A Systems Approach to Parkinson's Disease

– A Working Paper –

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Preamble

Purpose of the working paper

This working paper addresses the mechanisms and means by which we can apply a systems approach to the understanding of disease. At a practical level this means using the tools of systems biology – mathematical modelling, dynamical systems analysis and systems theory – to the study of disease. For this reason the parts of this paper which describe Parkinson's Disease are written with the systems analyst in mind. On a broader level the paper is also an attempt to show life scientists and clinicians how philosophies and techniques developed for the analysis of physical systems might be extended to the analysis of living systems and disease in particular.

I have selected a disease that is relevant to our times – Parkinson's Disease – and present it as if it were a systems problem in a highly complex machine. This viewpoint is then used to motivate a systems approach to disease in general. That is to say, an approach that is based upon the philosophical, mathematical and computational approaches developed for the analysis of physical and engineering systems. The scientific reason for selecting Parkinson's Disease lie in its complexity. Specifically, and with a high degree of probability, it has no single cause; rather it is the composite result of defects or changes in a number of biological processes, which when taken together trigger disease. The complex set of interacting factors that this involves leads us naturally to adapt techniques that have already proven their value in the analysis of complex interacting physical systems.

The aim is to develop a biological/physiological analogue of the approach that engineers take when presented with an apparently unfathomable deterioration in the performance of a machine. Specifically, they consider the various functional systems of the machine and consider which combinations of events in each of them could contribute to mal-function of the machine. They then test these ideas with computational models of the relevant components and compare the model responses with data observed from the actual machine.

The use of mathematical models in this way allows complex systems to be tested and potential failure patterns inferred. Our aim in this document is, using the tools of systems biology, to mirror this procedure and thus apply a systems approach to disease. The practical objective is to establish a 'Systems of Parkinson's Disease' study that addresses the search for potential causes of the disease in terms of the implicated biological and physiological systems.

The Importance of Neurodegenerative Diseases

> *Here, where men sit and hear each other groan;*
> *Where palsy shakes a few, sad, last grey hairs,*
> *Where youth grows pale, and spectre–thin, and dies;*
> (John Keats, Ode to a Nightingale)

Except that today we do not die so soon; good healthcare, diet and lifestyle ensure that our bodies last much longer than before. As a result, while remaining physically able into old age, our brains fall prey to degenerative conditions that we do not understand and cannot adequately treat.

All neurodegenerative diseases are important and in this working paper Parkinson's Disease is in some sense an examplar. It is representative of the neurodegenerative conditions that will increasingly affect us as our population ages. In terms of a systems approach to biology, it is a relevant because the causes of Parkinson's Disease are unknown and many biological and physiological systems are implicated. Moreover, Parkinson's Disease only occurs naturally in humans, and as a result direct in–vivo study is limited to imaging methods. In such circumstances, simulation, inferential modelling and analysis can be of significant benefit - just as in complex physical machines which must be tested online and while in operation. This said the study of neurodegeneration will test the mathematical and technical scope of a systems approach far beyond its current limits, and require new methods and theories to be developed.

From a strategic viewpoint, neurodegenerative conditions are 'Cinderella diseases'; they remain hidden in homes or institutes, while more dramatic diseases take centre stage[1]. All diseases should receive the best research resources we can deploy, however there is an overwhelming argument for focussed research into the causes of neurodegeneration. The social cost of neurodegeneration is huge, with care largely left in the hands of families and treatment rationed on economic grounds. The burden on society is already large; however if demographic trends continue, then caring for the victims of neurodegenerative diseases will overwhelm the developed world within the foreseeable future.

Layout

Creating a systems approach requires an understanding of the background and current approaches to Parkinson's Disease. In order to do this the

[1]For example, neurodegeration, Alzheimer's and Parkinson's Disease do not get mentioned in the WHO listing of world health topics

material is organised into several parts:

Part I is an introduction to the disease, consisting of some history, a discussion of treatments, current research areas and theories on potential causes. I have taken a broad approach suitable for an introduction for systems biologists, as such this material is primarily as a preparation for the systems approach outlined in the final two sections of this paper.

