The cover picture shows the Executive Wing of the New Zealand Parliament Building, corner of Molesworth Street and Lambton Quay, Wellington, colloquially known as “The Beehive.”

(Photograph by the Editor.)
Our Changing World in the South Pacific: 
Australasian and German Perspectives

Trevor R. Finlayson
(Editor)

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Preface

Our Changing World in the South Pacific: Australasian and German Perspectives is a collection of scholarly works based on presentations at the Humboldt Kolleg of the Australian and New Zealand Associations of von Humboldt Fellows (A&NZAvHF) held in the Royal Society of New Zealand Building, Wellington, New Zealand, from Friday, 17th to Sunday, 19th November, 2017. The AAvHF and the NZAvHF are the national professional Associations of von Humboldt Fellows in Australia and New Zealand, respectively. Membership of each Association is open to any resident of the respective country, previously awarded a Fellowship or Award by the Alexander von Humboldt Foundation (AvHF) and to any visiting Lynen Fellow from Germany, researching at an Australian or New Zealand Institution. Each Association facilitates professional and social contact amongst Humboldtians, as well as encouraging new and existing links between members and German researchers. The biennial scholarly colloquia provide opportunities to reciprocate the most generous hospitality afforded Australasian scholars visiting Germany under the auspices of the AvHF.

Presenting aspects of one’s research at a Humboldt Kolleg is invariably challenging, in the true spirit of Alexander von Humboldt, given that one’s audience will be representative of the physical and biological sciences, the humanities, the arts, etc. The chapters in this book, which have been prepared from 14 of the 32 presentations at the Kolleg, attest to this multidisciplinary scholarship. While some of these chapters contain multi-authorship, for convenience in setting out the Contents (page v) for the book, the presenter at the Humboldt Kolleg has been listed as the one author although at the beginning of each multi-author chapter, all details and respective bi-lines have been included. All chapters published have been peer-reviewed by two professional researchers and modifications/corrections have been carried out by authors in response to these two reviewers’ reports. Biographical Notes have also been provided for the authors at the end of the book, although in the cases of multiple authors for any chapter, the only Biographical Note provided is that for the presenter at the Humboldt Kolleg.

The Humboldt Kolleg was officially opened by the German Ambassador to New Zealand, Mr. Gerhard Thiedemann, who has kindly written an Introduction (Chapter 1) for this book, based on his opening remarks.

The financial support afforded to the Humboldt Kolleg by the Alexander von Humboldt Foundation and the New Zealand Ministry of Business, Innovation and Employment, is gratefully acknowledged. Sincere thanks must also be extended to the staff of the Royal Society of New Zealand for their cooperation and assistance and to the members of the Colloquium Committee, Professor Eamonn O’Brien (Chair, University of Auckland), Professor Sally Brooker (University of Otago), Associate Professor Trevor Finlayson (University of Melbourne (representing the AAvHF)), Professor John Hearnshaw (University of Canterbury), Dr. Andrew Matthews (Airline Marketing New Zealand) and Professor Barry Scott (Massey University), for the organisation of a most successful event.

Trevor R. Finlayson
Editor
<table>
<thead>
<tr>
<th>Title</th>
<th>Presenting Author</th>
<th>Chapter</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>G. Thiedemann</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>The Social Cost of Carbon Dioxide: Policy and Methods for Pricing</td>
<td>C.M. Kellett</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Greenhouse Gas Emissions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exceptional Symmetries and their Applications</td>
<td>J. Schillewaert</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Gastrointestinal Electrophysiology in Digestive and Disease for</td>
<td>P. Du</td>
<td>4</td>
<td>23</td>
</tr>
<tr>
<td>Aging Societies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A Glitch in the Matrix: Investigating Repetitive Sequences with the</td>
<td>D.A. Eccles</td>
<td>5</td>
<td>29</td>
</tr>
<tr>
<td>MinION</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>So-Called Experts? Knowledge Credibility in Fiction</td>
<td>A-S. Jürgens</td>
<td>6</td>
<td>35</td>
</tr>
<tr>
<td>The German Contribution to the Development of the Glass</td>
<td>A.H. Bretag</td>
<td>7</td>
<td>43</td>
</tr>
<tr>
<td>Micropipette Electrode</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tsRibo-Seq: An Approach to Zoom In into Translation of Single</td>
<td>Z. Ignatova</td>
<td>8</td>
<td>49</td>
</tr>
<tr>
<td>Transcripts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curvature Flow and Applications</td>
<td>G. Wheeler</td>
<td>9</td>
<td>55</td>
</tr>
<tr>
<td>Empathic Concern for Disability and Accessibility</td>
<td>M. Miyahara</td>
<td>10</td>
<td>71</td>
</tr>
<tr>
<td>Ambulatory Gastric Mucosal Slow Wave Recording for Chronic</td>
<td>N. Paskaranandavadivel</td>
<td>11</td>
<td>77</td>
</tr>
<tr>
<td>Experimental Studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superconductor Sandwiches: Strongly Interacting States in Thin-film</td>
<td>B.P.P. Mallett</td>
<td>12</td>
<td>83</td>
</tr>
<tr>
<td>Multilayers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Counting Faces of Polyhedra</td>
<td>D.T. Yost</td>
<td>13</td>
<td>89</td>
</tr>
<tr>
<td>Observations of Environmental Changes in the Antarctic Region</td>
<td>T.R. Finlayson</td>
<td>14</td>
<td>95</td>
</tr>
<tr>
<td>Tribute to Dr Heinrich Pfeiffer</td>
<td>G.L. McMullen</td>
<td>15</td>
<td>101</td>
</tr>
<tr>
<td>Biographical Notes on Presenting Authors</td>
<td></td>
<td>107</td>
<td></td>
</tr>
</tbody>
</table>
1. Introduction

I am delighted that I was given the honour to address the Biennial Colloquium of the Australian and New Zealand Associations of von Humboldt Fellows in Wellington from 17 to 19 November, 2017. The event marked another highlight in the four decades of fruitful scientific collaboration between Germans and both New Zealanders and Australians. In 2017, we celebrated the 40th anniversary of bilateral Science and Technology agreements which have contributed to make this partnership a vital pillar of our bilateral, dense, collaborative network. A number of statistics illustrate this fact: Some 30,000 of my countrymen live in New Zealand; about 3,000 New Zealanders in Germany; 200 German scientists have a permanent job in New Zealand’s universities; and 15% of New Zealand’s scientists cooperate with German colleagues. Our strong ties form a platform for developing more joint projects in the future.

