Chapter 1. Introduction

Peter V. E. McClintock[1] and Aneta Stefanovska[2]

[1] Department of Physics, Lancaster University, Lancaster LA1 4YB, United Kingdom aneta@lancaster.ac.uk
[2] Department of Physics, Lancaster University, Lancaster LA1 4YB, United Kingdom p.v.e.mcclintock@lancaster.ac.uk

There are numerous oscillatory systems that are not periodic. In striking contrast to the simple pendulum, which so often introduces the physics student to oscillation theory, their characteristic frequencies vary in time. Such oscillators are found universally in biology, and they also appear in other contexts too. Understanding their dynamics is challenging, not least because physicists new to the area must be willing to discard, or modify, many cherished notions dating back to their schooldays.

The problem is non-trivial, because in practice the origin of the time variability is often unknown (unlike e.g. heart-rate variability where respiration modulates the heart rhythm, or the diurnal rhythm). In mathematical terms, the oscillations are non-autonomous, reflecting the physics of open systems where the function of each oscillator is affected by its environment. Time-frequency analysis is essential. Recent approaches, including wavelet phase coherence analysis and nonlinear mode decomposition, were described during the Workshop and form parts of several of the contributions that follow. These methods are not yet in widespread use, and one purpose of the book (and of the Workshop before it) is to help to promulgate them.

Science is, of course, seamless and indivisible but, for the convenience of readers, we have divided the book into four Parts covering: theory; model-driven and data-driven approaches; biological oscillators; and applications. These are not rigidly separated topics but, rather, an indication of emphasis. The applications chapters, for example, draw freely on the ideas discussed in the first three Parts.

1 Theory

The theory Part opens with two chapters devoted to different aspects of phase reduction, applied to autonomous oscillatory systems, an approach that will be key to most of what follows on non-autonomous oscillators. The underlying idea is to reduce a multi-dimensional dynamical equation describing a nonlinear limit cycle oscillator to a one-dimensional phase equation. Many rhythmic phenomena can in practice be considered as nonlinear limit cycle oscillators, and hence described in terms of their phase dynamics, usually amounting to an enormous simplification. This approach is particularly useful in relation to the analysis of synchronising oscillators. In real-world situations the oscillators are of course subject to external perturbations that take the system away from its limit cycle temporarily, and much interest attaches to what happens when two such systems interact with each other. Note however that the core of the book involves consideration of the situation that arises when one or more of the oscillators is non-autonomous, so that the frequency of the limit cycle itself is being perturbed by external agency. Chapter 2 by Nakao makes use of a recently-introduced extension of the classical phase reduction method that also includes amplitude degrees of freedom. He considers phase-amplitude reduction in a spatially-extended reaction-diffusion system exhibiting stable oscillatory patterns, and its entrainment by optimized periodic forcing with additional stabilization by feedback. Chapter 3 by Pietras and Daffertshofer shows how different reduction techniques applied to a network of interacting neural oscillators can lead to different dynamics of the reduced network, thereby identifying some delicate issues in the application of the method. They demonstrate that an accurately-derived phase model can properly capture the collective dynamics and they discuss the effect of biologically plausible connectivity structures on the network behaviour.

In Chapter 4, Kloeden and Yang outline relevant ideas from the mathematical theory of non-autonomous attractors, explaining that the nature of time in a non-autonomous dynamical system is very different from that in autonomous systems. They point out that this difference has profound consequences in terms of the interpretation of dynamical behaviour, and that many of the familiar concepts developed for autonomous dynamical systems are either too restrictive, or invalid, in the non-autonomous context. Chapter 5 by MacKay presents a view of a non-autonomous oscillator as a mapping from input functions of time to a circle of possible solutions (state functions of time). The author indicates how this view encompasses chronotaxic systems and provides a picture of synchronisation in networks of oscillators, whether autonomous or not.

