



Book Reviews

Biomolecular Feedback Systems

Domitilla del Vecchio and Richard M. Murray
Princeton University Press, 2015, ISBN 978-0-691-16153-2

Introductory comments

The aim of synthetic biology is to build engineering devices using biological processes. Potential applications of such systems range from the production of specific materials (such as biofuels and drugs), through biological sensing and diagnostics (chemical detection, medical diagnostics) to the design of biological machines. The book under review provides an introduction to the principles and tools required for modelling and analysing biomolecular systems. In particular, it illustrates the use of feedback and control to ensure the correct operating behaviour of more complex devices obtained by connecting simple systems.

Many engineering systems are designed to use feedback to provide robustness to uncertainty and to ensure that desired dynamic behaviour is obtained. At first sight it appears surprising that techniques developed for physical engineering systems should find application in the design of 'soft' biomolecular systems. In fact, it is not surprising at all. Biological processes are usually subjected to a wide range of disturbances and consequently have built-in mechanisms to regulate their behaviour; this regulation often uses feedback. A running theme is that when biomolecular designs are envisaged as 'circuits' that analogies to standard engineering problems arise; known solutions can then be applied. Physical 'hardware' and biological 'software' are not so different.

It is suggested that potential readers for this book fall into one of three main pools: graduate students in biology and bioengineering, advanced engineering students, and established researchers. In the American context, the exclusion of mathematics students may be sensible. In the Australian context, students majoring in applied mathematics form a natural audience. Furthermore, one wonders how many biology graduates from Australian universities will have the necessary mathematical background to tackle this book? Even engineering graduates from some Australian universities will struggle with the required mathematical background.

Overview of the book

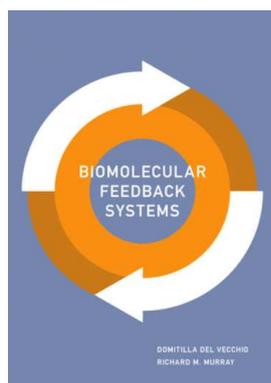
The contents of the book divide into three parts. Chapters one and two deal with introductory concepts and provide a broad outline of subsequent chapters. The second part, chapters three and four, cover the mathematical techniques that are to be used. In the final part, chapters five to seven, the emphasis is on analysing and designing biological circuits.

The first chapter provides an overview of the modelling approaches, both deterministic and stochastic, that are used and the tools that are needed to analyse and design biomolecular feedback systems. The toolkit principally combines techniques from dynamical systems, control theory and singular perturbation theory. A critical theme running throughout the book is that feedback can only be understood by combining the tools from these toolkits. Other toolkits in use include sensitivity analysis, uncertainty analysis and probabilistic analysis.

The goal of the second chapter is show how basic biological mechanisms can be represented by simple dynamical models. In sections 2.2–2.4 models are constructed for some core processes that occur within a cell. The final section hints at what is to come in chapters five to seven: core processes are combined to produce cellular subsystems having specific purposes.

In section 2.2 gene expression, i.e. the transcription of DNA into mRNA by RNA polymerase followed by the translation of mRNA into a protein, is modelled. In section 2.3 mechanisms for controlling protein activity, through modification of the process of transcription of DNA into mRNA, are investigated.

Mechanisms for post-translational regulation of proteins are considered in section 2.4. An important mechanism for subsequent chapters is phosphorylation. Tuning of parameter values allows such a system to operate as a ‘switch’: the concentration of activated protein is essentially either zero or 100%, depending upon if a control parameter is below or above a threshold value. Another important example is given by a group of proteins that can phosphorylate each other, phosphotransfer systems. These can be designed to function approximately as a linear amplifier.



An important message from these examples is that biological ‘circuits’ having prescribed functionality, switching or linear amplification, can be obtained if parameters take appropriate values. The parameters concerned are Michaelis–Menten constants, for switching, and a forward reaction rate between a phosphate donor and an inactive protein, for linear amplification. The authors suggest that our biochemical knowledge is such that these parameters can indeed be treated as control parameters. Thus, in principle, ‘biochemical circuits’ with prescribed behaviour can be designed. In chapters five to seven the process models developed in sections 2.2–2.5 are taken as building blocks which are to be combined to create more

complex biomolecular systems having prescribed functionalities.