The Alexander von Humboldt family in this region is a flagship of the flourishing collaboration between our two countries, with the biennial conference in Wellington playing an important part of the exchange. Face-to-face contacts are still valuable in the 21st century and often form the basis of trustful and productive cooperation. The event offered the opportunity for current and former Alexander von Humboldt Fellows to discuss, exchange ideas and establish contacts. As Fellows from different cultural, political and educational backgrounds came together, the conference provided the perfect setting for exchanging new ideas and inspiring joint research projects in the future.

The well-chosen topic, “Our Changing World in the South Pacific”, also helped to contribute to a successful event. As German Ambassador to New Zealand, I am also accredited to six Pacific Island nations even including Kiribati – 4500 kilometres north of Wellington. From my visits to the region, I have become familiar with the huge problems confronting these small states and their maritime environment. It is known to all of us: The world – and with it the South Pacific – is undergoing a process of significant change on many levels. Natural disasters caused by the global climate change affect not only societies, but politics and the economy as well. Fiji’s presidency of the world climate conference COP23 in Bonn drew attention to the issues and interests of the South Pacific nations. I greatly appreciate your scientific contribution to ensuring a sustainable future in our changing world in the light of the manifold challenges we face right now.

The German Embassy is pleased to have been able to support the Biennial Colloquium of the Australian and New Zealand Associations of von Humboldt Fellows in Wellington and encourages the further strengthening of the strong scientific ties between Germany and both Australia and New Zealand even more. I wish all members of the Australian and New Zealand Associations of von Humboldt Fellows great continued success in the pursuit of your projects.

Gerhard Thiedemann,
Ambassador of the Federal Republic of Germany,
Wellington,
New Zealand.

C.M. Kellett\textsuperscript{a,1}, E. Aydos\textsuperscript{b}, S. Rudolph\textsuperscript{c}, and S.R. Weller\textsuperscript{a}

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Anthropogenic climate change, driven by the large-scale emission of greenhouse gases since the 18\textsuperscript{th} century, can be traced to a market failure whereby polluters have not paid for the impacts of polluting. One estimate of the cost of greenhouse gas emissions is the Social Cost of Carbon Dioxide (SC-CO\textsubscript{2}). We describe the legal and policy frameworks where the SC-CO\textsubscript{2} has been used as well as the modelling and methods for estimating the SC-CO\textsubscript{2}. We indicate how the disciplines of law, economics, and climate science might collaborate to better address the emerging challenges posed by global warming.

1. Introduction

In the absence of deep and sustained reductions in greenhouse gas emissions\textsuperscript{2} the overwhelming scientific consensus points to global warming of several degrees Celsius by 2100. Warming of this magnitude poses profound risks to both human society and natural ecosystems [1]. In response to these risks, in late 2016 the Paris Agreement entered into force, committing signatory nations to urgent reductions in human-caused emissions of greenhouse gases, most notably carbon dioxide (CO\textsubscript{2}), in order to limit the increase in global average temperature to well below 2\textdegree{}C relative to pre-industrial levels.

In view of the tremendous challenges posed by the Paris Agreement and the necessity to decarbonise the global economy within this century, it is crucial that policy options are (re-) considered [2]. Greenhouse gas emissions pricing, particularly cap-and-trade schemes, have been almost unanimously regarded by economists as preferred instruments to address the climate change externality in a cost-effective manner [3]. Indeed, it is possible to design and implement efficient, effective, and fair carbon markets by referring to best-practice examples and lessons from modern environmental governance literature [4]. Cap-and-trade schemes have been rolled out across Europe, North America, and Asia on different governance levels and many have been recently reformed and significantly strengthened [5]. One example is the European Union (EU) supranational carbon market, operational since 2005. At the national level, carbon markets also exist in Switzerland, New Zealand, South Korea, and Kazakhstan. China launched its national emissions trading scheme in December 2017. US states in cooperation with Canadian provinces have advanced the establishment of inter-linked North American carbon markets.

\textsuperscript{1} Present address: School of Electrical Engineering and Computing, University of Newcastle, Callaghan, New South Wales, 2308, Australia. Email: Chris.Kellett@newcastle.edu.au
\textsuperscript{2} There are seven main Greenhouse gases (GHGs) in the atmosphere: Carbon dioxide (CO\textsubscript{2}), Methane (CH\textsubscript{4}), Nitrous oxide (N\textsubscript{2}O), Hydrofluorocarbons (HFCs), Perfluorocarbons (PFCs), Sulphur hexafluoride (SF\textsubscript{6}) and Nitrogen trifluoride (NF\textsubscript{3}). The first three GHGs occur naturally in the atmosphere, while the others are synthetic. While natural (non-anthropogenic) GHGs are essential to keep the earth warm enough to support life, human activities such as energy production, land clearing and agriculture have increased the volume and variety of GHGs present in the atmosphere, with severe impacts to the climate system.
Additional big emitters such as Brazil, Canada, and Mexico are actively discussing national schemes [2]. In Australia, a number of uncoordinated policies have been debated, introduced, and dismantled over the past ten years. After two years of a functioning Carbon Pricing Mechanism (CPM), in 2014 Australia earned the distinction of being the first country to discard a mandatory carbon pricing scheme.

The repeal of the CPM was not a consequence of design or implementation issues [6]. The scheme had a solid beginning and potential to achieve its environmental goals without serious harm to the economy [7]. In terms of its environmental effectiveness, data published on the Quarterly Update of Australia’s National Greenhouse Gas Inventory from June, 2012 onwards, confirms that emissions decreased after implementation of the CPM and, inversely, increased since its repeal [8]. However, one point of contention has been the perceived lack of a science-based price on carbon pollution to inform the pricing elements of the scheme mentioned above. During the fixed charge years of the Carbon Pricing Mechanism, the Australian permit prices were determined based on EU Emissions Trading Scheme price projections (based on 2005 prices), which were initially in the range of €10 to €25 per tonne of CO₂e [9]. However, the sharp decline in the cost of EU Emissions Trading Scheme permits in 2006 and again in 2008 weakened support for the CPM.