Part II - The Systems of Parkinson's Disease - further develops the classification started in Part I, but with an explicitly systems language and content. The functional biological and physiological systems are described and their implication in Parkinson's Disease justified by reference to the appropriate scientific literature.

Part III - Implementation of a Systems Approach - is a description of how a systems approach is developing at the Hamilton Institute, together with some suggested study areas for a systems approach to Parkinson's Disease.

Contents

Part I
Parkinson's Disease for Systems Biologists

1 The Shaking Palsy

In 1817 a London doctor, James Parkinson wrote 'An Essay on the Shaking Palsy' [24] in which he described the visible symptoms of the malady that is now associated with his name. His role in identifying the shaking palsy as a distinct disease was a remarkable example of practical inference and although this process has been elegantly described before [26] certain elements of the story bear retelling.

First, it is important to put the man in context. Although he was primarily a medical practitioner with a large practice in Shoreditch, London, James Parkinson was also a scientist and humanitarian with interests reaching beyond medicine. In particular, he was a distinguished geologist and a campaigner for humanitarian causes, including the care of the mentally ill and the welfare of children. Thus the man that wrote 'An Essay on the Shaking Palsy' was a doctor whose medical work was coupled with a general scientific curiosity and underpinned by a moral commitment to the welfare of his fellows. It was as much his social conscience as his professional medical position that led him to write his famous essay.

2 A Brief History of Parkinson's Disease

The 1817 essay is famous as the first account of a previously unclassified condition. Some 60 years later the famous French scientist and founder of modern neurology, Jean Martin Charcot, later coined the term Parkinson's Disease and in doing so linked Parkinson's observations to neurology [10]. Charcot's connection was crucial, but it was not until the late 19th Century and Sherrington's clarification of how the nervous system worked [8] that PD was related to specific changes in certain areas of the brain. In turn, this led to malfunction within the motor circuits of the brain being associated with Parkinsonian tremors.

The next significant development was in the 1960's [9] when Carlsson discovered that a lack of dopamine in the substantia nigra was implicated in PD. This was a major event since it gave a biochemical basis for the phys-

iological symptoms, and led to the first effective treatment for Parkinson's Disease. The treatment was Levadopa, a drug that could pass through the blood-brain barrier and be metabolised into dopamine, thus supplementing the depleted supply. Levadopa was followed by other drugs that attempt to make best use of existing dopamine in the brain by sensitising the dopamine receptors in brain cells, and further drugs which inhibit the breakdown of dopamine in the brain.

Only a small fraction of Parkinson's Disease cases are directly inherited. However, a study of the genetic basis for familial PD can help identify genetic mutations that might also contribute to the normal non-familial form of the disease (termed idiopatic or sporadic PD). In this context, results in the 1990's from genetic studies of families with a history of inherited Parkinson's Disease [30] discovered mutations in a number of genes, including alpha synuclein. Subsequently, the protein alpha synuclein was found to be a main component of protein agglomerations, called Lewy Bodies, in the brains of victims of the sporadic/idiopathic form of Parkinson's Disease. Since then the role of alpha synuclein in cellular function has become a major focus of study.

Separately from pharmacological and biological studies, Limousin and colleages working in the 1990's described their experiments [19] using an electrical stimulation treatment of tremors. Remarkable results were shown in which the electrical stimulation of the subthalmic nucleus dramatically reduced Parkinsonian tremors and restored normal motor function.

3 Treatments for Parkinson's Disease

With its cause unknown, current Parkinson's treatments aim to relieve the visible symptoms of the disease, in particular movement disorders caused by faults in the brain's motor circuits. In this spirit, current therapies take one of two forms: pharmaceutical treatment to restore the dopamine levels in the brain or electrical stimulation of the brain in a particular area. Specifically:

Chemical Treatment: Dopamine replacement. Subsequent to the discovery of the death of dopamine generating (dopaminergic) cells as the cause Parkinsonian movement disorders, the initial focus of treatment became the artificial supplementation of dopamine. Dopamine itself will not pass through the blood–brain barrier and to overcome this problem the drug Levadopa was developed. Levadopa is able to cross the blood-brain barrier, after which it is converted into dopamine and

supplements the deficit in intrinsic dopamine. Levadopa has numerous side-effects and becomes less effective with prolonged use. For this reason other treatments have been developed as detailed below.

