Computational modelling of neurological disorders
RSMG 2 (progress report)

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

Supervisor:
John Bullinaria

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

April 2010

Contents

1 Introduction **2**

2 Relevant research **4**
2.1 Medical background to Alzheimer's disease 4
2.1.1 Acetylcholine and runaway synaptic modification 4
2.1.2 Glutamate (NMDA) excitotoxicity 4
2.1.3 Beta-amyloid plaques 5
2.1.4 Alzheimer's disease and diabetes 5
2.1.5 Further research 6
2.2 Medical background to schizophrenia 6
2.2.1 Dopamine hypothesis 6
2.2.2 Glutamate hypothesis 7
2.3 Computational models 7
2.3.1 Alzheimer's disease 7
2.3.2 Schizophrenia 9
2.3.3 Spontaneous attractors in depression 12

3 Supplementary work **13**
3.1 Models implemented 13
3.2 Additional learning 14

4 Problems encountered **15**

5 Timetable for thesis proposal **16**

Chapter 1

Introduction

This report outlines the work undertaken since the start of my research over the first six months. The aim of the work is to utilise developments in connectionist neural network modelling in an effort to better understand the process and pathogenesis of various neurological disorders.

Two such disorders to have received a wide degree of interest are schizophrenia and Alzheimer's disease. The former is a psychotic disorder consisting of both negative symptoms (such as reduced cognitive function, poverty of speech, and poverty of ideas) and positive symptoms (such as delusions of grandeur, persecution, or thought broadcasting, and hallucinations such as voices discussing the patient's actions) (Frith, 1996). The lifetime prevalence in the general population is around 0.4% (Bhugra, 2005).

Alzheimer's disease is the basis of a specific form of dementia, and is characterised biologically by neurofibrillary tangles and beta-amyloid protein plaques (Tiraboschi et al., 2004), and symptomatically by a progressive decline in memory capabilities. In particular, recent memories are the first to be lost whilst distant memories are retained, but as the disease progresses this is followed by gradual total loss of recall, a corresponding loss of personality, motor control, and other bodily functions, and to finally death (Francis et al., 1999). Recent health reports have given warnings of future Alzheimer's epidemics in coming years: "Alzheimer disease poses one of the greatest threats to the future of healthcare systems, owing to the anticipated demographic shift to an aging population–the number of people worldwide above the age of 60 years is expected to double over the next 25 years" (Mount and Downton, 2006).

This work begins with the undertaking of a general literature review to better understand and attempt to synthesize the field of computational modelling of neurological disorders, and recent developments within it. The literature review is expected to identify a number of current computational models focussing on different aspects of the various disorders, as well as shortcomings of these models and potential ways forward. The main contribution of the work will be the development of improved and refined models that better represent the underlying biological processes. The work will involve testing of the improved

models against empirical evidence (either from medical literature or specifically-commissioned experiments) to ascertain the level of support which can be given to them. The approach adopted will involve various techniques from the fields of neural computation and computational neuroscience, and possibly evolutionary computation.

Chapter 2

Relevant research

2.1 Medical background to Alzheimer's disease

2.1.1 Acetylcholine and runaway synaptic modification

Spitzer (1998) in Stein and Ludik (1998) explains that "during learning, the spreading of activation through the network must be prevented to some degree, otherwise synaptic activation and change would spread like an avalanche through the entire network... acetylcholine selectively suppresses excitatory synaptic connections between neurons of the same cortical region. In contrast, signals from other cortical areas can pass through synapses unimpaired". In a computational analogy, the function of acetylcholine is to 'clamp' the activation of the network during learning such that recall of overlapping previously-stored patterns does not interfere with learning (Hasselmo, 1993).

In cases where this interference does occur when levels of acetylcholine are not sufficient to prevent the avalanche of synaptic activation (termed *runaway synaptic modification* (Hasselmo, 1994)), the subsequent over-activity of those neurons which use the neurotransmitter NMDA (also known as *glutamate*) causes these neurons to damage themselves by a process of excitotoxicity, leading to the neuronal death implicated in Alzheimer's disease (Spitzer, 1998; Maragos et al., 1987).

2.1.2 Glutamate (NMDA) excitotoxicity

It is believed that glutamate excitotoxicity is due to the excessive activation of NMDA receptor channels and the subsequent increase in Ca^{2+} ions inside the neuron beyond a critical level (Hynd et al., 2004). The beta-amyloid protein, which in Alzheimer's disease accumulates in an altered form to create neuritic plaques, has been suggested to play a role in regulating these internal Ca^{2+} levels in normal situations (Mattson et al., 1993), thus providing further evidence that the alteration of the beta-amyloid protein to a form which does not perform

Ca^{2+} regulation permits neuronal sites subject to runaway synaptic modification to succumb to excitotoxicity due to over-activation of NMDA receptors.