Indeed, an innovative feature of the CPM was the adoption of a phased approach to pricing, starting with a fixed price, with flexibility increasing over time [7]. During the first three years of the scheme, known as the fixed charge years (from 1 July 2012 until 30 June 2015) permits were issued for a fixed price, having the practical effect of a carbon tax. The permit price was A$23 per tonne of CO₂e in the financial year 2012-13 and A$24.15 per tonne in the financial year 2013-14 [10]. This price was consistent with Garnaut’s recommendation for an initial price between A$20 and A$30 per tonne, rising at 4 per cent (real) per annum [11].

From 1 July, 2015 onwards, the Clean Energy Act provided for the commencement of the flexible charge years, with the auctioning of Australian Carbon Units (ACUs). A safety mechanism was integrated into the first three flexible charge years. In the financial years beginning on 1 July, 2015, 1 July, 2016 and 1 July, 2017, the liable entities would have the option of purchasing carbon units for a fixed charge, set by regulations [7,10]. The issue of carbon units for a fixed charge would work as a price ceiling. The original design of the CPM also included a price floor (A$15, rising annually by 4%) in the first three flexible charge years [12], but this feature was removed on the basis of the need to ‘reduce the complexity of the linking arrangement and ensure the convergence of Australian and EU carbon prices’ [13].

In 2016, the World Bank conducted a review of the state of carbon pricing and reported that ‘an average carbon price of between US$80/tCO₂e and US$120/tCO₂e in 2030 would be consistent with the goal of limiting the global temperature increase to 2°C’ [14]. The report also states that the average internal carbon price used by OECD Governments for appraising long-term investment projects was US$153/tCO₂e and US$164/tCO₂e in 2050 for energy and transport investment projects respectively (2014 values) [14]. In a 2017 address, Stern stated that carbon prices must reach US$40-80 per tonne by 2020, and US$50-100 by 2030 [15].

Hence, one element of any stable, bi-partisan, future price on greenhouse gas emissions is broad agreement on how to arrive at prices. In the context of US regulatory policy, the Social Cost of Carbon Dioxide (SC-CO₂, or the Social Cost of Carbon) has been the accepted science-based price on carbon [16-21]. While this concept has not been without its detractors, major revisions in estimating the SC-CO₂ are being undertaken (see [22] and Section 4 below). However, even with improvements in the tools and techniques for estimating the SC-CO₂, significant work remains to make this a broad-based consensus approach to valuing greenhouse gas emissions.
This paper considers two key aspects of the SC-CO₂ as a principled means of pricing greenhouse gas emissions, namely: the SC-CO₂ in law and policy; and computational methods for estimating the SC-CO₂. In Section 2 we survey the legal and policy history of the SC-CO₂ in the regulatory framework of the United States as well as how the SC-CO₂ might be used in the context of cap-and-trade schemes. In Section 3 we outline the central features of Integrated Assessment Models (IAMs), which couple models of both geophysical and socioeconomic processes to compute the SC-CO₂; namely the (discounted) value of lost future consumption arising from the emission of one additional tonne of CO₂ to the atmosphere. In Section 4 we summarise recent progress towards improving estimates of SC-CO₂, including the use of techniques from feedback control theory.

2. Social Cost of Carbon Dioxide in Law and Policy

We first survey the legal and policy history of the SC-CO₂ in the regulatory framework of the United States and then discuss recent proposals to adopt the SC-CO₂ in the context of cap-and-trade schemes.

2.1 Cost-benefit Analysis of Policies, Programmes and Projects in the United States

The terms “policy appraisal”, “cost-benefit analysis”, and “regulatory impact analysis” are often used interchangeably. There is not one single definition of cost-benefit analysis [23]. In this article, we refer to policy appraisal or cost-benefit analysis as a process of policy assessment where a desired outcome is established and competing regulatory models to pursue this outcome are compared by weighing up their negative and positive impacts, including the impacts of inaction. An important principle of cost-benefit analysis is that a policy, programme, or project should only be implemented where its social benefits exceed the additional social costs [24].

Cost-benefit analysis of policies, programmes and projects has been extensively adopted in OECD countries, with standards and approaches varying according to jurisdiction [25]. This section focuses on the regulation of cost-benefit analysis in the United States (US).

The origins of cost-benefit analysis in the US can be traced back to the 1936 US Flood Control Act [24]. The Copeland Flood Control Bill began with a “declaration of policy” stating that flood control was a national responsibility and that a national flood control program should be implemented “if the benefits to whomsoever they may accrue are in excess of the estimated costs, and if the lives and social security of people are otherwise adversely affected” [26]. Despite some early examples such as the 1936 US Flood Control Act, the current legal framework for cost-benefit analysis was only implemented decades later by presidential Executive Order and has been reviewed twice in the space of 30 years.

The first Executive Order (EO 12291) related to cost-benefit analysis was issued in 1981 by President Reagan. It provided that “each agency shall, in connection with every major rule, prepare, and to the extent permitted by law consider, a Regulatory Impact Analysis” and that Regulatory action shall not be undertaken unless the potential benefits to society for the regulation outweigh the potential costs to society [27].

Twelve years later, President Clinton issued Executive Order 12866 (EO 12866) updating EO 12291 and providing for a statement of regulatory philosophy and principles of regulation. It reaffirmed the requirement for all federal agencies to adopt a cost-benefit analysis when assessing intended regulation and provided that agencies should “propose or adopt a regulation only upon a reasoned determination that the benefits of the intended regulation justify its costs” [28].

Finally, in 2011 President Obama issued Executive Order 13563 (EO 13563) to be interpreted as a supplemental order to EO 12866. EO 13563 reaffirms and enlarges the principles of regulation, specifically providing for public participation, transparency and
simplicity, integration, innovation, and scientific integrity, as well as use of the best, most innovative, and least burdensome tools for achieving regulatory ends [29].