Chemical Treatment: Levadopa breakdown inhibition. Only a small percentage of Levadopa reaches the brain, much of it is metabolised elsewhere in the body. The Levadopa breakdown inhibitors (COMT inhibitors) reduce the loss of Levadopa by metabolic action thus reducing the levels required in treatment.

Chemical Treatment: Dopamine agonists. This form of treatment does not to add external dopamine. Instead it introduces a substance that stimulates dopamine receptors in a way that emulates dopamine.

Chemical Treatment: Dopamine breakdown inhibition. After neurotransmitters such as dopamine have performed their function, the excess neurotransmitters are recycled back into the cell for reuse. In this third form of treatment (monoamine oxidase Type B (MAOB) inhibitors) the aim is to delay or inhibit the breakdown mechanisms so that what dopamine that is naturally secreted remains available for a longer period.

Electrical Treatment: Deep Brain Stimulation Deep Brain Stimulation (DBS) deals with the breakdown of motor movements associated with Parkinson's Disease. Trials of DBS have shown remarkable recovery of motor movement when a repetitive electrical pulse is applied using electrodes implanted in the subthalmic nucleus. The dramatic improvement in mobility of DBS have encouraged its general use; it remains however a relatively new treatment.

Chemical approaches to treatment are focussed upon the deficit of dopamine in the motor circuits of the brain using drugs. However, drugs become less effective over time and a periodic 're–balancing' of medication is required to maintain the clinical benefits. Eventually even this fails.

Electrical treatment (DBS) has the same aim as drug treatment in that it ameliorates movement problems. It does this by electrical stimulation of an appropriate part of the brain's motor circuit. DBS is a relatively new technique, the long term effectiveness of which is still unknown. Deep Brain Stimulation is usually applied with drug treatment and is not a replacement. In fact, both approaches share the common feature that they attempt to mitigate the visible symptoms of the disease – they do not address the

causes. In fact, the causes of Parkinson's Disease are unknown, but are most probably associated with a complex interaction of a number of different biological and physiological processes. In the paragraphs that follow we consider the possible causal factors. This will then be used to determine the various biological systems which might be implicated in the disease, with the overall aim of developing a systems approach to Parkinson's Disease.

4 Current Research Areas

This is a summary of some current research areas. It is incomplete [2], but provides a snapshot of the many areas. Having said this, much of the research into Parkinson's Disease is associated with finding drugs which can alleviate its symptoms - e.g. the premature death of dopaminergic brain cells or the consequence loss of dopamine to activate the motor circuit. Here we focus on research that relates to investigation of the causes.

4.1 Genetics

Genetic studies are currently a very active research area for Parkinson's Disease, even though only a small subset of sufferers have a direct familial link. In the few families with early onset Parkinson's disease or juvenile Parkinson's disease, the disease is thought to be transmitted via mutations in genes encoding proteins such as alpha-synuclein and parkin. However, in the majority of families affected by Parkinson's disease, the disease appears to skip generations, irrespective of the age of onset. As a consequence the familial forms of this disease are considered to be caused by interaction between one or more genes and the environment.

Despite the low incidence of familial PD, the study of genetic mutations in familial PD has led to a better understanding of how mutations in specific genes are associated with characteristics found in sporadic PD. For example, the Parkin gene (discovered during familial PD studies) has been associated with the cellular system for breaking down unwanted proteins (the Ubiquitin-Proteasome System) [17]. This in turn would potentially allow unwanted proteins to build to toxic levels and lead to cell death [22]. The Parkin gene may have other duties in toxic protection and promoting dopamine activity. This and other genetic connections are the subject of intense research and prolific publication.

[2] The various funding agencies give a good account of research in the area through their descriptions of funded projects – see the Appendix for useful links.