The third chapter introduces the mathematical tools that are used to analyse deterministic models. The material covered is: analysis near equilibria, robustness, periodic behaviour, bifurcations and model reduction through singular perturbation analysis. Three tools from feedback control are discussed. These are frequency domain analysis, integral feedback and incoherent feedforward loops. The first of these identifies how a system responds to a rapidly changing input stimulus. The

second and third are methods which provide a specified output response in the presence of external disturbances.

It is not uncommon for bimolecular systems to have different time scales. Thus in subsequent chapters a much used approach is to exploit time-scale separation by approximating the fast time scale dynamics by their equilibrium solutions and then analysing the reduced model on the slow time scale dynamic using the techniques covered in sections 3.1–3.4.

For standard ‘bucket chemistry’ the number of molecules involved is so large that nothing is lost, but much is gained, from modelling chemical dynamics in terms of *concentrations*, rather than the (integer) *numbers*, of molecules. As the number of molecules decreases it becomes increasingly important to keep track of individual events. The much smaller number of molecules involved in biomolecular processes occurring within cells means that deterministic models are not always very good representations of these systems; they are inherently noisy due to the random nature of molecular reactions. Ultimately, a deterministic representation of chemical reactions must be replaced by a viewpoint in which chemical reactions between species are viewed as a collection of stochastic events. (However, deterministic models may be a useful first step). Chapter four provides a stochastic counterpart to chapter three by introducing appropriate tools to simulate and analyse stochastic systems.

A useful figure to have in mind is figure 2.1, which shows how a variety of modelling frameworks can be used depending upon the timescale and concentration of interest. The most fundamental approach is to use the chemical master equation (CME). This gives a complete description of the evolution of the probability distribution of the system. As it is often quite cumbersome to work with the CME, approximations to it are often used in practice. Suitable approximations include the chemical Langevin equation (CLE), the Fokker-Planck equation (FPE), and, when stochastic effects are ignored, reaction rate equations. Which approach is best, depends upon the timescale and concentration scales of interest and the desired resolution.

The CLE assumes that the number of molecules in the system is large and that the time scale of interest is such that many reactions, not individual reactions, can occur. The CLE models chemical processes as a system of stochastic ordinary differential equations that describes the smooth evolution of the system state. The FPE provides an equivalent formulation in which the variation in time of the probability distribution function is modelled.

In section 4.1 a sketch derivation of the CLE and the FPE from the CME is provided, as is an outline of the derivation of the reaction rate equations. Section 4.2 discusses Gillespie’s direct method for simulating stochastic systems. Finally, in section 4.3 tools from stochastic control theory are discussed that allow an analysis of noise propagation around a fixed operating point.

In subsequent chapters only a very limited number of stochastic CLE models are discussed. Thus, on first reading, this chapter could be omitted.

Chapter 5 contains two themes. The first, covered in sections 5.2–5.6, uses the building blocks introduced in chapter two to construct, mostly deterministic, biochemical circuits having prescribed functionality. Topics covered are negative autoregulation, i.e. how the presence of negative feedback affects the dynamics and the noise properties of a system, the design of a toggle switch, two mechanisms to generate oscillatory behaviour and the implementation of an incoherent feedback loop to obtain robustness to external perturbations. These circuits are not a wish list, they have already been constructed in *Escherichia coli*. The second theme is to describe a more complicated circuit that appears in natural systems to implement adaptation.

Section 5.3 analyses the design of a toggle switch. The simplest model for a toggle switch is a system of two coupled non-linear differential equations, with state variables x and y , having two stable steady-state solutions: $(x^*, 0)$ and $(0, y^*)$. The output from this circuit can be ‘toggled’ from one solution to the other by applying an external stimulus that moves the system from the basin of attraction of one solution to the basin of attraction of the other solution.