2.2 The Use of SC-CO₂ Values in Cost-benefit Analysis in the United States

In the context of US Federal regulatory policy, the SC-CO₂ has been used in cost-benefit analysis since 2009 [20,21]. In 2006, the National Highway Traffic Safety Administration (NHTSA) issued the “Average Fuel Economy Standards for Light Trucks, Model Years 2008-2011” (“NHTSA fuel standards”) under the National Environmental Policy Act of 1969. Eleven states, the District of Columbia, the City of New York, and four public interest groups challenged the NHTSA fuel standards arguing, amongst others, that the “calculation of the costs and benefits of alternative fuel economy standards assigns zero value to the benefit of carbon dioxide (CO₂) emissions reduction”. In 2007, the US Court of Appeals for the 9th Circuit held that NHTSA failed to monetize the value of carbon emissions in its determination and ordered NHTSA to promulgate new standards that would take into account the benefit of CO₂ emissions reductions [30].

The Federal Court did not prescribe a methodology for calculating the costs and benefits associated with CO₂ emissions reductions. Therefore, in 2009 President Obama formed the Interagency Working Group (IWG) on the Social Cost of Carbon under EO 12866, later renamed the Interagency Working Group on the Social Cost of Greenhouse Gases. The IWG was responsible for providing SC-CO₂ estimates to be incorporated by agencies in their policy appraisal of regulatory actions that have “small, or ‘marginal’, impacts on cumulative global emissions” [20].

From 2009 onwards, US Federal agencies henceforth adopted the IWG SC-CO₂ values in cost-benefit analysis of regulation as the accepted science-based price on carbon. The IWG released interim SC-CO₂ values in 2009, which were then revised in 2010, 2013, and 2016. In 2016 the IWG released its final report, calculating a SC-CO₂ for 2015 at $36 per ton of CO₂ in 2007 US dollars³ [21].

In 2017, President Trump issued the Presidential Executive Order on Promoting Energy Independence and Economic Growth, disbanding the IWG and revoking all of the IWG Technical Support Documents and Technical Updates on the SC-CO₂ from 2010 until 2016 [31]. The EO also required that future cost-benefit analysis of the impacts of CO₂ be based on a 2003 Circular on Regulatory Analysis [32].

The termination of a uniform approach for the estimation of the SC-CO₂ at the Federal level is likely to lead to ad-hoc calculations and inconsistent approaches across Federal agencies. It is also likely to result in the collapse of the ‘value for a ton of carbon pollution’, impacting the effectiveness and efficiency of environmental regulation in years to come [33].

2.3 The use of SC-CO₂ Values in Subnational Cap-and-Trade in the United States

From an economics perspective, global warming is a result of market failure which can be corrected by internalisation of externalities, but requires knowledge about the extent of external costs. In climate policy, this is precisely the SC-CO₂. Economists have convincingly shown that markets only lead to an optimal allocation of scarce resources if producers take into account all costs associated with production as initially described by Pigou [34]. If costs are externalised, markets fail. Production decisions become inefficient, and, in the case of negative externalities or external costs, lead to overproduction beyond the socially optimum output. Correcting this market failure requires the internalisation of external costs.

However, Pigou’s proposal to internalise negative externalities by implementing a tax has a major flaw. It requires setting the tax rate equal to the difference between private

³ Note that the value referenced here assumes a 3% discount rate.
production costs (the costs for production factors such as material or labour) and social costs, which additionally include external costs to society. Critics of the Pigou approach have emphasised that “the basic trouble with the Pigouvian cure for the externalities problem [lies] in the fact that we do not know how to determine the dosages that it calls for” and that the task of calculating the tax rate “assumes Herculean proportions” [35]. In the context of climate policy, however, the external costs of using the global atmosphere as a dump for greenhouse gas emissions are given by the SC-CO₂. Hence, in spite of the Pigouvian requirement of knowledge about the external costs at the optimal output level, the SC-CO₂ provides at least a partial answer to the necessary tax “dosage”.

Practice-oriented approaches could also greatly benefit from improved estimates of the SC-CO₂. Due to the above-described challenge of the Pigouvian approach, economists and policy makers currently favour a cost-efficiency approach. The goal here is not an economically optimal internalisation of external costs, but only the compliance with a politically determined environmental target, e.g., a domestic CO₂ reduction target, at lowest cost to society [35]. Environmental taxes and cap-and-trade (or emissions trading) schemes follow this approach. In the case of carbon cap-and-trade, the preferred approach in the US, the price is a result of polluters’ reactions to a scarce, regulator-set cap, limiting the total quantity of emissions, e.g., for one particular US state [36]. However, since price fluctuations might significantly disturb market performance and investment decisions, price corridors have been discussed intensively [37]. A price floor, a lower price limit below which the regulator does not sell CO₂ allowances, could guarantee a minimum price level and hence secure at least some innovation incentives and revenues. An upper price limit, a price ceiling, could act as a “Break Glass in Case of Emergency” for cases of unexpected price surges due to extreme events such as the California 2000 electricity crisis [38]. Here, the SC-CO₂ could act as guidance for decisions on price corridors as discussed in some detail below.

US states using carbon cap-and-trade have already recognised the merits of price corridors and the SC-CO₂ has been part of discussions on this issue [39]. Since its implementation in 2013, the California Cap-and-Trade Program (CalCaT) has used a reserve populated with a share of the cap increasing from 1 to 7%, from which allowances are sold in three equal tiers at US$40, US$45, US$50 (+5% over the inflation rate per annum) as a cost containment measure; i.e., a “soft” price ceiling. The price floor was set at US$10 (+5% over inflation per annum). CalCaT is linked to Canadian provincial partners under the Western Climate Initiative (WCI) and the price management mechanisms of both Québec and Ontario are closely aligned to those of California. The Californian follow-up regulation for 2021 and after will again rely on a cost containment reserve and two trigger prices for cost containment, but might also use a “hard” price ceiling on top of that. Some stakeholders have explicitly argued to “[s]et the price ceiling … at least as high as the social cost of carbon” [40].

The Regional Greenhouse Gas Initiative (RGGI) in the US Northeast has also used price management measures. From 2009 to 2013 a cost containment reserve was populated with a 10% share of the cap. Auction sales from the reserve were triggered if the allowance price exceeded US$4 in 2014, US$6 in 2015, US$8 in 2016, and with a 2.5% per annum price increase over inflation from 2017 onwards. The price floor was set at US$1.89 (+2.5% per annum over inflation). In the 2013 major program reform, cost containment trigger prices were set at US$10 for 2017 (+2.5% per annum over inflation) and US$13 for 2021 (+7% per annum over inflation). Also, allowances will be withheld from circulation via auctions if prices are below US$6 in 2020 (+7% per annum over inflation).