2.1.3 Beta-amyloid plaques

Prevailing medical opinion is that "accumulation of beta-amyloid in the brain is the primary influence driving AD pathogenesis. The rest of the disease process, including formation of neurofibrillary tangles containing tau protein, is proposed to result from an imbalance between beta-amyloid production and beta-amyloid clearance" (Hardy and Selkoe, 2002). However, regarding the apparent targeting of Alzheimer's disease towards memory structures during initial onset of the condition, Wallenstein and Hasselmo (1998) outline a theory proposing that the causality should in fact be reversed; that "the selective cortical neuropathology associated with the progression of [AD] may be rooted in the breakdown of the essential mechanism of cortical memory function". The beta-amyloid plaques found in the autopsied brains of Alzheimer's patients "tend to be broadly distributed, appearing throughout the cortex, with a greater density in regions of frontal, parietal and temporal association cortex ... [leading to] the suggestion that they reflect the degeneration of axonal processes from the same set of neurons that develop neurofibrillary tangles... [and] result from a breakdown in the normal mechanisms for modification of synaptic strength" (Wallenstein and Hasselmo, 1998).

In either case, this breakdown due to the lack of sufficient acetylcholine to moderate synaptic activations between neurons of the same cortical region is shown to lead to the initiation of runaway synaptic modification in the brain, and in turn to over-activity of NMDA channels and subsequent excitotoxicity (Hasselmo, 1993). This interaction between insufficient acetylcholine and subsequent excessive NMDA levels in the brain is supported by the observations resulting from the administration of two differing forms of medication: acetylcholinesterase inhibitors, which enable acetylcholine to remain for longer in the synapse by preventing its breakdown by the enzyme acetylcholinesterase (Francis et al., 1999), and NMDA receptor antagonists which moderate damage from excessive glutamate release by blocking the ability of the receptor to bind to the neurotransmitter, and therefore reducing the levels of Ca^{2+} in the neuron (Rothman and Olney, 1987; Mount and Downton, 2006).

2.1.4 Alzheimer's disease and diabetes

A recent review by Sima and Li (2006) summarises the observed relationship between insulin resistance in both diabetes and brain signalling channels in Alzheimer's disease, postulating that there may be an alternative pathology whereby impaired insulin signalling leads to the formation of tau protein neurofibrillary tangles in the brains of Alzheimer's patients, and implicating that Alzheimer's disease could be a third type of diabetes. This theory receives a level of experimental support showing that high-calorie diets, such as those known to

increase the risk of diabetes, also impairs synaptic plasticity in the hippocampus (an important brain structure for memory and learning) in rats (Stranahan et al., 2008). It is not yet clear, however, how valid this theory is likely to become or how it is likely to relate to the existing theories of acetylcholine and beta-amyloid deposition.

2.1.5 Further research

Questions still to be answered through further reading include how neuronal death due to excitotoxicity (at the rate of approximately 10% in Alzheimer's disease (Menschik and Finkel, 1999), although greater in computational models for the same level of memory impairment (Horn et al., 1993)) translates to a much larger degree of synaptic deletion, and how viable the hypothesis of Wallenstein and Hasselmo (1998) is in context of the prevailing medical opinion that beta-amyloid plaques are a primary cause of interrupted synaptic function, rather than the reversed causality (Hardy and Selkoe, 2002). Evidence in favour of the former (prevailing) theory includes research by Knowles et al. (1999) showing a "predicted delay of several milliseconds over an average plaque [which] disrupts the precise temporal firing patterns of action potentials, contributing directly to neural system failure and dementia".

2.2 Medical background to schizophrenia

Currently this section is not fully-researched, and as such the relevant precise mechanisms are not yet known, but initial findings are that the roles of two neurotransmitters, dopamine and glutamate, are heavily implicated in the development and progress of schizophrenia. The theories regarding their roles are separate but not contradictory, and it is possible that they may yet be combined into a single theory (Lisman et al., 2008).

2.2.1 Dopamine hypothesis

Dopamine is essential for synaptic plasticity and by extension the processes of long-term potentiation and long-term depression by which lasting memories are formed (Centonze et al., 2001; Calabresi et al., 2007). Excessive synaptic plasticity is assumed to assist the process of runaway synaptic modification and subsequently enable damage to associative memory circuits (Abbott and Nelson, 2000), leading to the conclusion that excessive levels of dopamine in the brain can be a precursor to the development of schizophrenic symptoms. The hypothesis of the involvement of dopamine in schizophrenia is supported by the observed schizophrenic-like symptoms (psychosis) following the ingestion of dopamine-increasing drugs such as amphetamine and cocaine (Robinson and Becker, 1986), and by the observed reduction of schizophrenic symptoms in patients who are given dopamine receptor antagonist (i.e. blocking) drugs (Seeman, 2004).