In Chapter 6, Lucas *et al.* start from the viewpoint that the concept of thermodynamic openness is key to the functioning of living systems. The authors model openness in coupled oscillators through an external driving force with time-varying parameters. They consider a single, driven oscillator with a periodic, noisy frequency and a time-varying driving frequency, followed by driven networks with time-varying frequency and coupling. They characterise system stability by short- and long-time Lyapunov exponents, both analytically and numerically, and they also describe the different dynamical regimes in time-frequency representations. They show that time-variation of parameters can enlarge the parameter space within which synchronous behaviour is stable, as well as yielding additional phenomena such as intermittent synchronisation. The authors also demonstrate that the stabilising effect of deterministic non-autonomous driving is similar to that of bounded noise over longer times, although the short-time dynamics is very different.

Chapter 7 by Newman *et al.* addresses the question of non-asymptotic-time dynamics where the usual assumption of long-time-asymptotic properties like traditionally defined notions of stability and neutral stability, as well as asymptotic Lyapunov exponents, are inapplicable. By consideration of the non-autonomous Adler equation with slowly-varying forcing, they illustrate three limitations of the traditional approach. They then propose an alternative, “finite-time slow-fast” approach, that is more suitable for slowly time-dependent one-dimensional phase dynamics, and likely to be suitable for describing the dynamics of open systems involving two or more timescales.

In the final chapter the Theory Part, Yuvan and Bier discuss synchronisation phenomena from yet another point of view. They come to the topic through a consideration of phase transitions in large systems of interacting units, leading to a mathematical description of an order parameter’s power-law behaviour near the critical temperature of the system. The authors also discuss the phenomenon from an entropy point of view and indicate implications for real-life experiments on the oscillatory behaviour of yeast cells (cf. Chapter 13).

2 Model-driven and data-driven approaches

The relationship between (often idealised and abstract) mathematical theory and phenomena measured in the real world almost invariably involves modelling, the usual aim being to build the simplest possible model capable of encompassing the observations. Sometimes the model is created mainly on the basis of physical intuition, and several may be considered before arriving at the seemingly optimal one. In other cases, the model can emerge directly from the observations i.e. from the data that are measured. Part II comprises four chapters in which modelling plays a key role.

In Chapter 9 Kovačič *et al* introduce a mechanics perspective by considering the oscillations on a chain of masses connected by linear springs and focus, in particular, on localised modes where only parts of the chain oscillate. They relate their model to the mechanical oscillations of trees, where the branches move but usually not the trunk. Chapter 10 by Ben-Tal presents some thoughts on the (sometimes controversial) question of how non-autonomous model systems can be converted to autonomous ones by application of an appropriate transformation. The author discusses the procedure, not only for periodic forcing, but also for other special cases. In Chapter 11, Stankovski offers an overview of the coupling functions that can be used to model the interactions between oscillatory systems and which mediate the non-autonomous effects seen in a particular system under examination. He focuses on the use and suitability of coupling functions in neuroscience and their use in accounting for neuronal oscillations and brain (EEG) waves. The final contribution to Part II, Chapter 12 by Gengel and Pikovsky, tackles one of the central questions confronting an experimentalist making measurements on an oscillatory system, not necessarily a biological one: how best can the recorded time series be analysed to illuminate understanding of the underlying dynamics? The authors show that *iterated Hilbert transform embedding* provides a good reconstruction of the phase dynamics, provided that the amplitude variations are relatively small.

3 Biological oscillations

Although the biological oscillators of Part III are not the only examples of non-autonomous oscillatory systems, they are overwhelmingly the most widespread and important. Living systems are inherently non-autonomous on account of the internal interactions between their component parts, in addition to the influence of the external environment. Each oscillator affects some of the other oscillators, thus giving rise to the time-variations in frequency and amplitude that are observed. Furthermore, living systems are never stationary but, rather, are in a state of continuous evolution from birth until death, with corresponding evolution of their characteristic parameter values.