However, since mid-2013 CalCaT prices have stayed very close to the price floor and RGGI allowances were even sold at the actual floor price between September, 2009 and December, 2012. The “soft” price ceiling via allowance sales from cost containment reserves has never been used in California because prices have remained far below the cost
containment trigger prices. RGGI triggers were only hit in March, 2014 and September, 2016 auctions. The major reason for low prices are loose emission caps that do not reflect the real scarcity of the resource. Hence, the SC-CO2 could fulfil two major tasks in cap-and-trade design and evaluation. First, it could act as a benchmark for evaluating the stringency of the cap. Second, it could provide guidance for deciding price floors and price ceilings.

To be concrete, the final report of the IWG under the Obama Administration, estimated the SC-CO2 for 2020 to be within a range of US$12 to US$123, depending largely on the discount rate, with a central estimate of US$42, [21]. Even in this conservative central estimate, the SC-CO2 will increase to US$69 in 2050, while the High Impact scenario expects SC-CO2 values of up to US$212 in 2050. This obviously means, first, that current allowance prices of around US$15 in CalCaT and, even more so, of US$4 in RGGI are far too low for the emission caps to reflect the real scarcity of the resource. Second, the price floor should be set at a level equal to or higher than the lowest SC-CO2 estimate, e.g., US$12 for 2020, while “hard” price ceilings which should only take effect in the cases of extreme events, could use the High Impact estimate, e.g., US$123 for 2020, for guidance.

The political economy of carbon markets should also be kept in mind. In most political debates – even in jurisdictions that now have carbon markets in operation –, opponents justify their opposition by emphasising additional net costs to production and resulting international competitive disadvantages, and these additional costs can even be easily pointed out as they are advertised as stock-market, CO2-allowance prices [41]. The SC-CO2 could act as a counterbalance to these arguments as it shows the externalised costs to society in the case of inaction and makes them more easily perceivable in political debates.

In summary, SC-CO2 calculations are an extremely valuable means not only for estimating the external costs of global warming but also for concrete policy design such as carbon markets in the US. As carbon markets have been spreading across the globe and at all governance levels, improving estimates of the SC-CO2 could also greatly benefit carbon market design and reform in other jurisdictions and even act as a countermeasure against unjustified political opposition.

3. Modelling for the Social Cost of Carbon Dioxide

Having provided an overview of the regulatory frameworks where the SC-CO2 has been and is used, we now turn to how estimates are derived and provide a working definition. In general terms, the SC-CO2 is the (discounted) lost future consumption due to an extra unit (e.g., 1 tonne of CO2) of emissions in a particular year5. At its core, then, estimating the SC-CO2 requires a model of how greenhouse gas emissions lead to lost consumption6. Such a model necessarily draws from many disciplines as it must include physical processes (such as carbon, climate, and sea-level rise models) as well as socioeconomic processes (such as population growth and technological progress models). Such multi-disciplinary models are referred to as Integrated Assessment Models (IAMS).

3.1 Common Features of Integrated Assessment Models

Many different IAMs have been proposed to estimate the SC-CO2. The three most frequently cited are DICE (Dynamic Integrated model of Climate and Economy) [42,43], PAGE (Policy Analysis of the Greenhouse Effect) [44], and FUND (Climate Framework for

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4 All estimates of the SC-CO2 from the IWG are in 2007 US dollars.
5 Despite its nomenclature as the Social Cost of Carbon Dioxide, estimates of the SC-CO2 are generally calculated based on the social cost of emissions of all long-lived greenhouse gases.
6 Here, it is important to note that we use consumption in a narrow economic sense to refer to all economic output that is not re-invested into capital.
Uncertainty, Negotiation, and Distribution) [45]. While these models differ in their details, they all share four common elements (see Fig. 1):

1. Models of geophysical processes: In order to capture the impact of greenhouse gas emissions, all IAMs require model elements that react to emissions, such as estimates of how long greenhouse gases remain in the atmosphere, how global temperature changes based on atmospheric concentrations of greenhouse gases, or how melting permafrost releases methane into the atmosphere.

2. Models of socioeconomic processes: Many elements contribute to economic output that is available for consumption. Consequently, IAMs include estimates of socioeconomic processes such as population growth, capital investment, or technology growth, and may even go so far as to attempt to model different economic sectors or geographic regions.

3. Estimates of climate-related damages: Coupling the two elements above requires an estimate of how much economic activity or output is reduced due to the negative effects of climate change. Examples here may include reduced crop production due to desertification, reduced fishery stocks due to ocean acidification, or loss of infrastructure due to extreme weather events. Different models use estimates that range from a general global estimate (e.g., a lost percentage of global GDP for a given temperature rise) to detailed sectoral or regional estimations of the economic impact of climate change.

4. Discounting future losses: In order to arrive at a present-day value for all lost future consumption, all IAMs make use of some form of discounting. For example, 100 dollars of lost consumption 20 years into the future is only valued at some percentage of 100 dollars now (e.g., 95 dollars or 60 dollars).

It should be clear that all of these elements are subject to uncertainty and, to some extent, are even open to debate. A clear example of these issues is the choice of discount rate. In part, discounting is justified on the basis of coping with uncertainty. Indeed, rates of warming or technological innovation are subject to significant uncertainty and the further into the future we look the more uncertain our projections become. Hence, it may be difficult to justify estimating economic impacts on long, multi-generational time scales. On the other hand, physical processes around persistence of greenhouse gases in the atmosphere or the response of the Earth’s temperature under the enhanced greenhouse effect are known to be very long-lived. Furthermore, discounting raises issues of intergenerational equity as increased emissions now will have impacts far into the future. As a compromise, most (though not all) models make use of discount rates that are much smaller than those typically used in economic analyses such as in examining infrastructure investment where the infrastructure might have an expected lifetime of 30-50 years.

With the above discussion in mind, it is important to note that there is not a single value for the SC-CO₂, but rather there are estimates of the SC-CO₂ that will depend critically on the assumptions made in constructing the models. Consequently, one way to view such models is

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7 It is important to note that some negative impacts of climate change, such as extinction of species or loss of biodiversity, are difficult, if not impossible, to quantify.
as a discussion framework to collectively encode both our knowledge and our assumptions about climate change and its impacts.