The design and analysis of oscillating ‘bimolecular circuits’ is important for two reasons. Firstly, they provide insights into the mechanisms that are used in the cell to regulate natural processes. Secondly, they provide a module that can be used to synchronise processes leading to complex outcomes.

Section 5.4 analyses a system comprising three genes, conceptually arranged in a ring, each of which expresses a protein that represses the next gene in the loop. This arrangement, known as the ‘repressilator’, can give rise to limit cycle oscillations having periods much slower than cell-division times. This allows the state of the oscillator to be transmitted between generations from mother to daughter cells. The experimental construction of a repressilator (Elowitz and Leibler, 2000) is considered to a milestone of synthetic biology; a development that was guided by the insights generated by simple mathematical models.

In section 5.5 an activator-repressor clock is analysed. At its simplest this consists of an activator protein, which promotes the expression of itself, and a repressor protein, which provides a negative feedback loop. This system has two natural timescales: one for the link between the dynamics of the activator and repressor and one for the link between the protein and mRNA dynamics. As these timescales are changed, a variety of different behaviours is exhibited by the model.

Organisms do not just move by diffusion, they can preferentially move both up and down chemical gradients; moving towards food or away from toxins (chemotaxis). Continuum models to describe the spatial variation in the concentration of a micro-organism in the presence of a chemical gradient date back to Keller and Segel (1970, 1971). These models have found particular application in understanding the aggregation of slime molds. In this case it is the cells themselves that release a chemical attractant that draws the population together.

Chemotaxis models are now widely used, and indeed can be considered to be a ‘classic’ feature of mathematical biology. However, how is it that a bacterium can move along a (spatial) chemical gradient when on the length scale of a bacterium

(hint, very small) the (spatial) gradient is not detectable? Instead of using spatial gradients, temporal gradients are used. However, in order to use a temporal gradient a bacterium must ‘know’ both the current and past concentration. How does it do this? Section 5.7, a highlight of the book, provides a detailed look at the mechanism that allows sensing of temporal gradients in *E. coli*.

The behaviour of simple biomolecular modules is analysed in chapters two and five. A natural step forward is to combine modules to create circuits with more complicated functionality. However, the act of connecting ‘upstream’ and ‘downstream’ biomolecular modules can change the functionality of the upstream module. For example, connecting an activator-repressor clock, which generates periodic oscillations in the concentration of a protein, to a downstream component may quench the desired periodic stimulation.

This phenomena, known as retroactivity, is not restricted to biomolecular modules. It may occur in any system where an ‘upstream’ component sends a signal to a ‘downstream’ component; it is commonplace in electrical and mechanical systems. The underlying problem then is how to guarantee that the performance of an upstream module is not lost when it is connected to a downstream module? The model equations can be readily analysed using techniques developed to analyse and eliminate retroactivity in ‘mechanical’ problems. The challenge is to realise the mathematical solution in the biomolecular setting.

In chapter six models exhibiting retroactivity are analysed. Solutions to these problems are obtained using the feedback principles introduced in chapter three. Sections 6.3 and 6.4 provide examples of the adverse effects of retroactivity upon gene circuits and in signaling systems respectively.

Retroactivity can be eliminated by redesigning the downstream module to minimise its effect on the upstream module. This strategy is not always feasible, since the downstream module may have been designed and optimised for another purpose. Instead retroactivity can be reduced by implementing the feedback principles introduced in chapter three. Section 6.5 describes how to ensure that the downstream module receives the desired input signal by adding an insulation device between the two modules. Attenuation of retroactivity to the output can be achieved either by using high gain feedback or by exploiting time scale separation. In both cases it is first shown theoretically, in an approach applicable to any engineering problem of this form, that the proposed mechanism solves the problem. The authors then discuss how to implement each mechanism using appropriate biomolecular structures. Analysis of the relevant models leads to important practical insights regarding the range of values that key biochemical parameters must take to attenuate the retroactivity.