In particular, densities of the D_2 type of dopamine receptor in the brain have been shown to be higher in schizophrenia patients, and it is this type of receptor which is targeted by anti-psychotic drugs, leading to what is known as the *dopamine theory of schizophrenia* (Wong et al., 1986). However it is now believed that the relationship between D_2 receptors and schizophrenia is more complex than as described in this theory, particularly due to the observed similarities in patient responses to 'typical' and 'atypical' anti-psychotic drugs (Pilowsky et al., 1992). The newer, atypical types of drug appear to have a lower dopamine receptor-blocking effect and also affect levels of serotonin in the brain, indicating that D_2 receptor over-activity is not the sole mechanism underlying schizophrenia (Jones and Pilowsky, 2002).

2.2.2 Glutamate hypothesis

The second neurotransmitter heavily implicated in schizophrenia is glutamate. This is supported by the observed effects of glutamate-blocking drugs such as ketamine in producing psychotic symptoms in normal controls (Lahti et al., 2001), and by the treatment of negative schizophrenic symptoms using drugs which stimulate (agonise) NMDA receptors (Heresco-Levy et al., 1999).

As opposed to its effects in Alzheimer's disease, where an increase in glutamate leads to influx of Ca^{2+} ions in neurons and thus to the death of the cell, in schizophrenia the activity levels of glutamate (NMDA) receptors are below normal, causing related disfunction in the hippocampus (Tamminga, 1998; Coyle, 2006).

2.3 Computational models

2.3.1 Alzheimer's disease

Synaptic deletion and compensation

Ruppin and Reggia (1995a), based on work by Horn et al. (1993), show how a variant of an attractor network model proposed by Tsodyks and Feigel'Man (1988) is capable of storing patterns in a biologically-plausible Hebbian *activity-dependent* manner. This is achieved using a repetitive-learning process whereby each pattern to be stored "must be presented to the network several times before it becomes engraved on the synaptic matrix with sufficient strength, and is not simply enforced on the network in a 'one-shot' learning process" (Ruppin and Reggia, 1995a). The authors then lesion the network model to simulate the progress of Alzheimer's disease by deleting synapses or neurons at random and implementing a process of *variable synaptic compensation*, where "the magnitude of the remaining synapses is uniformly strengthened in a manner that partially compensates for the decrease in the neuron's input field" (Ruppin and Reggia, 1995a) by multiplying the weights of the remaining synaptic connections by a uniform compensation factor.

The authors then examined the overall degradation in recall performance and the sparing of older memories versus recently stored patterns, as observed in Alzheimer's patients (Kopelman, 1989). Amongst other interesting findings regarding the behaviour of this network model, the research demonstrates that whilst "at low levels of damage re-learning [of previously-stored patterns] improves performance, at high levels of damage it actually worsens it" (Ruppin and Reggia, 1995a), which could lend credibility to the recommendation that Alzheimer's patients should be prevented from coming into contact with large amounts of new information such as might be encountered by following complex storylines in books or on television (Duch, 2000).

Willshaw model

The T-F model suffers from a number of flaws, notably that "Hopfield neural networks are not plausible from the neurobiological point of view because they require symmetric weights, have only point attractors and are trained using non- local learning procedures" (Duch, 2007). An associative Willshaw model (Willshaw et al., 1969) is used instead by Horn et al. (1996) in work building upon Ruppin and Reggia (1995a) as it provides a more biologically plausible model due to "two important differences:... in the Willshaw model, the retrieval of some memories may decline while others are preserved. Furthermore, while in the [Tsodyks and Feigel'Man] model once a memory pattern vanishes it is lost forever, in the Willshaw model memory patterns which are lost may later be adequately retrieved due to ongoing compensation". A further unexplained feature of both of these models is that they suggest that significant neuronal death is required before memory function is seriously impaired (Ruppin and Reggia, 1995a), which is significantly different to the 10% death rate observed clinically in the latest stages of Alzheimer's disease (Menschik and Finkel, 1999).

Runaway synaptic modification

One mechanism suggested to underlie the initial cause and the subsequent spreading of this over-activity to other regions of the brain is that of runaway synaptic modification (also known as *synaptic runaway*) (Hasselmo, 1994) within cortical regions with a strong capacity for synaptic modification, such as the hippocampus (Wallenstein and Hasselmo, 1998). Ruppin (1995) describes runaway synaptic modification accordingly: "when a new memory pattern is being stored in the network, the resulting network activity is not only guided by the new pattern but also by all the previous memory patterns which are engraved in the synaptic matrix".

Hasselmo (1994) provides an early model of runaway synaptic modification via an exponential strengthening (or compensation) of existing synapses, similarly to Ruppin and Reggia (1995a), but in the framework of the observed effects of acetylcholine in preventing the activation of previously-stored patterns during learning, and additionally showing that development of beta-amyloid plaques and tau tangles may be attributable to the runaway synaptic modification, in a

similar manner to Wallenstein and Hasselmo (1998) who present a hypothesis of "reversed causality" (i.e. that plaques and tangles are a result of the initial degradation of synaptic modification circuitry, and not a first cause).

