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Systems Biology of Parkinson's Disease

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Preface

The term *Systems Biology* first appeared in 1968 [1] and immediately attracted attention in both the life and physical sciences. It was important because it provided a name, and therefore a focus, for an emerging interdisciplinary activity. The intervening years have been fruitful for systems biology. Many countries now have institutes dedicated to the area (some have several!) and the number of interdisciplinary courses linking systems theory and biology continues to expand. Rapid growth is not generally a harmonious affair and so it is with systems biology. There are continuing debates as to what systems biology means, what it should do, and how it can best deliver benefits to society. However, no matter how animated these discussions may become, there is a clear consensus on one point: interdisciplinary effort is essential if we are to adequately understand the complexities of the human body and the diseases that afflict it.

Systems biology in the service of disease research is the motivation for this book. The choice of Parkinson's disease (PD) for the study was determined by the problems that PD, and other neurodegenerative disorders, pose to society. Parkinson's disease affects approximately 0.3% of the world's population and 1% of people over 60 years old. And PD exacts a high price: in the USA for example it costs over 20 billion dollars per year, and this sum will continue to grow as life expectancy increases. Beyond the financial issues, PD brings a considerable long-term personal burden to sufferers: with no cures or preventative strategies, it typically takes more than a decade of decline to run its course. There are interventions to alleviate the principal symptoms of motor dysfunction, but no treatment can prevent its progression.

For medical science, the problems of PD lie with its complexity, variability and multi-factorial origins. Each of these issues presents huge challenges for traditional life science; together they form an immense obstacle to progress and understanding. The aim of this book is to demonstrate how systems biology tools—new measurement methods, mathematical modelling, computer simulation and theoretical analysis—can help in disease research. The chapters in this volume present specific examples of these, as applied to PD. They represent a snapshot of the state-of-the-art in the systems biology of Parkinson's disease.

Background

Because this book addresses two scientific constituencies, we offer two contrasting introductory backgrounds: one for the systems biology community and the other for PD researchers. First for systems biologists.

On Parkinson's Disease

Modern lifestyles and modern healthcare mean that people live longer, and as a consequence, they increasingly fall prey to neurodegenerative conditions like PD. But PD is not a product of modern life styles—ancient Ayurveda literature describes a disease resembling PD [2, 3]. Much later, around 170 A.D., Galen made a good first definition of motor tremor (which would have included PD); distinguishing it from other forms of involuntary movement [4]. Since Galen there have been numerous descriptions of tremor and "shaking palsies," with the first comprehensive attempt in the English language being James Parkinson's famous essay [5]. As part of his important work, Charcot [6] extended Parkinson's description and coined the term Parkinson's disease. Subsequently, Sherringham [7] moved things on considerable by making the link between PD tremors and the specific region of the brain responsible for motor control.

What was going wrong in the motor region remained unknown until the 1960s, when a deficit of dopamine in the motor control circuits of the *basal ganglia* was associated with Parkinsonian tremor [8]. This discovery led to the use of L-dopa as the first effective therapy for PD. L-dopa is a dopamine precursor and was the first of a family of therapies that attempt to regulate dopamine levels in the *striatum*. To this day, these drugs remain the standard treatment.

Further important illumination came in the staging theory [9] in which, by tracing intracellular accumulations of a protein (alphasynuclein) residue, a progressive pattern was observed. This consists of a stage-wise trajectory of PD damage, starting at brain stem and spreading in a sequential manner to different brain sectors. Within the staging process each brain region responds differently, but the dopaminergic neurons of the *substantia nigra* (*SN*) are most vulnerable: it is their death that causes the debilitating tremors associated with PD.

This book is about systems biology used to study the causes of PD and biochemical mechanisms of PD, rather than therapies. However, it is interesting to mention, at least in passing, an important new electrical therapeutic from the 1980s. This takes the form of low intensity periodic (~130 Hz) stimulation of deep-brain elements associated with the motor circuits—particularly the *subthalamic nucleus* [10]. When it works, the technique, known as deep brain stimulation (DBS) is capable of remarkable results, often with complete alleviation of motor tremors. There are a number of plausible DBS theories, but how DBS works in detail is a subject of current research.