The chapter finishes with a case study on the use of insulation devices to protect the periodic signal arising from an activator-repressor clock when it is connected to a downstream system.

The final chapter considers two of the design tradeoffs that need to be considered when designing biomolecular circuits. The first issue is concerned with how the

competition for shared cellular resources effects the behaviour of synthetic circuits — the competition leads to retroactivity. The second issue uses the Langevin equation to investigate the influence of stochastic effects on the design of devices requiring high gains.

These two studies reveal that there is a tradeoff when designing insulation devices: the larger the attenuation in retroactivity the more sensitive the device may become to noise. As biological circuits become increasingly complex, problems associated with resource sharing, noise and retroactivity will become more important. The design of robust biological circuits that can operate in such environments requires the development of new mathematical models. The models will borrow from a heritage in both applied mathematics and engineering. Understanding the implication of models results will require an understanding of cellular biochemistry.

Each chapter, except the first, finishes with a list of exercises. A solutions manual and illustration package is available to lecturers at press.princeton.edu. My only, slight, criticism of the book is that only the first chapter contains a section on ‘further reading’. In the book’s defense it can be pointed out that appropriate references are provided in each section. However, I would like to have seen a discussion of extensions of the material covered in the book.

Concluding thoughts

How can this book be used? There are some examples that can be used in a first-year calculus subject and further examples relating to the solution of systems of linear differential equations. A much larger number of non-linear examples can be used either in an applied dynamical systems subject or a mathematical biology subject. (This assumes that content has not been unnecessarily prescribed.) Some of the problems discussed in latter chapters are suitable as projects. Although it is suggested that the reader should have taken an introductory subject in feedback and control theory the necessary background could be developed *in situ* if time permitted. (If time does not permit, there are plenty of examples not using this theory.)

To benefit the most from Chapter 4 (‘Stochastic Modeling and Analysis’) readers are required to have a good working knowledge of basic probability and some exposure to simple stochastic processes. Although this content is not proscribed, the coverage is insufficient for a reader without this background to learn how to either simulate or analyse such systems. As there are relatively few stochastic examples, this is not such a big drawback.

An honours subject can therefore be built entirely around the deterministic content, the stochastic content can be covered if the instructor fills out the required background.

In many physical models parameters are tunable. Are parameters in bimolecular models ‘tunable’? Due to our increasing knowledge of biochemical processes the answer is increasingly ‘yes’. For example, it is now possible to build synthetic gene circuits from a set of transcriptional components. These components can be

chosen from a library of basic parts which are classified based upon biochemical properties. Appropriate model parameters may be tuned by making single or multiple base-pair substitutions or by adding appropriate degradation tags to gene expressing proteins. Such procedures are hinted at, but rightly not described in detail.

This book promises much for the reader with a background in both biochemistry and mathematics. Such a reader will not only learn how to analyse models for bioengineered bimolecular systems but they will have the insights to both build these systems and to ‘tune’ the biochemistry to obtain desired parameter values.

The 21st century promises ‘designer medicines’ with very specific properties targeted for the needs of an individual. As these medicines become available it is unlikely that the role of mathematics will be promoted in the popular press. But mathematics will be essential to the design and operation of such medicines; without mathematical modelling there can be no brave new world of ‘beauteous mankind’.

My final observation is the belief that the applied mathematician of the 21st century should be equipped with a tool kit containing a mixture of deterministic and stochastic tools.

The full text for this book, along with supplementary material is available on the website <http://press.princeton.edu/titles/10825.html>.