4.2 Role of Alpha-Synuclein

Genetic studies have shown that α–synuclein gene mutations are associated with familial PD. Alpha-synuclein was subsequently identified as a main component of the protein agglomerations (Lewy Bodies and Lewy Neurites) that appear in and around neurons of sporadic PD victims. The strong association of alpha-synuclein with the disease pathology have given rise to research into the more general role of this protein. Specifically, mutations in α–synuclein have subsequently been associated with damage to cell membranes and mal-function of the protein disposal machinery. In particular, mutated α–synuclein may interfere with the lysosome pathway and hence allow toxic levels of proteins to build.

4.3 Deep Brain Stimulation

See the separate working paper: *The Systems of Parkinson's Disease: Deep Brain Stimulation* and [33].

4.4 Oxidative Stress

Oxidative stress occurs when excessive reactive oxygen products are produced - more than the cellular mechanisms can absorb. This can occur by a number of mechanisms. For example, elevated levels of iron have been observed in the brains of Parkinson's sufferers and this in turn has been linked to increased oxidative stress and (potentially) the aggomeration of alpha-synuclein. A significant research effort addresses the use of chelation. This technique prevents metals from forming reactive oxidative products that may damaged proteins and cause oxidative stress. In a similar vein, excessive highly reactive molecules in the brain (free radicals) can cause cellular damage in part by oxidative stress.

5 Causal Factors of Parkinson's Disease

As previously noted, the essential features of Parkinson's Disease are: the death/malfunction of neurons in certain parts of the brain. As demonstrated by Braak and co-workers [7], this process takes place in a staged sequence that apparently enters the brain at the brain stem, damaging the olefactory bulb, gradually progressing and culminating in the death of dopaminergic cells in the substantia nigra. The cell death stages are accompanied by the

build up of excess quantities of the protein alpha–synuclein in the corresponding components of the brain. What causes this sequence of events is however unknown. Indeed there may be no single unique cause, instead it is more likely that a number of issues come together to cause the disease. In this sense, Parkinson's Disease may be a family of disease mechanisms which all give rise to similar symptoms.

As it is currently understood, the following is a list of possible causal factors:

Environmental Toxins. Various studies have indicated a linkage between the incidence of Parkinson's Disease and environmental toxins such as certain herbicides and pesticides associated with agriculture. For example, the environmental toxins Paraquat, Rotenone and Maneb, [32] have been associated with cell death via damage to the cell mitochondria. Studies have also linked the disease to solvents used in industrial processes and certain drugs. In fact, the search for environmental toxins was triggered by the discovery that drug addicts using preparations contaminated with the chemical MPTP also developed Parkinson type symptoms [18].

In addition to environmental toxins, many substances that occur naturally in the body and have specific biological and physiological uses are toxic when they occur in excessive amounts at the wrong place and time. Thus a failure in the internal mechanisms that breakdown unwanted molecules or an excess number of normally useful molecules may also contribute to Parkinson's disease.

Genetics. The studies of Parkinson's Disease in families has established a genetic basis for some forms of the disease. In particular, mutations in a number of genes have been identified as being implicated - notably the Parkin gene, but also the alpha-synuclein gene and others [31, 11]. Familial Parkinson's Disease is relatively rare (approximately 5 percent of cases) compared to the normal form (idiopathic/sporadic Parkinson's Disease). However, study of mutations in genes that cause cell functions to breakdown and lead to PD may indicate the cellular mechanisms that are implicated in sporadic/idiopathic Parkinson's Disease.

Energy stressing. Neurons need energy in order to function, and if denied energy they will start to selectively shut down less essential functions and eventually die. Thus a possible contributory factor is a deficit in either the acquisition and/or effective use of energy by neurons.

Neurons require much more energy than other body cell types and thus may be more prone to failures associated with cellular inefficiencies. In addition, there is evidence that the neurons most effected are those with the highest energy requirements – these are usually neurons with extended axons and/or lightly myelinated axons.

Brain aging. Because the risk of Parkinson's Disease increases with age, then it is possible that cell death occurs as a natural process of cell aging. Why neurons should apparently selectively die in different brain parts is not known, but may be related to their work–rate and this again maybe associated with energy stress issues, long term nutritional deficiencies (see below) or some other stressing mechanism.