Although the causes of PD are unknown, a good deal is known about various environmental, genetic and biological issues that are implicated in the condition. Most of these will be described in detail within the chapters that follow, but an initial overview will provide some orientation. A number of genetic irregularities have been associated with PD. However, the number of truly genetic cases of PD (familial PD) is small (less than 10%). In most instances, the cause of PD is unknown—this is termed idiopathic or sporadic PD. For this majority of sufferers the general view is that advancing age, life-experiences and a number of environmental issues can be responsible. What happens in a neuron during PD is known only in qualitative terms and the general description is of several sets of biochemical species interacting in a "vicious cycle." Why certain neurons are more vulnerable than others is also unknown, although the chapters of this volume will use systems ideas to make some suggestions.

On Systems Biology

This section is for PD specialists and researchers.

In its broadest definition, systems biology is the application to living things of techniques (mathematical modelling, theoretical analysis and computer simulation) originally developed to understand how physical/engineering systems work. Such interdisciplinary transfers of ideas from the physical to the living world (and vice versa) are not new. They occur periodically in the development of science, with a relevant example from 1679 being Borelli's *De Motu Animalium*. In this justly famous work, Borelli used the methods of Galileo's in the field of mechanics to explain movement in humans, animal and fishes.

Attempts to apply ideas from technological systems theory to biology started in earnest during the mid-twentieth century, notably with Norbert Wiener's book, *Cybernetics* [11]. In this important book, Wiener gave accounts of control and communications theory applied to understand biological phenomena. Despite its importance, *Cybernetics* was in fact indicative of a wider interdisciplinary movement, which is typified by other works, such as Schrödinger's *What is Life?* [12]; Cannon's, *The Wisdom of the Body*, [13]; and Hodgkin and Huxley's research [14]. These contributions gave important indicators of how ideas from physics, applied mathematics and technological systems theory could usefully help explain how living things work—with Hodgkin and Huxley showing a "proof of the pudding."

In the 1960s, systems theorists and life scientists began to formalise systems biology as the application of mathematical modelling, dynamical systems analysis and computer simulation in life science [1]. Cheap computing and new sensing technologies became available, and by the last decades of the twentieth century it became feasible to model and analyse complex biological systems on personal computers. This task was made easier by free software and open source directories of models (for example the CellML directory of mathematical models).

The enthusiasm of cheerleaders such as Kitano [15], and others, generated an expectation that systems biology could give deeper understanding of cellular processes and help solve big problems in drug development. In the sequel to the Human Genome Project there was a belief among geneticists that systems biology would help extract hidden information (particularly concerning complex diseases [16]) from genomic and proteomic data. In another fundamental development, many systems biologists hope to elucidate the hidden dynamics of gene expression and cell signalling pathways. In parallel with fundamental research aims, there has always been a "problem-solving" view of systems biology. Features of this include a systems approach to (1) mathematical modelling of entire organs [17], (2) "personalised medicine" for delivery of healthcare [18] and (3) understanding the causes of complex diseases. In the latter context, mathematical models have been used to study HIV-AIDS, with emergent work on systems biology approaches to cancer, diabetes, etc.

Possibly because of their extreme complexity, a systems biology approach to neurodegenerative disorders has been late coming. However, reports such as *Dementia 2010* and others [19] have exposed the social and economic imperatives associated with our ageing populations. Fortunately, and with help from forceful publicity campaigns, neurodegeneration has moved to the front rank of diseases to be addressed with urgency and by every available means. This book is the first to approach Parkinson's disease from a systems viewpoint. We hope that it will create focus and direction for further effort and give a platform for systems approaches to other neurodegenerative conditions.

Layout of the Book

The contributors to this volume approach a range of PD issues from a systems perspective. The complexity and variability of PD make it hard to classify the contributions precisely, but a useful way in which to attempt this is through the temporal and spatial spectrum of PD's features (Fig. 1). Notice in particular that the underlying mechanisms of PD's aetiology and pathology span several orders of magnitude in both time and space. At one end, PD involves imbalances in ion transport at the sub-cellular level, operating in the order of milliseconds. At the other end, physiological changes operate over decades and throughout the entire brain. It is extremely hard, if not impossible, to synthesise all the available knowledge on such a complex disease in a way that would reconcile the time and length scales involved. We do not pretend to resolve this issue, but we do find it useful to organise and present the content of this volume with this consideration in mind. Ultimately, and in the spirit of the Human Physiome project [20], modelling efforts will achieve a certain extent of unification of PD's multiple dimensions. The material presented here is a step in this direction.