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Mark Nelson

School of Mathematics and Applied Statistics, The University of Wollongong, Wollongong, NSW 2522. Email address: mnelson@uow.edu.au

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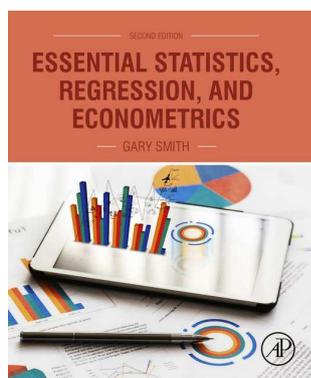
Essential Statistics, Regression, and Econometrics, 2nd edn

Gary Smith

Academic Press, 2015, ISBN 978-0-12-803459-0

There is a joke on *The Simpsons* where the Duff Beer Company is giving a tour showing vats of its three different types of beers (Duff, Duff Lite, and Duff Dry) and you see a big pipe delivering beer into all three vats from the same identical source. In the same way, statisticians sometimes laugh at introductory statistics books ‘for engineers’, ‘for scientists’, ‘for economists’ because we know they are all essentially the same book, just marketed to a different audience. I was therefore

pleasantly surprised when I read *Essential Statistics, Regression, and Econometrics* (2nd edn) by Professor Gary Smith, because there is a genuine infusion throughout the book not just with econometric data and examples, but also with discussion of historical events, economic theory, and specific statistical issues which manifest commonly in this context. Reading the book one certainly gets the sense of being ‘involved’ in econometrics, like an economic analyst looking over historical data and policies, and applying the tools of statistics to test theories and hypotheses.



The mathematical content and topics in this book are in many ways typical of introductory books written to impart basic understanding of statistics and regression to an undergraduate student, but certain topics are expanded or contextualised into the field of econometrics and social science. Although much of the content is common in introductory statistics books, the author has made a special effort to leave out material which would distract from the essentials of this course of study. I can do little better in describing this aspect of the book than to quote the intention of the author, as set out in his introduction. To the chagrin of the author, university

courses requiring the use of data analysis ‘...are traditionally preceded by an introductory statistics course that adheres to the fire hose pedagogy: bombard students with information and hope they do not drown. Encyclopaedic statistics courses are a mile wide and an inch deep, and many students remember little after the final exam. This textbook focuses on what students really need to know and remember.’

To avoid the ‘fire hose’ approach, the author focuses on those aspects of statistics which logically precede linear regression analysis, with a view to building up to linear regression as the endpoint. Chapters 1–3 give an introduction to measurement and data, graphical displays of data, and basic descriptive statistics. Chapters 4–7 introduce the reader to the rules of probability, principles of random sampling from a single population, and estimation and hypothesis testing of the population mean. Chapters 8–11 introduce simple and multiple linear regression and then go slightly beyond this to look at polynomial and logarithmic regression and auto-regression. The author intentionally leaves out other common introductory topics that are unrelated to linear regression — there is a focus on normal random variables, and aside from a brief introduction to the central limit theorem there is no explicit coverage of the binomial distribution or other distributional families. Similarly there is no coverage of non-parametric testing or contingency tables. All of this allows the book to focus on its key goal without distraction, which is a sensible approach.

Although the mathematical content is quite standard for an introductory statistics textbook, I found this book to be of high quality in an already competitive field. The main strengths of the book lie in its focused approach to topics, outstanding work in alerting students to common mistakes and misinterpretations, and the use of a number of interesting real-life data sets and historical events to flesh

out the statistical theory with examples. Much of the analysis—and many of the pitfalls of bad statistical work—are illustrated by reference to real-life errors from academics, politicians, pundits, economic advisers, etc., with examples from economics and the social sciences as well as medicine and law.

The best aspect of this book is that it makes a concerted effort to explicitly address common errors by students. There is guidance on dealing with economic variables that need to be standardised into real terms—e.g. by adjustment to account for monetary inflation or population growth. There are specific sections devoted to addressing the conflation of correlation and cause, *post hoc* conclusions made without getting new data, the conflation of statistical significance with practical significance, the regression fallacy, and other common statistical errors. In the section on confidence intervals for the population mean, there is even a short section entitled ‘Do not forget the square root of the sample size’ which gives an example of this error (p. 175). This kind of explicit attention to common errors leaves students with no excuse for the kinds of mistakes one regularly sees in statistics!