Pathogens. It has recently been proposed by Braak and colleagues that Parkinson's Disease could be caused by an unknown pathogen, [5]. In the Braak theory, the pathogen would enter the enteric nervous system through the wall of the gut. It would then work backwards and upwards through the axons that connect the enteric system to the brain and eventually enter at the brain stem. Although Braak's staging theory is accepted, the corresponding pathogen theory remains controversial.

Nutrition. Nutritional studies have shown that there is a link between nutrition and neurodegeneration generally. These range from the role of long-chain fatty acids to the antioxidant properties of flavonoids. We will not pursue this specifically in this working paper, but for further information the readers is referred to section or the web site of the Nutrition Society (`www.nutritionsociety.org`).

6 Implicated Systems

From the preceding section we see that there are a number of potential causal mechanisms associated with PD, but no single clear defining feature. The only thing we know is that Parkinson's Disease causes neurons to die in a staged manner, starting at the olefactory bulb at the base of the brain and proceeding to the dopaminergic neurons in the substantia nigra in the last stages. Numerous sections of the brain are affected at various stages in the disease, but it is dopamineric neurons which are particularly vulnerable. A molecular marker of Parkinson's Disease is the presence of protein agglomerations consisting largely of α–synuclein. These are found both within

neurons and in fibrils in the extracellular space. Environmental toxins are also known to cause Parkinsonian symptoms and a buildup of intrinsic toxins has been observed in Parkinson's Disease.

Based on these characteristics, and the points from elsewhere in this document, we can identify key systems within the body that contribute to the disease:

Cellular Systems. The genetic and cell biology focus of much research [32] means that a number of cellular processes and signalling systems have been implicated in Parkinson's Disease. We consider just a few key items here.

1. At the top level, a global understanding of programmed cell death (apoptosis) is of central importance. In the case of Parkinson's Disease, it is crucial to understand the cellular mechanisms that trigger apoptosis in neurons affected by Parkinson's.
2. The accumulation of α–synuclein in the form of Lewy Bodies (within a cell) and Lewy Neurites (in the intercellular space) is the key indicator of a diseased brain. The build up of these objects suggest that the cellular mechanisms for breaking down unwanted proteins (the ubiquitin – proteasome system) may be damaged in a diseased brain.
3. The mitochondria function is also known to be damaged in PD brains and there is a link between mitochondrial function and genes associated with PD. As will be indicated later, this has implications for the neuronal energy system, since damaged mitochondria will reduce the energy available to a cell.

Motor Circuit Systems. The most important consequence of PD is impairment of chemo–electrical communication mechanisms in the brain. Practical experience with DBS has shown that external electrical stimulation can ameliorate the effects of impaired neural communication, but the mechanisms for this are not known in detail. Thus although electrical failure is not a cause of Parkinson's Disease, the neuronal electrical system deserves study as an implicated system that has therapeutic importance both in Parkinson's disease and other situations of neurological damage.

Staging Systems. There is evidence from the Braak laboratories [5] that Parkinson's Disease is a progressive process that proceeds in stages

through the brain. The Braak team have proposed a pathogenic process whereby neuronal damage commences in the nervous system associated with the gut, progresses upward to the brain stem and into other areas of the brain. The hypothesis is that an unknown pathogen enters the body via the gut wall and progresses by a process of reverse transport up the spinal cord into the brain. This is a controversial hypothesis, but the staging process of the disease deserves a systems study.

Neuronal Energy Systems. I know of no research (apart from the mitochondria work mentioned elsewhere) into the role of brain energy supplies in the death of neurons in Parkinson's Disease. However, it is plausible that a reduction in cellular energy may contribute to cell death in the staged pattern observed in Parkinson's Disease. First, the malfunction of mitochondria in PD (caused, amongst other things, by environmental toxins) will lead to a reduction in a neuron's ability to create an energy supply. Second, the neurons that are susceptible to damage in PD are those whose high energy requirements, (e.g. cells with long or lightly myelinated axons, [5]). It is therefore reasonable to implicate cellular energy systems in one of three possible ways:

1. The mechanism that supplies energy to the cells may be impaired or damaged.
2. The cell mitochondria maybe damaged by environmental or intrinsic toxins, thus reducing its efficiency in synthesizing ATP.
3. The energy requirements of cells with long or unprotected axons may become too much for the energy supply mechanisms to support.