Chapter 13 by Folke Olsen and Lunding is devoted to oscillations in yeast glycolysis. These have been known about for over six decades, but their mechanism remains uncertain and their purpose is still a mystery. The authors present experimental evidence that many variables, seemingly unrelated to glycolysis, oscillate in synchrony with glycolytic intermediates. They suggest that the function of metabolic oscillations is to maintain the cell in a state of constant low entropy. In Chapter 14 Lloyd provides a general discussion of biological oscillations, including yeast cell oscillations, and he too considers what their purpose may be. He discusses a model in which ultradian (faster than circadian) rhythms are the synchronizing signatures that organize the coherence of the living state. Chapter 15 by Amemiya *et al.* addresses glycolytic oscillations in cancer cells. It reviews the first direct observation of glycolytic oscillations in HeLa cervical and DU145 prostate cancer cells. The authors propose a mathematical model to account for the oscillation mechanism, show that it can reproduce the experimental results, and consider the wider implications. They find that, the greater the malignancy of the cells, the more they tend to exhibit glycolytic oscillations and the higher the frequency becomes.

In Chapter 16, Jacobsen and Aalkjaer provide a brief review of vasomotion. These are oscillations that occur in the tone or diameter of arteries and lead to the phenomenon of flowmotion, where the flow of blood into tissue occurs in an oscillatory manner. They discuss the mechanisms and how these can be studied. The authors hypothesise that vasomotion is beneficial because it ensures more efficient delivery of oxygen and removal of waste products, but point out that there is still a need for confirmatory experimental evidence. Chapter 17, by Colantuoni and Lapi provides another succinct review of research on vasomotion, but from an historical perspective, focusing on the seminal contributions made by their own research group.

The next two chapters relate to oscillations observed in skin blood flow. Chapter 18 by Tankanag *et al.* describe an investigation of paced and depth-controlled respiration in which they measured the phase coherence between skin blood flow oscillations at the pacing frequency in the left and right index fingers. They find that pacing the respiration results in a significant increase in phase coherence compared to spontaneous respiration. They attribute these results to the effect of the autonomic nervous system on vascular tone regulation under controlled breathing. In Chapter 19, Thanaj *et al.* review non-linear complexity-based approaches to the analysis of microvascular blood flow oscillations, with a particular focus on the extent to which they are able to identify changes in microvascular function. They conclude that, although such approaches have utility in understanding the fundamental mechanistic contributors to microvascular (dys)function, it has yet to be demonstrated that they can usefully discriminate between different (patho)physiological states in order to inform treatment regimens or to predict clinical outcomes.

Chapter 20, by Penzel *et al.*, examines the changes in cardiovascular and electroencephalograph (EEG) oscillations that take place during sleep. The autonomous nervous system is regulated in totally different ways during slow-wave (non-REM) and REM sleep, so that analysis of instantaneous heart-rate variations allows for automatic scoring of sleep stages. The authors also find it possible, to some extent, to track transitions from wakefulness to sleep solely by analysis of heart-rate variations. ECG and heart rate analysis allow assessment of sleep disorders as well.

The final chapter in Part III, Chapter 21 by Vuksanović, reviews current knowledge of the modular properties of brain networks, as derived from *in vivo* neuroimaging of cortical morphology (e.g. thickness, surface area), and their relationship to function. The focus is on the cross-level and cross-modal organisational units of the brain, and the relationships to their modular topology. Recent approaches in network science enable the formation of bridges across different scales and properties, and suggest that cross-modal neuroimaging and analysis may provide a tool for understanding brain disorders at the system level.

4 Applications

One of the main impediments to widespread use of physiological oscillations in diagnostics and medical instrumentation has, arguably, been their inherently non-autonomous character and variability. Traditionally, these features have been extremely hard to model. However, the substantial progress currently being made towards an understanding of such processes – forming the main *raison d'être* of the book – shows that this problem is being overcome so that faster progress in the development of useful applications in medicine may now be anticipated. In Part IV we consider some examples, both actual and potential.