Biophysical model

A third class of model developed by Menschik and Finkel (1999) builds upon the work of Ruppin and Reggia (1995a) and Hasselmo (1994) to investigate the neuromodulatory effects of acetylcholine in a specific region (CA3) of the hippocampus, in an attempt to rectify the disparity between the large rate of neuronal death observed in computational models and the 10% rate observed clinically. Rather than use the abstracted and simplified Hopfield-based attractor network models reviewed earlier, Menschik and Finkel present a detailed biophysical model of individual neurons collected together in an anatomically-inspired network model of the CA3 region of the hippocampus.

Their results indicate that the role of acetylcholine in cellular-level regulation is to effectively switch neurons between one of two firing modes ('burst' and 'regular spiking'), related to a transition between fast learning and consolidation of memory. The simulations also confirm the anti-excitotoxic effects of acetylcholine, in support of the runaway synaptic modification theory. On the network level, the simulations show that reduced a acetylcholine level translates into reduced time for the attractor network to settle into the appropriate basin of attraction for a given input, leading to an increase in the retrieval failure rate of the network.

Further research

Further research is expected to reveal the disparity between the mechanisms of the model of synaptic deletion and compensation, where reduced numbers of synapses are expected to be found in the brain, and the model of runaway synaptic modification, where exponential synaptic growth and a resulting pathological increase in the number of synapses is expected to be found. It is also hoped that further understanding of the role of beta-amyloid plaques and tau tangles in Alzheimer's disease will be found; i.e. whether the plaques and tangles are a cause of the breakdown of synaptic processes or a result of this breakdown.

2.3.2 Schizophrenia

Degeneration of temporal lobe projections and synaptic regeneration

Ruppin et al. (1996) describe a model of schizophrenia based on the same Tsodyks and Feigel'Man model presented in Ruppin and Reggia (1995a), in which they examine the theory that the "onset of schizophrenia is associated with regenerative synaptic changes occurring in the frontal lobes after the degeneration of incoming temporal lobe projections" (Ruppin and Reggia, 1995a), specifically "reactive anomalous sprouting and synaptic reorganization in the projection sites of dystrophic medial temporal neurons" (Stevens (1992) in

Ruppin et al. (1996)). This is modelled by a process of "external synaptic weakening (i.e., temporal lobe degeneration) [and simultaneous] internal synaptic strengthening (i.e., frontal regeneration)" in a network employing Hebbian activity-dependent learning [see section 3.1] and associative recall. (Ruppin et al., 1996)

Based on Stevens' hypothesis, Ruppin et al. (1996) show that "while preserving memory performance, compensatory synaptic regenerative changes... may lead to adverse, spontaneous activation of stored patterns". These spontaneous retrievals, or *parasitic attractors*, take the form of unexpected and repeated retrieval of previously-stored memory patterns in the network in the absence of any relevant external input (Ruppin et al., 1996). The authors speculate that this mechanism could underlie some of the positive symptoms of schizophrenia, specifically thought insertion, hallucinations and delusions, which Frith (1996) argues could "result from the patient attributing his own actions to an external agency... due to an inability to distinguish between external events and perceptual changes caused by his own actions", including spontaneous activation of auditory circuitry (Hoffman and McGlashan, 2001), leading to the reported symptoms of "bizarre delusions (e.g. thought broadcasting [where] thoughts leave the patient's mind and enter the minds of others) and/or prominent hallucinations of a voice (e.g. voices discussing the patient's actions)" (Frith, 1996).

As the network attempts to compensate for the degenerating external temporal lobe inputs by employing internal synaptic strengthening (regeneration), the synaptic matrix gradually becomes altered according to the same Hebbian activity-dependent manner as the original learning process. This results in a bias towards certain previously-stored states (the parasitic attractors representing hallucinations) through a continual enlargement of their basins of attraction, and eventually to the formation of a single mixed-state attractor not representing any of the stored patterns, onto which the network converges on every iteration. The authors speculate that this mechanism underlies "more complex forms of delusions and hallucinations" (Ruppin et al., 1996) but there is evidence to suggest that this "end-state" attractor instead represents negative symptoms of schizophrenia (reduced cognitive function, poverty of speech, poverty of ideas) or even catatonia, a complete loss of motor skills (leading to the holding of rigid poses or constant hyperactivity for several hours) and total abstraction from the effects of external stimuli (Finkel, 2000).

The authors link this work to the theory of the effects of increased dopamine on the schizophrenic brain by speculating that "part of the therapeutic effect of dopaminergic blocking agents in reducing the positive symptoms of schizophrenia may be due to the attenuation of Hebbian, activity-dependent synaptic changes" (Ruppin et al., 1996).