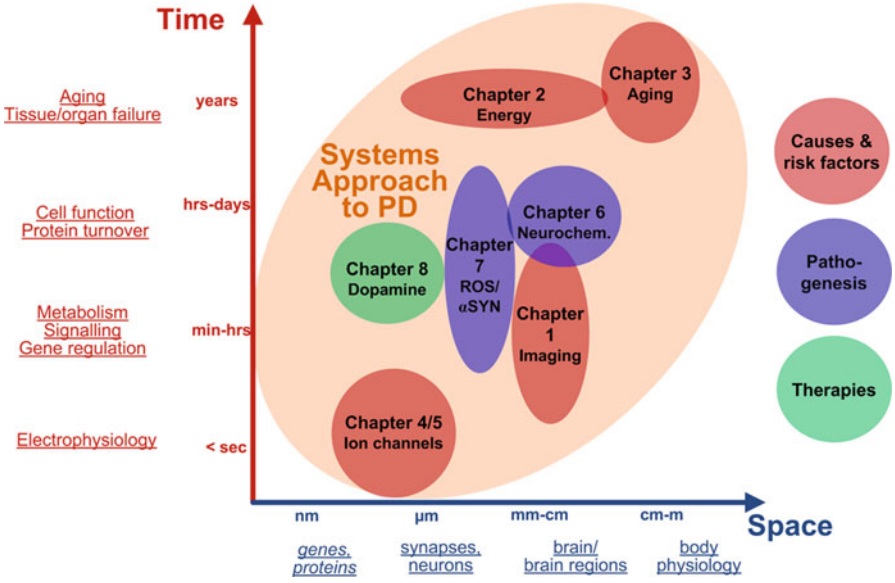

Fig. 1 Overview of the book's content in terms of the spatial and temporal scales involved in Parkinson's disease

As shown with colour codes in Fig. 1, the main features of PD can be sub-divided as follows:

1. The causes and risk factors in PD.
2. The inception (pathogenesis) of the PD state.
3. Dopamine therapies for PD.

With this sub-division in mind, chapters are laid out as follows.

Causes and Risk Factors

Chapter 1 describes how innovative imaging techniques have been able to reveal previously unknown structures of dopaminergic neurons of the *SN*. The dramatic images shown in the chapter reveal new information and give insights into the special vulnerability of SN neurons to energy-stresses and their compensatory redundancy mechanism. These energy-related findings have special implications for Chap. 2, which uses a mathematical model of brain energy metabolism to assess how energy-stress forms a common denominator in PD risk factors. The most common risk factor for PD—advanced age—gets detail treatment in Chap. 3.

Here, the techniques of fuzzy logic are used to develop a mathematical model of ageing phenotypes and assess the implications of cellular ageing for PD.

As noted previously the neurons of the *SN* are most vulnerable to PD damage. A special feature of these neurons is their use of calcium ions to facilitate signalling—in particular pace-making signalling. Chapter 4 takes this as its theme and, using mathematical models of electrochemical signalling, explains the potential part played by dysregulated signalling in the vulnerability of SN neurons. Chapter 5 continues with the role of calcium-facilitated signalling in neurons. It constructs a mathematical model of calcium metabolism in *substantia nigral* neurons and estimates the additional energy budgets associated with calcium signalling.

Pathogenesis of PD

The transition from a healthy neuron with a predisposition to PD, to a neuron where PD is established is termed *pathogenesis*. Whereas, as discussed in Chap. 2, the preconditions for disease can grow over many years, it is generally agreed that pathogenic mechanisms proceed over a period where hours and days are the relevant temporal scale. The measurement of such rapid changes requires special in vivo sensing methods, and Chap. 6 deals with a sensing technology designed for just such purposes. These take the form of electrochemical sensors that produce accurate records of both the short and long-term changes that occur during neuronal and glial cellular transitions. This has important implications for the neurochemical processes of pathogenesis that are modelled in Chap. 7. Here, the interactions between reactive oxygen species and mis-folded alphasynuclein are modelled mathematically and used to demonstrate a neurochemical "switch" associated with the pathogenic transition to the disease state.

Dopamine Therapy

Therapy based on restoring/retaining dopamine levels is the gold standard treatment for PD motor dysfunction. However, design and administration of dopamine therapy require expert knowledge and management. Better, more accurately personalised management of dopamine-related treatments would greatly benefit sufferers. Computational modelling of dopamine metabolism is a strong first step in this direction, and our concluding chapter—Chap. 8—addresses this area. It describes the development of a mathematical model of dopamine metabolism, and illustrates its uses through simulation of a range of PD scenarios.