Part II
The Systems of Parkinson's Disease

In this part we take an explicitly systems viewpoint and consider specific aspects of the implicated systems mentioned in Section 6. These are then used to consider those implicated biological and physiological processes that might be tractable from a systems biology viewpoint. In this context and from a systems perspective, we make a distinction between:

1. (a) Signalling systems that have relevant biological function within a cell.
2. (b) Issues that concern the electro–chemical systems associated with the brain's motor circuit systems.
3. (c) Possible staging systems associated with the Braak hypothesis.
4. (c) Metabolic systems for handling energy in the cell,

7 Cellular Processes

7.1 Programmed Cell Death

When Parkinson's disease reaches the brain regions that control movement, it triggers the death of dopaminergic cells in the substantia nigra. This in turn causes the dopamine deficiency that makes the motor circuit's malfunction. The cellular systems that govern programmed cell death, (apoptosis) of brain cells are therefore of central importance in Parkinson's disease. Although mitochondria complex I inhibition and oxidative stress have been implicated, the biological triggers for apoptotsis pathways in PD are unknown.

7.2 Oxidative stress and free radical damage

There is evidence of increased oxidative stress and free radical damage in the substantia nigra in Parkinson's disease sufferers.

7.3 Inflammatory Processes

Inflammatory processes have been implicated in PD. For example, as a demyelinating agent in axons [23], a process that would open the neuron to energy stressing.

7.4 Protein Degradation

The pathological feature of Parkinson's disease is the accumulation of the protein alphasynuclein in intracellular plaques (Lewy Bodies) and extracellular fibrilla. Normally the cell prevents excessive protein build–up by recycling them when they have fulfilled their function. Two cellular systems exist to prevent intracellular proteins accumulating to excessive levels. The ubiquitin-proteasome system [1] breaks down excess proteins produced during regular cellular function and the lysosomal system [2] digests unwanted proteins entering via the cell membrane. It is believed that if these disposal systems fail to work correctly, toxins and other substances may build up to harmful levels and thus trigger the programmed cell death process mentioned above.

The ubiquitin-proteasome system involves interactions between several proteins, including the Parkinson gene - parkin and UCH-L1. Mutations in the parkin gene also interfere with normal proteasomal function, and scientists have shown that treatment with a toxin that inhibits the ubiquitin-proteasome system causes cells with mutant alpha-synuclein to be susceptible to programmed cell death. This is accompanied by activation of caspases and by injury to the mitochondria described below.

The digestion of cellular organelles and other cell components in the lysomal machinery (autophagy autophagocytosis) is a normal part of cell growth, development and homeostasis. It forms a mechanism for a starving cell to re-allocate resources and nutrients from non-essential to essential processes. There is a suggestion that apoptosis autophagy may occur in the Substantia Nigra during Parkinson's disease.

7.5 Mitochondrial Systems

The mitochondria within a cell are important because of their role in the cellular energy provision. In particular, one function of cellular mitochondria is to synthesis the high–energy compound adenosine triphosphate (ATP) from nutrients that enter through the cell membrane and are transported into the mitochondria. Thus failures in Complex I of the mitochondria reduces the efficiency of energy conversion in a cell. As a result mitochondrial

systems are implicated because damage to mitochondria will cause energy stressing within the cell, with its implications for apoptotic triggering. Also mitochondrial damage has been shown to result from mutations in genes (such as parkin) associated with familial PD. Likewise, it has been reported that mitochondrial damage may cause α–synuclein aggregation via oxidative stress.

8 Motor Circuit Systems

There is a significant literature that considers the motor circuit of the central nervous system from a control systems perspective, e.g. [3, 25]. This work generally use a high-level description of the motor circuits which does not include sufficient biological detail to be of value in studying the potential causes of Parkinson's Disease. Likewise, the understanding of the motor circuits has advanced in recent years and in away that renders many control studies of the motor circuit obsolete. Thus in order to be biological informative motor circuit control models require radical reworking based upon the latest information on brain topology, communication and biology.