As well as dedicated discussion of common errors, the book also includes an interesting section on the ‘Good, Bad and Ugly’ of graphical outputs, showing some standard ways in which poor graphical techniques (e.g. removing the origin or axes values, toying with axes or starting points for time series, graphing data out of proportion to size) can give misleading impressions of the data. Real-life examples are used, including a seriously misleading graph on Nobel prizes in science from the National Science Foundation!

Although the book is well written overall, there are a few small aspects that could be improved or augmented by an attentive teacher. The section on auto-regressive models is purely focused on defining the model, and fails to tell students how to estimate the parameters. Its juxtaposition with the sections on regression analysis might suggest to students that they should apply the regression formula and just plug in a lagged response variable as one of the predictors, but there is no explicit instruction on this point. (This also introduces a complication because the MLE of the autoregressive parameter is not the least-squares estimate.) The section on sampling from a finite population (p. 177) is roughly correct, but not quite—while the author notes that the confidence interval formula for the population mean implicitly assumes an infinite population, he declines to tell the reader the simple correction term that can be added to the formula to account for a finite population, and his remarks about the lack of effect of population size are therefore overstated.

Despite these small issues, I can wholeheartedly recommend this book as an introductory book for a statistics course taught to early undergraduate economics students. It is clear and well-written and contains a wealth of interesting examples, exercises, and historical anecdotes. The author has done an excellent job in elucidating statistical methods in an econometric context.

Ben O’Neill

School of Physical, Environmental and Mathematical Sciences, University of New South Wales (Canberra Campus). Email address: ben.oneill@adfa.edu.au



Alexandre Grothendieck: a Mathematical Portrait

Leila Schneps (Editor)

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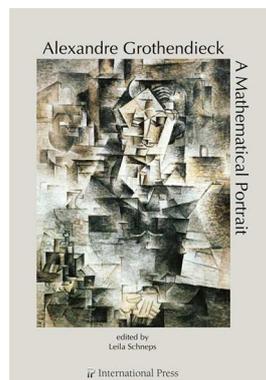
By its genesis, ubiquity and applicability, algebraic geometry is the centrepiece of mathematics, as illustrated by the fact that more than a quarter of all Fields medals have been awarded for work related to the topic. Alexandre Grothendieck, (1928–2014) occupies a pivotal rôle in 20th century algebraic geometry. Between 1956 when he joined the Centre National de la Recherche Scientifique (CNRS) and 1970 when he abruptly abandoned conventional mathematics, Grothendieck produced an astonishing amount of important mathematics. This was not all published in mainstream mathematical journals but mainly in the form of series of seminar proceedings known by their acronyms EGA (Eléments de la Géométrie Algébrique), SGA (Séminaire de la Géométrie Algébrique), and FGA (Fondaments de la Géométrie Algébrique). As well as these seminal works, which were partially collaborations with Jean Dieudonné, and were usually written up by his colleagues and students, Grothendieck also published in more conventional format; in particular his revolutionary 1957 100-page paper *Sur quelques points d'algèbre homologique*, which introduced abelian categories into algebraic geometry, was undoubtedly the most celebrated paper ever to appear in the Tôhoku Mathematical Journal.

In 2008, Leila Schneps and her husband Pierre Lochak, together with Winfried Scharlau, organised a conference entitled 'Alexandre Grothendieck: Biography, Mathematics, Philosophy'. It took five years to complete this book, the Proceedings of that conference, which appeared a few months before the death of the legendary mathematician in his self-imposed exile in the tiny Pyrenean village of Lasserre. The cover image, which was chosen by Schneps herself, is a 1910 Picasso portrait of Daniel-Henry Kahnweiler which bears a striking resemblance to Grothendieck, the fragmented nature of the portrait reflecting the book itself and the different points of view of the various authors, each giving his or her own angle.

For this report, I have also drawn on two issues of the *Notices of the American Mathematical Society*, Volume 63, Nos 3 and 4, (March and April 2016) containing tributes to Grothendieck by his colleagues and students as well as a multi-authored article 'The life and work of Alexandre Grothendieck' appearing in the *American Mathematical Monthly*, Volume 113, No. 9, (November 2006).