In Chapter 22, Lehnertz provides an update on the use of EEG oscillations to predict epileptic seizures. These are usually associated with an overly-synchronized firing of neurons, as detected from the observed EEG oscillations, which often appears via a transformation of otherwise normal brain rhythms. The aim is therefore to apply methods from nonlinear dynamics, statistical physics, synchronization and network theory to identify precursor rhythms that can be used to warn the patient of an impending seizure. It is a long-term project that has been running for more than three decades. The author discusses progress to date and recent developments, including implantable devices for seizure prediction and prevention, and considers the remaining problems still to be solved.

The next two chapters both deal with anæsthesia and, in particular, exploitation of the changes in physiological oscillations that occur between the awake and anæsthetised states to provide a quantitative measure of the *depth of anæsthesia*, i.e. how close the patient is to becoming aware. There is obvious potential for preventing the unintentional awareness that still occurs occasionally, and which can be very distressing for everybody involved, not just the patient. In Chapter 23, Raeder reports on the European project BRACCIA (brain, respiration and cardiac causalities in anæsthesia). Although publication of the results has not yet been completed, it has already been shown that, even without inclusion of EEG data, measurements of the oscillations in ECG, respiration, skin temperature, and skin conductivity, coupled with the use of a classification analysis based on an optimal set of discriminatory parameters, can distinguish with 95% success between the awake and anæsthetised states. Chapter 24, by Martínez-Vázquez *et al.* describes an anæsthetic monitor that is already on the market: the qCON™ from Quantium Medical (Barcelona). Like the market leader BIS™, its operation is based on the analysis of EEG oscillations. The authors describe the main EEG activity changes induced by hypnotic anæsthetic agents, and the analysis perspectives. They also discuss the design principles, minimal necessary validation requirements, current limitations and challenges yet to be overcome.

In Chapter 25, Thorn and Shore review medical products that have been developed to enhance the oscillatory nature of blood circulation through the external application of intermittent pneumatic compression (IPC). They remark that further research is required, at a microcirculatory level, to understand and optimise the observed clinical benefits of IPC.

Chapter 26, by Abdulhameed *et al.* discusses recent work on cardiovascular oscillations in malaria. In particular, the authors show how a non-autonomous dynamics approach, using time-resolved analyses of power spectra and phase coherence, reveals significant differences between malaria patients and a healthy control group. These differences appear to be attributable to the specific effects of malaria on red blood cells, which cause them to stiffen and to stick to the endothelial lining of the blood vessels, markedly altering the flow properties of the blood. Following this approach leads to a classification accuracy of 88% in distinguishing malaria patients from healthy subjects, and may provide the basis for a new noninvasive diagnostic test. Further work will, however, be needed to compare the physical findings in malaria with those in other febrile infections.

5 Outlook

Finally, in Chapter 27, MacKay *et al* take note of the contributions made in the preceding chapters, and address the question of where the subject is going. It is now well appreciated that understanding living systems requires more than just traditional dynamical systems theory. In taking account of the fact that they function far from equilibrium, the authors comment that the minimum entropy production rate, valid near equilibrium, needs to be replaced. They discuss other principles that are potentially more relevant, and the possibility that a reformulation and mesoscopic interpretation of thermodynamics itself may be needed.

6 Using the book

As will be apparent from the summary remarks above, the chapters that follow are highly diverse in character although they all, whether explicitly or implicitly, grapple with aspects of non-autonomous dynamics. They range from relatively abstruse mathematics, which will mean little to most biologists and many physicists, to the practical details of physiological experiments which will mostly be lost on the theoretical physicists and mathematicians. Only a small minority of readers will start at the beginning and peruse the entire book from beginning to end. Most readers will probably prefer to pursue in detail topics that are of particular interest to them, in just a few chapters, while remaining aware of the larger reality presented by the rest of the book, and moving out into the latter when needed.

Each chapter is written by an expert, or experts, in the relevant subfield and each of them provides an extensive bibliography. So readers should have no difficulty in following up topics that are important to them.