model of neural interactions and learning in the neocortex*. PhD thesis, Carnegie Mellon University, 1996.
- R.C. O’Reilly and J.W. Rudy. Computational principles of learning in the neocortex and hippocampus. *Hippocampus*, 10(4):389–397, 2000.
- M.A. Papon, R.A. Whittington, N. El Khoury, and E. Planel. Alzheimer’s disease and anesthesia. *Frontiers in Neuroscience*, 5, 2011.
- R.F. Reinhart and J.J. Steil. Attractor-based computation with reservoirs for online learning of inverse kinematics. *ESANN, April*, 2009:257–262, 2009.
- E. Ruppin and J.A. Reggia. A neural model of memory impairment in diffuse cerebral atrophy. *The British Journal of Psychiatry*, 166(1):19–28, 1995.
- A. Savioz, G. Leuba, P.G. Vallet, and C. Walzer. Contribution of neural networks to Alzheimer disease’s progression. *Brain research bulletin*, 2009.
- U.D. Schiller and J.J. Steil. Analyzing the weight dynamics of recurrent learning algorithms. *Neurocomputing*, 63:5–23, 2005.
- David H. Small. Network dysfunction in alzheimer’s disease: does synaptic scaling drive disease progression? *Trends in Molecular Medicine*, 14(3):103 – 108, 2008. ISSN 1471-4914. doi: DOI:10.1016/j.molmed.2007.12.006.

- J.J. Steil. Backpropagation-Decorrelation: Online recurrent learning with $O(N)$ complexity. In *Proceedings of the International Joint Conference on Neural Networks (IJCNN)*, volume 1, pages 843–848, 2004.
- K. Supekar, V. Menon, D. Rubin, M. Musen, and M.D. Greicius. Network analysis of intrinsic functional brain connectivity in Alzheimer’s disease. *PLoS Comput Biol*, 4(6):e1000100, 2008.
- D.J. Watts and S.H. Strogatz. Collective dynamics of ‘small-world’ networks. *Nature*, 393(6684):440–442, 1998.