Related to motor control circuit models, but more immediately relevant, would be a systems study of motor circuit stimulation techniques (Deep Brain Stimulation in particular) that have both therapeutic value and help us understand the neural signalling mechanisms. Specifically, in the space of about ten years since its discovery [19], the use of Deep Brain Stimulation (DBS) has been shown to be an effective treatment in advanced Parkinson's Disease (PD) [20]. It can yield dramatic, and in some cases lasting, improvement in motor action such that Parkinson's patients who have had DBS electrodes implanted in their subthalamic nucleus can go rapidly from highly impaired movement to apparently normal movements.

This restorative process seems not to be connected with direct biochemical systems. Specifically, the restoration of walking and hand movements in Parkinson's patients is (in drug treatment) associated with an increase in dopamine in the striatum of the central nervous system motor circuit. However, experimental evidence with living parkinsonian humans does not show any increase in striatal dopamine concentration under effective DBS applied to the Subthalmic Nucleus [14]. From this we conclude that the mechanisms of DBS are due to a change in the electro-physiological function of neurons in the motor circuit.

9 Staging Systems in Disease Progression

Braak and co–workers have described a staging of brain damage as it occurs in Parkinson's Disease [6]. The theory is based upon extensive post-mortem observations, which indicate that Parkinson's Disease passes through a series of stages, including destruction of the dopaminergic neurons in the substantia nigra and subsequent final stages of dementia. While the associated theory that a pathogen is responsible [5] is controversial, the staging process is of great potential importance to determining the causal mechanisms. A systems study of this would be of great value.

10 Energy Systems

A lack of energy with which to power the functions of a cell would cause the reallocation of cellular resources, progressive selective breakdown of cell function and eventually cell death. Based on the remarks concerning brain energy in Section 6, we believe that failings in the brain energy system is implicated in Parkinson's Disease. Failure in the energy systems of a neuron can be caused by systematic faults in any of three main processes:

1. Input: the acquisition of glucose from the brain capillaries.
2. Conversion: The synthesis of glucose into ATP within the cell mitochondria.
3. Usage: Excessive energy demands within the neuron, due to damage, insufficient axon myelination, or long axons.

In this context, we consider the last two of these options (mitochondrial damage) as being a cellular system (see Section 7.5).

10.1 Energy Input Systems

The metabolic mechanism by which neurons obtain energy relates to the transfer of glucose and oxygen from brain capillaries to the neurons. There is lack of agreement on the details of the mechanisms that take place when neural signalling creates demands [12, 13], nonetheless there is sufficient knowledge to indicate that stimulation of neural circuits causes transient increases the energy demands. Inefficiencies in this process may cause stressing in the cell with concomitant failures.

10.2 Energy Usage Systems

The argument that energy may be a contributory factor is supported by the proposition that thinly myelinated cells and cells with long axonal connections are preferentially effected in Parkinson's disease [5], with concomitant implications in Alzheimer's disease [4]. It follows that these will have a high transient energy budget such that signalling through such channels will necessarily stress the energy input mechanisms [4].

Part III
Implementation of a Systems Approach

In this part we describe how a Systems of Parkinson's Disease can be implemented and what it might do.

11 Practical Mechanisms for Proceeding

11.1 Basics

The underlying assumption is that the task of understanding Parkinson's Disease is so complex and large that no one institution has the resources required. Thus we propose a mechanism whereby information and resources may be shared via the internet. The intention is create a framework within which researchers can associate, share information and publish their activity through a web site (www.systemsofparkinsons.org). The model for this approach is the remarkable work of Peter Hunter and his many collaborators in developing the Physiome Project [16, 15].

With www.systemsofparkinsons.org we will construct a web–based repository of models. As the mechanism for model documentation we will use the Systems Biology Markup Language [28] as the standard. Where specific models are implemented, we will encourage the use of Henning Schmidt's public access toolbox for systems biology [29]. In the same spirit, we will create a means for reports and research results relating to the Systems of Parkinson's Disease to be exchanged and accessed.