3.2 Computing the Social Cost of Carbon Dioxide

Returning to the above definition of the SC-CO₂ as the lost consumption due to an extra unit of carbon dioxide, the other element necessary to estimate the SC-CO₂ is a baseline emissions pathway or a projection of how emissions will evolve into the future. Such a pathway can be defined (and justified) directly by the modeler. Alternatively, the Intergovernmental Panel on Climate Change (IPCC) 5th Assessment Report (AR5) provides so-called Representative Concentration Pathways (RCPs) [1]. While the RCPs themselves are not anthropogenic emissions pathways, they can serve as a starting point to specify plausible baseline emissions pathways (see, e.g., [46]).

The Representative Concentration Pathways (RCPs) are four time-dependent greenhouse gas concentration trajectories developed in preparation for the IPCC AR5 [1]. The four RCPs are called RCP2.6, RCP4.5, RCP6 and RCP8.5, in reference to their associated radiative forcing values in the year 2100, namely +2.6, +4.5, +6 and +8.5 W/m², respectively. RCP2.6 is also referred to as RCP3PD, for Peak–Decline, since the forcing under this trajectory reaches a peak forcing level of approximately 3 W/m² mid-century before declining to +2.6 W/m² in 2100. The RCP3PD pathway represents an aggressive mitigation scenario, while RCP8.5 is characterised by continued increasing greenhouse gas concentrations over time. The RCP4.5 and RCP6 pathways lie between these two extremes.

We are now in a position to provide a graphical description of the SC-CO₂, shown in Fig. 2. As previously described, we start with a pre-defined baseline emissions pathway in the top left. Using an Integrated Assessment Model, we then compute a baseline consumption pathway as an output of the model on the top right. We then perturb the emissions baseline by adding a small (e.g., 1 tonne) additional amount of greenhouse gas emissions in the year of interest, shown in the bottom left of Fig. 2 by the solid red line. With this perturbed emissions pathway, we again use the Integrated Assessment Model to determine a new, reduced consumption pathway shown in the bottom right by a solid red line. Finally, the SC-CO₂ is given by appropriately discounting and adding up the “lost” consumption shown on the bottom right of Fig. 2 by the blue arrows.

3.3 Endogenous Greenhouse Gas Emissions

One approach to compare results from different IAMs involves trying to harmonise these models as much as possible, for example, by modifying the models so that they all can take the same emissions pathway as an input. While this can be done with the DICE model, it is neither how the model was originally conceived nor how it is most commonly used. Rather, emissions in the DICE model are an endogenous quantity. In other words, emissions are not defined external to the model but are computed as part of the model evolution. Specifically, this is done by assuming values for greenhouse gas emissions per unit of economic output (e.g., 1 tonne of CO₂ emissions for $1 of GDP).

In this way, the DICE model involves a feedback loop that is not present in either PAGE or FUND. Specifically, the economic model generates greenhouse gas emissions, which drive a carbon model, which feeds into a temperature model, which, via a damage

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8 The RCPs specify atmospheric greenhouse gas concentrations rather than emissions. Due to uncertainties in the Earth biogeochemical processes, there is not a unique anthropogenic emissions pathway that generates a particular RCP.

9 Radiative forcing at the top-of-atmosphere due to the greenhouse effect is the physical process behind global warming and refers to the imbalance between incoming solar radiation and outgoing Earth radiation. The unit for radiative forcing is Watts per square metre (W/m²).
Fig. 2. Graphical representation of the SC-CO₂ as discounted lost consumption due to emissions perturbation. (See Fig. 3.) Hence, as they are normally used, the DICE model is fundamentally different to either the PAGE or FUND models. Indeed, the former is referred to as a general equilibrium model while the latter are referred to as partial equilibrium models.

4. Recent Developments in Estimating the Social Cost of Carbon Dioxide

As described in Section 2, the Interagency Working Group (IWG) on the Social Cost of Carbon released initial SC-CO₂ estimates in 2009, with updates in 2010, 2013, and 2016. The approach taken by the IWG involved harmonising the three most widely cited models (the previously mentioned DICE, PAGE, and FUND models) in certain ways in order to make valid inter-model comparisons, and then taking the average SC-CO₂ values across the three models.

In 2015, the US National Academies were asked to undertake a review on updating estimates of the SC-CO₂, culminating in a substantial report released in 2017 [22]. While the report contains many recommendations, it also has three recurring themes as to fundamental requirements for improving estimates of the SC-CO₂:

1. Transparency: models and methodology should be thoroughly documented;
2. Modularity: any integrated assessment models should have well-defined sub-models to facilitate updates based on improved models in any one domain; and

3. Methods for quantifying uncertainty: as previously discussed, integrated assessment models are subject to significant uncertainty and this uncertainty needs to be appropriately quantified and communicated.

In our view, of the three models used by the IWG, the DICE model is the preferred starting point for subsequent model development in line with the recommendations of [22]. In particular, while the primary sources for many of the model parameters have never been fully documented, computer code for the DICE model (in the GAMS language) has been available since the 2007 version of the model. Recently, we have re-coded the model in Matlab (a platform more widely used than GAMS) and made the code publicly available [47,48]. Additionally, in [47,48] we have provided complete and concise mathematical definitions of the models.

The DICE model is modular in structure with well-defined components for carbon and climate cycles, population growth, technology advance, economic growth, etc. This allows for incremental improvements in individual modelling components. For example, in [49] we developed a technique to arbitrarily set two key climate parameters in the DICE climate cycle; the so-called Transient Climate Response and the Equilibrium Climate Sensitivity. This allows the DICE climate model to replicate key behaviours of larger, atmosphere-ocean general circulation models as provided in [1].

Following one recommendation in [22], we examined an alternate carbon and climate cycle model (called FAIR) proposed in [50]. It is known that there are feedbacks between rising temperature and oceanic carbon uptake, but this is not captured in the simple carbon and climate models of DICE. However, due its modular nature, it is possible to replace the default carbon and climate models of DICE with those of [50]. Preliminary outcomes of this work appear in [51]. The use of FAIR in [51] was undertaken in response to the recommendation in [22]. However, the use of other simplified carbon and climate models, such as MAGICC [52], is certainly possible.