The volume contains articles of two types: personal reminiscences of their interactions with Grothendieck by noted mathematicians such as Max Karoubi, Steven L. Kleiman, David Mumford, Robin Hartshorne, Luc Illusie, Pierre Cartier and Yuri Manin, and technical papers placing into context Grothendieck's mathematical discoveries in functional analysis, K -theory, algebraic topology, schemes and motives. Schneps herself contributes a long chapter on the correspondence between Grothendieck and Serre between 1955 and the 1980s which recounts the history of the events as they occurred. Consequently, the volume is of interest not only to the professional algebraic geometer but also to all mathematicians who are intrigued by the way important new ideas germinate and spread.

By now, the extraordinary career of Grothendieck is well known, accounts having appeared not only in mathematical journals but in the popular press, including *The New York Times*, *The Times* and *The Spectator*. He was born in Berlin of radical anarchist parents who took part in the leftist struggles in Europe in the 1930s. Hidden on a farm in northern Germany from 1933 to 1939, he rejoined his parents in Vichy France, from where his father was deported and murdered in Auschwitz. He survived with his mother and after the war entered the Université de Montpellier, from where he made contact with the leading Parisian mathematicians including Henri Cartan and André Weil. On their advice he attended the Université Nancy where he obtained his doctorate under Laurent Schwartz and Jean Dieudonné, on the tensor product in topological vector spaces and nuclear spaces.



Being stateless, Grothendieck had difficulties obtaining a regular position in France, and held visiting positions in São Paulo, the University of Kansas in Lawrence and Harvard before being admitted to the CNRS in 1956. He gave a notable invited address at the 1958 Edinburgh International Congress of Mathematicians (ICM). The same year, he became one of the first two professors at the newly inaugurated Institut des Hautes Etudes Scientifique (IHES). The other foundation professor was Dieudonné, who was the original choice, but who only accepted on the condition that Grothendieck be appointed too. He was awarded a Fields Medal at the Moscow ICM in 1966 for his work in algebraic geometry, K -theory and homological algebra.

In 1970, Grothendieck abruptly resigned from the IHES, ostensibly because a small part of its income was derived from the French military establishment. It is clear that he was deeply affected by the student unrest of 1968 and decided to focus his energy on issues more important than mathematics, such as environmental degradation, global poverty and weapons proliferation. He founded an international group called *Survivre et Vivre* (usually called *Survival* in English), spoke at its meetings throughout the world and wrote for its publications.

However, he did not abandon mathematics altogether. He briefly held irregular positions at the Collège de France, the Université de Paris Orsay, the Université de Montpellier and the CNRS again. During this period he introduced several novel ideas in algebra, geometry and number theory which were later exploited by others and which even now have not been exhausted. He also produced his mathematical and personal testament, *Récoltes et Semailles* (Harvests and Sowings) of which an English translation by Roy Lisker is now available on the Internet. He finally seems to have retired from mathematics in 1988 to live as a hermit in the remote Pyrenean village of Lasserre, a vegan and a deep green environmentalist. When he died there in 2014, he left behind thousands of pages which have still to be analysed.

This broad outline seems to suggest an aloof if not arrogant figure, but Grothendieck's relations with his colleagues and students detailed in this volume show that