Runaway synaptic modification due to delayed maturation of NMDA receptors

Greenstein-Messica and Ruppin (1998) present models based on the Willshaw and Tsodyks and Feigel'Man networks to investigate the effects of delayed mat-

uration of NMDA (glutamate) receptors in schizophrenia, in accordance with observations that "during normal development, NMDA receptors undergo a process of maturation, where earlier subtypes, which provide greater plasticity, are replaced by less malleable forms, thereby stabilizing the mature synaptic connections" (Greenstein-Messica and Ruppin, 1998), but with this process reduced in schizophrenia such that there is a 50% increase in the numbers of immature NMDA receptor subtypes compared to normal controls.

The effect of delayed maturation of NMDA receptors is modelled by a decreased learning threshold, causing the network to become overloaded at an early stage (significantly earlier than would be expected in normal subjects, and far short of its explicit capacity limits), leading to runaway synaptic modification (defined as "the growth of erroneous synapses that may accompany activity-dependent memory storage" (Greenstein-Messica and Ruppin, 1998)), which in turn leads to the spontaneous retrieval of parasitic attractors and eventually convergence to a single mixed-state attractor (Ruppin et al., 1996).

In addition to providing a possible mechanism underpinning the glutamate theory of schizophrenia, this model supports the hypothesis that increased levels of dopamine are a factor in schizophrenia, as dopamine is thought to enhance synaptic plasticity (Centonze et al., 2001), which would only exacerbate the effects of runaway synaptic modification when it occurs.

Reduced corticocortical connectivity and excessive pruning

Hoffman and McGlashan (2001) present a model of auditory hallucinations due to a process of Darwinian pruning (removal of synapses betweeen neurons which are distant from and/or weaker than stronger, more local connections between neurons) which is observed to occur during the maturation of the human brain in late childhood through to early adulthood (Gogtay et al., 2004) but which, in schizophrenic individuals, is assumed to have been undertaken by an excessive amount, particularly between different modules of the cortex. The resulting reduced corticocortical connectivity is shown to produce parasitic attractors in an associative memory model, mirroring hallucinogenic (positive) symptoms in schizophrenia. Additionally, the authors present a simplified model of auditory language understanding in the brain, which responds to the appearance of parasitic attractors by generating new 'audio' output distinct from the associations expected from the given input, as well as exhibiting subtle impairments in narrative speech perception, a negative symptom of schizophrenia observed in human subjects and confirmed by medical imaging of patients by the authors.

Dopamine modulation

The effect of decreased dopaminergic modulation can be modelled by a reduction in the signal-to-noise ratio in associative memory, leading to a disruption in the stability of short-term memory networks and hence a greater 'distractability' of the network. This is assumed to describe some of the negative effects of schizophrenia such as poor attentional focus and poverty of ideas (Rolls et al.,

2008). A full review of the implications of this research on the dopamine and glutamate theories of schizophrenia will be provided in the thesis proposal.

2.3.3 Spontaneous attractors in depression

An interesting question to investigate further would be the role of spontaneous activation of pathological attractors in depression. Depression is often linked with the spontaneous appearance of unwanted (often violent, to oneself or to others) images or thoughts, as in schizophrenia (Grisso et al., 2000). However it appears that, unlike with schizophrenia, in cases of depression the patient remains capable of attributing the appearance of these thoughts to his or her own cognitive actions rather than to an external agency (and therefore suffering from delusions of thought control).

A model of reduced serotonin activity in the brain (implicated in depression (Owens and Nemeroff, 1994)), which results in the creation and retrieval of spontaneous pathological attractors would be an interesting development, although the specificity of these attractors towards thoughts representing violence, and the differentiation between depressive and schizophrenic patients' abilities to correctly attribute these thoughts to their own actions rather than those of an external agency, could be somewhat more difficult to model.

Chapter 3

Supplementary work

3.1 Models implemented

As part of the process of understanding the paper on "A neural model of memory impairment in diffuse cerebral atrophy" by Ruppin and Reggia (1995a), I implemented in Java the basic Tsodyks and Feigel'Man model on which the paper was based. This took the form of an associative Hopfield network which learns patterns through a process of activity-dependent learning, according to the update rule

$$W_{ij}(t) = W_{ij}(t-1) + \frac{\gamma}{N}(S_i - p)(S_j - p)$$

where W is the weight matrix between neurons i and j, γ is a constant determining the magnitude of activity-dependent changes, N is the number of neurons in the network, S refers to the neuronal state $\{0, 1\}$, and p is the coding rate denoting the proportion of *1*s compared to *0*s in the stored memory patterns ($p << 1$ as cortical networks are assumed to have very low coding rates (Abeles et al., 1990)).

This implementation was enhanced by causing the network to be partially connected in a Gaussian spatial manner rather than fully-connected, as described in Ruppin and Reggia (1995b), thereby permitting the use of much larger network sizes than those possible at the time of (in the order of 10,000 units, compared to 800 units in Ruppin and Reggia (1995a)) as well as causing the model to be more biologically plausible. Initial non-lesioned results appear consistent with those mentioned in the literature.