Historically, quantifying uncertainty in SC-CO$_2$ estimates generated by DICE has been its least studied aspect. In part, this is due to its structure as a general equilibrium model as discussed in Section 3.3. Due to the feedback structure shown in Fig. 3, particular tools and techniques are required to correctly propagate uncertainty through the model. One recent approach is to treat the model in a feedback control loop, whereby the model evolves subject to some uncertainty, but the model inputs are adjusted at each time step of the model based on the model variables available at the previous time step [53,54]. Another approach that directly solves the model with uncertain parameters was proposed in [55].

5. Conclusions and Outlook

The deep and sustained reductions in greenhouse gas emissions required to stay below the 2°C of the Paris Agreement will require a myriad of solutions and approaches. When viewed as a market failure, one approach to anthropogenic global warming clearly involves pricing greenhouse gas emissions. Economic theory indicates that preferred strategies include either Pigouvian taxes or cost-efficiency approaches such as emissions trading schemes. Additionally, in managing the transition to a (net) zero-emission economy, cost-benefit analyses have a clear role to play to phase in reductions when and where such reductions will have the greatest impact. In both of these approaches, a science-based price on carbon derived in a transparent manner will provide policymakers and all stakeholders with a common understanding of how prices are set.

As is evident from Sections 2-4 above, significant work remains to be done in the design of legal and regulatory regimes as well as in the estimation of the SC-CO$_2$. On the one
hand, the cost-benefit analysis framework described in Sections 2.1 and 2.2 is by no means representative of frameworks in other jurisdictions. Similarly, the current design of cap-and-trade schemes, for example, in setting price corridors and in fixing caps, relies only loosely (if at all) on scientifically justified emissions prices. On the other hand, the models and methods used in estimating the SC-CO2 have known shortcomings that can be addressed via incremental model improvements and improved uncertainty quantification techniques. While we are actively engaged in these independent topics, in our view an important direction of research is the bringing together of these qualitative and quantitative research streams. For example, as partially described in Section 2.3, we are investigating how to better use SC-CO2 estimates in the design of cap-and-trade schemes. Conversely, it may be possible to incorporate elements of these schemes into the socioeconomic component of the DICE model to better reflect both the expected value and the range of values for the SC-CO2. A similarly synergistic approach may be possible when considering the use of SC-CO2 estimates in cost-benefit analyses where it may make sense to consider different SC-CO2 values for different economic sectors. Given the expected impacts of global climate change in all disciplines, addressing the challenges posed by climate change necessitates an interdisciplinary approach and dialogue.

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References


3. Exceptional Symmetries and Their Applications

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The five Platonic solids and their symmetries have fascinated people for at least 2000 years. Exceptional symmetries occur in higher dimensions, the most elusive one is E8 in 248 dimensions. At the heart of these symmetries are slightly esoteric, algebraic structures, the quaternions and the octonions. I will give an overview of these objects and their applications in adjacent fields such as theoretical physics, computer graphics, and robotics.

1. Introduction

Geometry deals with spatial structures and their symmetries, and humans seem evolutionarily pre-conditioned to love the latter. Symmetries have been studied for thousands of years, e.g., the ancient Greeks already knew all five regular (Platonic) solids in three dimensions which are depicted on the right. Symmetries can be abstractly described by algebraic structures (groups), where composition of symmetries corresponds with multiplication in the group.

The leading theme of this paper is that increasing the complexity of (geometric) concepts forces us to consider more elaborate algebraic structures.

The origins of algebra are in arithmetic. You may recall learning how to count to ten or have a (grand)child doing so, i.e., you worked with the natural numbers and a bit later you discovered the negative numbers. You also soon worked out that it is (often) impossible to distribute a bag of lollies evenly amongst a group of friends, i.e., the existence of rational numbers, e.g., \( \frac{7}{3} \).

Hippasus [18] was the first to notice that not all numbers are rational (and allegedly was murdered because of it), e.g., the length of the hypothenuse of the triangle depicted on the right cannot be rational. Suppose \( \sqrt{2} = \frac{x}{y} \) where we may assume that \( x \) and \( y \) have no factor in common, (i.e., that it is a simplified fraction), then squaring yields \( x^2 = 2y^2 \) and hence \( x \) must be even, but then the left-hand side is divisible by 4 and hence also \( y \) must be even, a contradiction as then \( x \) and \( y \) are both divisible by 2.

In high school you developed familiarity with the real numbers without defining them (as this is too technical at that stage) and learnt to solve equations in the algebra class. When solving quadratic equations, you encountered \( x^2 + 1 = 0 \) which has no solutions in the real numbers as the square of a real number is always positive. But in analogy with the extensions we described above, maybe there is a bigger number system which can capture this concept?

2. Complex Numbers

A complex number, \( z \), is expressible in the form \( a + bi \), where \( a \) and \( b \) are real numbers and \( i \) is a number for which \( i^2 = -1 \). They are often represented as a vector, \( v = (a,b) \) in the plane and the length of \( z \) is defined to be the length of \( v \). They were first studied in the 16th century...
in Italy to solve equations of degree 3 and 4 with, to say the least, some controversy over who was first to discover the formulas to solve those equations [20].

Taking a square root of a negative number may seem unnatural, but consider a rotation, \( R \), over 90 degrees in the plane. If you apply \( R \) twice to an object, \( A \), then you obtain the reflection in the origin of \( A \), and applying \( R \) twice more puts \( A \) back in place. In fact multiplication is defined such that multiplying with a complex number, \( a + bi \), of length, 1, corresponds to a rotation in the plane over the angle formed by the corresponding vector \((a,b)\) with the X-axis.

The complex numbers are of fundamental importance in a large number of areas of mathematics and have applications both to other pure sciences, e.g., they are the heart of quantum mechanics as well as in industry including electrical engineering and medicine [21].

3. **Quaternions**

Hamilton tried for a number of years in vain to define a three-dimensional algebra over the real numbers and worked out why he could not possibly succeed, leading to the theory of eigenvalues and eigenvectors now taught in a typical undergraduate linear algebra course. In 1843 he discovered the quaternions which at that time were considered very esoteric and unpractical. He carved their formulas into a Dublin bridge [19].