11.2 Current Status

The beginnings of this process can be seen by following the 'research by topic' links on the Hamilton Institute web site wwww.systemsbiology. This will take you to the Hamilton Institute research projects in this area. They include research into the brain energy metabolism (see 12.2 below), the theory of deep brain stimulation (see 12.4 below) and visualisation tools for data from Parkinsonian brains.

12 Proposals for Study Areas

In this section we outline potential study areas within the Systems of Parkinson's project.

12.1 Cellular Processes: Study Proposals

Given the number of cellular mechanisms implicated in Parkinson's Disease, I anticipate a large number of mathematical modelling and associated systems analysis opportunities here. In the first instance this would necessitate mathematical modellers developing computational models in a standard framework for the cellular systems mentioned previously. This would start with:

- The mathematical modelling of neural apoptosis and possible trigger mechanisms.
- The mitochondrial systems and in particular the complex I function.
- The ubiquitin-proteasome system and lysomal machinery and their implications in alpha-synuclein agglomerations.
- Possible cellular mechanisms for apoptotic triggering.

12.2 Brain Energy Metabolism: Study Proposal

The hypothesis here is that Parkinson's disease maybe associated with a compromised energy metabolism such that vulnerable cells begins to shut down the less essential functions. If these include the protein breakdown systems required to remove excess proteins then causality is established. The Hamilton Institute are working with collaborators in the Chemistry Department of NUIM with the following plan [33]:

1. To develop a 'gold standard' mathematical model of the brain energy metabolism based upon in-vivo extracellular measurements obtained on a common basis and with a range of stimulii.

2. To use the model as an objective quantitative tool for understanding how the brain energy metabolism works.

3. To then extend the model to investigate how inefficiencies or failures in the brain energy metabolism might influence the breakdown of cellular functions – such as the ubiquitation process.

12.3 The Cerebral Motor Circuit: Study Proposals

As noted earlier, there are a number of control oriented mathematical models of the indirect motor circuit (see for example [25]). However, such studies were based upon knowledge of the brain's motor circuitry that is now outdated, thus there is a strong case for reconsidering the area in a way that embraces new knowledge of the interconnections of different parts of the brain and a better appreciation of the signalling methods based upon biological research and brain imaging research of recent years.

12.4 Deep Brain Stimulation: Study Proposal

The 'calming' of motor circuit disturbances by electrical excitation is the quoted reason why Deep Brain Stimulation DBS) works [19], but apart from this general remark there is limited understanding of the phenomena. However, the sensitivity of patients to pulse frequency in DBS suggests that there is a role for mathematical modelling of the coordination properties of signals in axonal connections [21] [27][3].

The Hamilton Institute are working with collaborators on a mathematical model that attempts to explain how Deep Brain Stimulation works [33] according to the following plan:

1. To develop abstract models of synchronisation in finite communitities of coupled oscillatory systems.

2. Extend the abstract model to more be more representative of oscillatory mechanisms in neural systems.

3. To then use the models to provide guidance to clinicians on the using and managing DBS therapies.

[3] see also `http://www.math.pitt.edu/~rubin/pub/pub.html`.

12.5 The Braak Staging Hypothesis: Study Proposal

The staging theory has been developed by Braak and others in a compelling manner. There is therefore a need to illuminate the argument with a mathematical model of the staging process based upon tools from computational physiological. This in turn may lay a foundation for a mathematical model with which to understand the staging process and test the controversial pathogen proposals.

A Additional Sources

A.1 Useful links

- European Parkinson's Disease Association: `http://www.epda.eu.com`
- The UK Parkinson's Disease Society: `www.parkinsons.org.uk`
- The USA is represented by a number of charitable organisation. One which has many useful links is: `www.parkinson.org`
- The Nutrition Society (`www.nutritionsociety.org`)

A.2 Research Centres

In the USA, the National Institute of Neurological Disorders and Stroke (NINDS), part of the National Institutes of Health (NIH) supports Parkinson's research with the purpose of finding a cure or treatment for this disease, and to award Core Center Grants designated as Morris K. Udall Centers of Excellence for Parkinson's Disease (PD) Research for research and training for scientists undertaking PD research. For further information to go `www.ninds.nih.gov/disorders/parkinsons_disease`

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