Actual lesioning experiments and implementation of the synaptic compensation mechanism have not yet been performed on this model, but it provides a solid framework for replicating the experiments of Ruppin and Reggia (1995a), Ruppin et al. (1996) and Greenstein-Messica and Ruppin (1998) on a larger scale and proposing alterations to the model in light of more recent medical and neural modelling findings.

3.2 Additional learning

Good Brain, Bad Brain Throughout the first and second semesters of this year (2009–2010) I have attended lectures in the School of Neuroscience of the University of Birmingham as part of the *Good Brain, Bad Brain* module. This has provided me with a basic but thorough grounding in aspects of neuroscience, from the physical structure of the human brain through to the chemical gateways which provide signalling paths between different parts of the cortex. A wide variety of brain disorders were presented, including Alzheimer's disease, Parkinson's disease, and schizophrenia, along with the relevant neurochemical mechanisms believed to underlie these conditions. Additionally the lectures provided me with a number of contacts in the School of Neuroscience and local NHS clinical departments who have expressed willingness to be consulted on aspects of their relevant fields of expertise.

NCAF, January 2010 During January 2010 I attended the *Natural Computation and Applications Forum* conference on Complexity in Aston, Birmingham. This provided an insight into current natural computation work which, whilst not directly relevant to my research at present, could prove useful in designing efficient optimisation systems in the latter evolutionary computation stage of my planned work. Due to its small, community-like nature and relevance to aspects of natural computation and clinical science, this conference series would present an ideal venue for presentation of initial papers to arise from my research.

Chapter 4

Problems encountered

In general my research has progressed steadily and without major issue. The largest obstacle has been understanding the vast quantity of medical literature relating to the various theories of AD and schizophrenia, although to this end attending the School of Neuroscience's *Good Brain, Bad Brain* module has helped as it has given me a basic grounding of neuroscience-related terminology.

With regards to the more long-term direction of the research, it still remains unclear to me how much focus should be devoted to either of the two disorders studied so far (Alzheimer's disease and schizophrenia). There is plenty of scope to produce an incremental improvement in the current knowledge of both of these disorders via an improved model or set of models, but currently I lack a clear remit for precisely what level of attention I should give to either or both of the disorders. If only one of the two disorders was chosen to form the long-term focus of my research, it should be possible to draw from the relevant research already undertaken towards the other disorder to further enhance my arguments, so it would not be time wasted. However a clear direction for future research, and a decision regarding whether Alzheimer's disease or schizophrenia (or indeed both jointly) should form the main branch of the research so that something meaningful can definitely be produced in the allotted time, remains forthcoming.

Chapter 5

Timetable for thesis proposal

The main focus of the thesis proposal will be towards selecting candidate models for enhancement or combination into a new class of models, in the context of more recent medical research regarding Alzheimer's disease and schizophrenia (although at this present moment it is unclear whether both disorders will be pursued to this level, or just one of them; see section 4). A further branch of potential research could be investigation and modelling of the relationship between the spontaneous pathological attractors observed in schizophrenia and depression (see section 2.3.3).

There is also scope to combine improved models of Alzheimer's disease and/or schizophrenia with a model of memory maintenance (e.g. Horn et al. (1998)) in an attempt to show how routine maintenance processes in the brain representing 'everyday operation' could break down to create one or the other of the disorders. This could be achieved in an evolutionary framework, whereby the parameters representing the neurobiology of the brain are subject to an evolutionary algorithm, and the fitness function consists of an automated recogniser for symptoms of Alzheimer's disease or schizophrenia over the 'lifetime' of the network. This may enable a large variety of initial parameters to be tested, and provide insight (in context of the medical literature reviewed) regarding which parameters are likely to have the greatest effect from a medical perspective.

General timetable for May to August 2010:

May 2010 Continue reading medical papers on current theories of Alzheimer's disease and schizophrenia, and summarise the accumulated knowledge as part of the overall literature review.

June 2010 Collate and evaluate a selection of recent computational models of Alzheimer's disease and schizophrenia, as well as investigating the plausibility of building automatic degradation via an evolutionary process into a model of routine memory maintenance. Implement some models of par-

ticular interest to gain a better understanding of how they work.

July 2010 Identify weaknesses in current models based on the acquired medical knowledge, and suggest how these models could be improved (there may be scope for publishing of papers in relevant conferences or journals following on from this work). Reflect on how the resulting work can be made to be testable for the purposes of critical evaluation.

August 2010 Complete and submit thesis proposal.

Bibliography

L.F. Abbott and S.B. Nelson. Synaptic plasticity: taming the beast. *Nature Neuroscience*, 3:1178–1183, 2000.