this impression is incorrect. Karoubi, who participated in the Cartan–Schwartz Seminar on K -Theory in 1964 speaks of his habitual generosity; Kleiman, who contributed to sections of SGA, of his instinct for matching people with open problems; Mumford of his hypnotising presence at Harvard. However, his personal qualities are most in evidence in his correspondence with Jean-Pierre Serre. No two more diverse personalities could be imagined. Serre was a brilliant prodigy, still the youngest person to be awarded a Fields Medal, at the 1954 Amsterdam ICM at the age of 29. This was largely for his theory of sheaves, a theory which Grothendieck adopted with enthusiasm. Serre was your typical establishment French mathematician, entering the Ecole Normale Supérieure at 19 and writing a brilliant thesis on Leray’s spectral sequences under Henri Cartan, before producing his influential *Faisceaux Algébriques Cohérent*. Thus he was four years older than and academically senior to Grothendieck. Their correspondence begins in 1955, Grothendieck posing questions and suggesting results on homology, sheaves and projective limits, which Serre proves or refutes. Later, after the Tôhoku paper, Grothendieck proposes problems that Serre is unable to settle, and the questions begin to flow the other way. Serre, who is also an expert in number theory, suggests applying Grothendieck’s ideas to number theoretic problems, particularly the Weil Conjectures on the solutions of polynomial equations over fields of positive characteristic, and later to the theory of motives, a generalisation of sheaves and functors. Very few personal remarks occur in the correspondence, just occasional signs that Grothendieck is concerned about the health of his mother, with whom he lives at that time, and some delightful comments on the refreshing mathematical climate at Harvard and Princeton compared to the more oppressive atmosphere in Paris in 1961, during the days of the Algerian war. Curiously, in spite of their close interaction in the 30 years following 1955, Serre and Grothendieck never published a joint paper.

The most deeply personal chapter in the book is that written by Pierre Cartier, who describes Grothendieck’s own views on his research programme, seeking maximal generality not for its own sake but in order to simplify algebraic geometry by using only the most fundamental categorical axioms. Cartier also describes his own research into intimate details of Grothendieck’s origins and life. While always a serial monogamist, he had several relationships, fathering with three different mothers five children, all of whom he acknowledged and tried to support.

We come now to the more technical papers in this volume. It would take too long and exhaust my competence to discuss all contributions, so I just mention those I found most interesting. Joe Diestel recounts Grothendieck’s first foray into functional analysis, and particularly into Banach space theory. This led to five publications including a Memoir of the American Mathematical Society which describes his work on tensor product topology and nuclear spaces. These works foreshadow his preferred procedure of defining mathematical objects by the properties of functions which map that object to other objects.

A short essay by Karoubi outlines Grothendieck’s introduction and development of K -theory, an essential precursor to his important development of homology and cohomology in both algebraic and topological contexts. Michel Raynaud shows how Grothendieck generalised Serre’s theory of schemes from the Zariski topology

on complex analytic varieties to functors from ringed spaces to smooth quasi-projective varieties. This significant generalisation caused a mathematical sensation by providing an extension and a new proof of a classical result in algebraic geometry, the Riemann–Roch Theorem. Originally, this was a conjecture by Riemann and a proof by his student Roch of an equality between a numerical topological invariant of a projective algebraic curve over an algebraically closed field and algebraic invariants of the corresponding variety. Grothendieck’s version replaced the geometric paraphernalia by a functor between sheaves which simplified the proofs and made transparent the reason why such a relation must hold.

Luc Illusie claimed that of all Grothendieck’s work, it is the introduction of étale cohomology which most profoundly influenced the evolution of algebraic geometry. The word étale itself was coined by Grothendieck from the French verb meaning to separate or spread out. Classical algebraic geometry involves local isomorphisms between vector bundles and open subsets of manifolds, but because open sets in the Zariski topology are so large, it is difficult to define local isomorphisms in abstract sheaves. Étale morphisms are the algebraic analogues of the notion of local isomorphisms. They have precisely the properties needed to construct a cohomology theory. This enabled the construction of étale topologies on categories and thence stacks, motives and toposes. By now, there is a whole industry of étale constructions, revolutionising not just algebraic geometry but also Galois theory, category theory and the logical foundations of mathematics.

To summarise, this book is for the general reader a homage to an inspiring mathematician and an admirable human being; for the student of some part of Grothendieck’s mathematics an account which puts that area into context; and for the specialist an explanation of how and why the concepts they deal with first arose.

Phill Schultz

School of Mathematics and Statistics, The University of Western Australia.

Email address: phill.schultz@uwa.edu.au