Acknowledgements This book has its origins in the *Symposium on Systems Approaches to Parkinson's Disease*, which was held at the Hamilton Institute in 2010. The event was made possible by the farsighted actions of Science Foundation Ireland who, in 2003, agreed to fund

speculative research on the systems biology of a then unfashionable disease. We gratefully acknowledge their visionary support and assistance. In addition, we thank the contributing authors to this book, and other collaborators, who are helping to shape the systems biology of Parkinson's disease. As their ideas are collectively developed, and other groups add their contributions, we look forward to further advances in the understanding of Parkinson's disease, and ultimately to a better future for sufferers.

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Chapter 1
Imaging of Dopaminergic Neurons and the Implications for Parkinson's Disease

Wakoto Matsuda

Abstract The Systems Biology of Parkinson's disease (PD) will be underpinned by new measurement techniques. This is particularly true of the pathology of PD, where recent developments in brain imaging have offered new insights into the morphology of dopaminergic (DA) neurons that have profound implications for the special vulnerability and role of this class of neurons. In this chapter, we describe these new morphological measurement techniques and how they contribute to our understanding of PD.

We begin with an overview of the conventional understanding of the morphology of DA neurons, as seen from a historical perspective. We then describe novel imaging techniques that reveal important new structural information concerning DA neurons. In particular, we outline some new methods for labeling DA neurons, together with the technical aspects of labeling and measuring axonal structure.

Detail morphological images of DA neurons derived from this new approach are used to elucidate the role of DA neurons in PD. First, we point out how the new images reveal how DA neurons have a massive axonal arborization in the striatum. This arborization is on a scale not previously known, and of a form that implies both a particular vulnerability and a redundancy in DA neurons. Second, we describe how the imaging results indicate that DA neurons innervate both the striosome and the matrix compartments of the striatum. This dual innervation has implications for reinforcement learning in the basal ganglia and for how normal behavior is driven and how it may be disrupted by Levodopa PD therapies.

The chapter concludes with a summary of how these results contribute to our understanding of PD and how it forms a part of the Systems Biology of PD.

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Introduction

The classic denominator of disorders associated with Parkinsonism (including Parkinson's disease (PD)) is neuronal loss in the substantia nigra (*SN*) of the midbrain, especially of DA neurons in the *SN* that project mainly to the striatum. As seen in the *SN*, the ventrolateral tier of neurons appears to be more vulnerable than medial groups of neurons that send projections to the ventral striatum, forebrain, and the medial temporal lobe [10]. Why DA neurons should be more vulnerable to PD damage than neurons in other brain regions is not well understood, although there is evidence that, in a certain sense, DA neurons exhibit a high degree of redundancy. Clinically, there is prodromal phase in PD [39]. Pathologically, there is also a presymptomatic phase, including a loss of nigrostriatal neurons, which is believed to represent a middle stage of a degenerative process that starts in the lower brainstem and olfactory nuclei and ascends throughout the cortex [6, 38].

In this chapter, the chronological progress of labeling and methods of tracing neurons is described in the field of neuroanatomy (section "Basic Structure and Historical Overview of Morphology of Basal Ganglia and DA Neurons"). A novel virus tracer is outlined in section "New Methods for the Imaging (Labeling) of DA Neurons, Including Technical Aspects of Labeling and Measurement of Axon," along with a detail description of the reconstruction technique of single neuron and axonal arborization. Subsequently, based on anatomical findings from the novel neuronal imaging method, the implications for PD are discussed (section "Implications for PD and Learning Models: Two Aspects of Two Findings"). The chapter concludes with a discussion of preliminary results in DA neurons in the other nucleus of the midbrain, and non-DA neurons in the midbrain (section "Preliminary Results in DA Neurons in the VTA, RRF, and Non-DA Neurons in the Midbrain").

Basic Structure and Historical Overview of Morphology of Basal Ganglia and DA Neurons

Basic Structure of Basal Ganglia and DA Neurons

The basal ganglia are central to the cardinal motor manifestations of PD, comprising bradykinesia, rigidity, resting tremor, and postural instability. They consist of a collection of bilateral subcortical nuclei that are so named because they lie at the base of the forebrain in primates. The major components of this region of the brain are the caudate nucleus, the putamen, the globus pallidus (GP), the subthalamic nucleus (STN), and *SN*. The caudate nucleus and putamen are collectively known as the neostriatum. The term "striatum" is often used to encompass both the neostriatum (also called the dorsal striatum) and ventral striatum, the principal