M. Abeles, E. Vaadia, and H. Bergman. Firing patterns of single units in the prefrontal cortex and neural network models. *Network: Computation in Neural Systems*, 1(1):13–25, 1990.

D. Bhugra. The global prevalence of schizophrenia. *PLoS Medicine*, 2(5):372, 2005.

Paolo Calabresi, Barbara Picconi, Alessandro Tozzi, and Massimiliano Di Filippo. Dopamine-mediated regulation of corticostriatal synaptic plasticity. *Trends in Neurosciences*, 30(5):211 – 219, 2007.

D. Centonze, B. Picconi, P. Gubellini, G. Bernardi, and P. Calabresi. Dopaminergic control of synaptic plasticity in the dorsal striatum. *European Journal of Neuroscience*, 13(6):1071–1077, 2001.

J.T. Coyle. Glutamate and schizophrenia: beyond the dopamine hypothesis. *Cellular and molecular neurobiology*, 26(4):363–382, 2006.

W. Duch. Therapeutic applications of computer models of brain activity for Alzheimer disease. *Medical Informatics and Technologies*, 5:27–34, 2000.

W. Duch. Computational models of dementia and neurological problems. *Methods in Molecular Biology*, 401:305–336, November 2007.

L.H. Finkel. Neuroengineering models of brain disease. *Annual Review of Biomedical Engineering*, 2(1):577–606, 2000.

P.T. Francis, A.M. Palmer, M. Snape, and G.K. Wilcock. The cholinergic hypothesis of Alzheimers disease: a review of progress. *Journal of Neurology, Neurosurgery & Psychiatry*, 66(2):137, 1999.

C. Frith. Neuropsychology of schizophrenia: What are the implications of intellectual and experimental abnormalities for the neurobiology of schizophrenia? *British medical bulletin*, 52(3):618, 1996.

N. Gogtay, J.N. Giedd, L. Lusk, K.M. Hayashi, D. Greenstein, A.C. Vaituzis, T.F. Nugent, D.H. Herman, L.S. Clasen, A.W. Toga, et al. Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences*, 101(21):8174, 2004.

A. Greenstein-Messica and E. Ruppin. Synaptic runaway in associative networks and the pathogenesis of schizophrenia. *Neural Computation*, 10(2):451–465, 1998.

T. Grisso, J. Davis, R. Vesselinov, P.S. Appelbaum, and J. Monahan. Violent thoughts and violent behavior following hospitalization for mental disorder. *Journal of Consulting and Clinical Psychology*, 68(3):388–398, 2000.

J. Hardy and D.J. Selkoe. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science*, 297(5580):353, 2002.

M.E. Hasselmo. Acetylcholine and learning in a cortical associative memory. *Neural computation*, 5:32–32, 1993.

M.E. Hasselmo. Runaway synaptic modification in models of cortex: Implications for Alzheimer's disease. *Neural Networks*, 7:13–40, 1994.

U. Heresco-Levy, D.C. Javitt, M. Ermilov, C. Mordel, G. Silipo, and M. Lichtenstein. Efficacy of high-dose glycine in the treatment of enduring negative symptoms of schizophrenia. *Archives of General Psychiatry*, 56(1):29, 1999.

R.E. Hoffman and T.H. McGlashan. Neural network models of schizophrenia. *Neuroscientist*, 7(5):441–454, 2001.

D. Horn, E. Ruppin, M. Usher, and M. Herrmann. Neural network modeling of memory deterioration in alzheimer's disease. *Neural Computation*, 5(5): 736–749, 1993.

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.

D. Horn, N. Levy, and E. Ruppin. Memory maintenance via neuronal regulation. *Neural Computation*, 10(1):1–18, 1998.

M.R. Hynd, H.L. Scott, and P.R. Dodd. Glutamate-mediated excitotoxicity and neurodegeneration in Alzheimer's disease. *Neurochemistry international*, 45 (5):583–595, 2004.

H.M. Jones and L.S. Pilowsky. Dopamine and antipsychotic drug action revisited. *The British Journal of Psychiatry*, 181(4):271, 2002.

R.B. Knowles, C. Wyart, S.V. Buldyrev, L. Cruz, B. Urbanc, M.E. Hasselmo, H.E. Stanley, and B.T. Hyman. Plaque-induced neurite abnormalities: implications for disruption of neural networks in Alzheimers disease. *Proceedings of the National Academy of Sciences of the United States of America*, 96(9): 5274, 1999.

M.D. Kopelman. Remote and autobiographical memory, temporal context memory and frontal atrophy in Korsakoff and Alzheimer patients. *Neuropsychologia*, 27(4):437–460, 1989.

A.C. Lahti, M.A. Weiler, BA Tamara Michaelidis, A. Parwani, and C.A. Tamminga. Effects of Ketamine in Normal and Schizophrenic Volunteers. *Neuropsychopharmacology*, 25(4):455–467, 2001.

J.E. Lisman, J.T. Coyle, R.W. Green, D.C. Javitt, F.M. Benes, S. Heckers, and A.A. Grace. Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. *Trends in neurosciences*, 31(5): 234–242, 2008.

W.F. Maragos, J.T. Greenamyre, J.B. Penney Jr, and A.B. Young. Glutamate dysfunction in Alzheimer's disease: an hypothesis. *Trends in Neurosciences*, 10(2):65–68, 1987.

M.P. Mattson, R.E. Rydel, I. Lieberburg, and V.L. Smith-Swintosky. Altered calcium signaling and neuronal injury: stroke and Alzheimer's disease as examples. *Annals of the New York Academy of Sciences*, 679:1, 1993.

Elliot D. Menschik and Leif H. Finkel. Cholinergic neuromodulation and Alzheimer's disease: from single cells to network simulations. *Disorders of Brain, Behavior, and Cognition: The Neurocomputational Perspective*, page 19, 1999.

C. Mount and C. Downton. Alzheimer disease: progress or profit? *Nature medicine*, 12(7):780–784, 2006.

M.J. Owens and C.B. Nemeroff. Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. *Clinical Chemistry*, 40(2): 288, 1994.

L.S. Pilowsky, R.M. Murray, R.W. Kerwin, D.C. Costa, P.J. Ell, and N. Verhoeff. Clozapine, single photon emission tomography, and the D2 dopamine receptor blockade hypothesis of schizophrenia. *The Lancet*, 340(8813):199–202, 1992.

T.E. Robinson and J.B. Becker. Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. *Brain Research Reviews*, 11(2): 157–198, 1986.

E.T. Rolls, M. Loh, G. Deco, and G. Winterer. Computational models of schizophrenia and dopamine modulation in the prefrontal cortex. *Nature Reviews Neuroscience*, 9(9):696–709, 2008.

S.M. Rothman and J.W. Olney. Excitotoxity and the NMDA receptor. *Trends in Neurosciences*, 10(7):299–302, 1987.

E. Ruppin. Neural modelling of psychiatric disorders. *Network: Computation in Neural Systems*, 6(4):635–656, 1995.

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, 1995a.

E. Ruppin and J.A. Reggia. Patterns of functional damage in neural network models of associative memory. *Neural computation*, 7(5):1105–1127, 1995b.

E. Ruppin, J.A. Reggia, and D. Horn. Pathogenesis of schizophrenic delusions and hallucinations: a neural model. *Schizophrenia bulletin*, 22:105–123, 1996.

P. Seeman. Dopamine receptors and the dopamine hypothesis of schizophrenia. *Synapse*, 1(2):133–152, 2004.

A.A.F. Sima and Z. Li. Diabetes and Alzheimer's disease-is there a connection? *The Review of Diabetic Studies*, 3(4):161, 2006.

M. Spitzer. The history of neural network research in psychopathology. *Neural Networks and Psychopathology: Connectionist Models in Practice and Research*, page 14, 1998.

D.J. Stein and J. Ludik. *Neural networks and psychopathology: connectionist models in practice and research*. Cambridge University Press, 1998.

J.R. Stevens. Abnormal reinnervation as a basis for schizophrenia: a hypothesis. *Arch Gen Psychiatry*, 49(3):238–43, 1992.

A.M. Stranahan, E.D. Norman, K. Lee, R.G. Cutler, R. Telljohann, J.M. Egan, and M.P. Mattson. Diet-induced insulin resistance impairs hippocampal synaptic plasticity and cognition in middle-aged rats. *Hippocampus*, 18(11): 1085, 2008.

C.A. Tamminga. Schizophrenia and glutamatergic transmission. *Critical reviews in neurobiology*, 12(1-2):21, 1998.

P. Tiraboschi, L. A. Hansen, L. J. Thal, and J. Corey-Bloom. The importance of neuritic plaques and tangles to the development and evolution of AD. *Neurology*, 62(11):1984–9, June 2004.

M.V. Tsodyks and M.V. Feigel'Man. The enhanced storage capacity in neural networks with low activity level. *EPL (Europhysics Letters)*, 6:101–105, 1988.

G.V. Wallenstein and M.E. Hasselmo. Are there common neural mechanisms for learning, epilepsy, and Alzheimer's disease? *Neural Networks and Psychopathology: Connectionist Models in Practice and Research*, pages 316–344, 1998.

D.J. Willshaw, O.P. Buneman, and H.C. Longuet-Higgins. Non-holographic associative memory. *Nature*, 222(5197):960–962, 1969.

D.F. Wong, H.N. Wagner Jr, L.E. Tune, R.F. Dannals, G.D. Pearlson, J.M. Links, C.A. Tamminga, E.P. Broussolle, H.T. Ravert, A.A. Wilson, et al. Positron emission tomography reveals elevated D2 dopamine receptors in drug-naive schizophrenics. *Science*, 234(4783):1558, 1986.