As opposed to real and also complex numbers, the multiplication order matters for quaternions as e.g., \( ij = ji \). If you ever played with a Rubik’s cube, you will recognise that this is again a natural phenomenon as there the order of the turns you make is very important.

3.1 **Gimbal Lock, the Resolution Using Quaternions and its Applications**

The movement of airplanes can be described by a rotation along three axes (the Euler axes), as in the left picture below. However, when two of these axes coincide as on the picture on the right, a degree of freedom is lost, leading to a so-called gimbal lock [16]. Practical problems arise already before they exactly coincide. For commercial airplanes this usually does not occur as they do not fly under extreme angles. But this has to be taken care of for fighter jets.

As we saw in Section 2, multiplication with complex numbers of length, 1, describes rotations in the plane. Similarly, instead of using three axes, spatial rotations can be described in one go by multiplication with quaternions of length, 1, thus avoiding gimbal lock. The image of robot automobile assembly (at right) shows an industrial application where gimbal lock occurs, and hence where quaternions have practical importance. A second application is in digital imaging, in particular in 3D visualization, pictured on the following page.
The conversation pictured below is part of the transcript of the epic Apollo 11 mission and should be seen in the light of discussion prior to the flight whether or not to install a system with a fourth gimbal (i.e., quaternion based) to prevent gimbal lock, which NASA decided against.

In physics, spinors play a fundamental role, they only become the identity under a 720 degree rotation and can be described by quaternions. Such phenomena occur in nature, as one can see in the picture of the Möbius strip on the right. A fun way to illustrate this is the Dirac belt trick [17], named after one of the greatest physicists of all time.

4. **Octonions**

Why stop there? Perhaps there are even more abstruse algebraic structures capturing even deeper phenomena. The octonions [3] form an eight-dimensional algebra, which is not even associative, meaning that x(yz) is not necessarily equal to (xy)z, as one can observe in their multiplication table (next page). Amazingly they are at the heart of Lie groups and Lie algebras, a central area of mathematics describing continuous symmetries developed by Sophus Lie (pictured on the next page).
Around 1890, Killing and Cartan classified simple Lie groups into the classical groups and five exceptional families, the biggest one being the elusive E8. (See Garibaldi’s excellent article [5].) The classical groups are of fundamental importance for physics and include the rotation group, the Lorentz group (used in special relativity) and the symplectic group (used in Hamiltonian mechanics). The exceptional families are closely linked with the octonions.

Weil and Chevalley generalized Lie groups to algebraic groups and in the 1950s Tits reversed Klein’s Erlangen program by associating geometric objects (known as buildings [14,15]) to algebraic groups, e.g., for the general linear group consisting of invertible linear transformations. The building is a projective space.

In the 1960s Freudenthal and Tits (pictured below) [4,11,12,13] provided a remarkable uniform construction of the exceptional algebraic groups which are represented at right with their Dynkin diagram. This construction involves composition algebras (complex numbers, quaternions, octonions). The aim of an ongoing joint project between Hendrik Van Maldeghem and me [7,8,9,10] is to gain a complete understanding of the exceptional algebraic groups in this table.

Classical groups can be viewed as isometry groups of bilinear and sesquilinear forms, and for E6 (used in the standard model in particle physics) and E7, such descriptions were obtained by Aschbacher [1,2]. The main objective of our project is to solve the long-standing problem of finding a similar explicit geometric description of a module for E8.

Our key new idea is a geometric approach to this algebraic problem, studying the projective varieties associated with the algebraic entries in the table and viewing them as abstract geometric buildings.

The rows indicate the so-called rank (the number of circles in the picture) and hence the complexity of the geometry, and the columns indicate the complexity of the underlying algebras. The bottom right corner is E8.

Our recent discovery of an abstract combinatorial framework suggests the exciting possibility that we can obtain a universal characterisation for all the geometries occurring in the table.
4.1 Relevance for Physics

In 1934 Jordan, Von Neumann and Wigner discussed the potential relevance of octonions for modern physics, in a paper on the foundations of quantum mechanics [6]. Early attempts were not very successful until, in the 1980s it was discovered that octonions explain some curious features of string theory. The octonions are used in a number of proposed unifying theories in theoretical physics, which are the subject of ongoing research.

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References

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Gastrointestinal (GI) electrical activity, also known as slow-waves, is an electrophysiological event that governs the motility of the stomach and intestines. In recent years, multi-electrode, high-resolution mapping has been used to elucidate the detailed spatiotemporal profiles of GI slow-waves. In addition, multi-scale mathematical modelling has also been developed to address key physiological questions regarding the effects of cellular channelopathy on slow-wave dysrhythmias, and development of whole-organ dysrhythmias.

1. Introduction

Rhythmic contractions of the gastrointestinal (GI) tract are governed by periodic and propagating bioelectrical events, termed slow-waves. The relationship between functional GI disorders and abnormal slow-waves remains an area of active research. Recordings taken directly from the GI surfaces using an array of multiple electrodes, i.e., high-resolution (HR) mapping in the in vivo state, offer the best evidence on the genesis of slow-waves in both the stomach and the intestines to date [1-4]. Based on recent HR mapping studies, gastric slow-waves of the stomach are shown to emerge from a single pacemaker region located in the proximal stomach along the greater curvature. The preferential conduction of slow-waves in the circumferential direction of the stomach allows a rapid encirclement of the wave around the organ and establishes a coherent propagation in the antegrade direction towards the distal stomach, terminating at the pylorus. In addition, HR mapping studies have demonstrated the association between increased prevalence of spatial gastric slow-wave abnormalities and functional disorders, such as gastroparesis, chronic nausea and vomiting [5]. Though the prevalence of these two diseases is limited in the general population, their prevalence increases significantly in the diabetic population [6]. Furthermore, it is likely that the role of gastric, slow-wave abnormalities is underestimated in functional GI disorders, which currently have no reliable electrophysiological tests.

The challenge of investigating digestive electrophysiology and motility arises not only from the complex interactions between the multiple participating cell types, such as smooth muscle cells, various mucosal cells, neurons and the interstitial cells of Cajal (ICC), but also their overlapping control systems. Moreover, as in all physiological systems, these events must be understood separately and collectively across vast spatiotemporal scales, from milliseconds and micrometres for intracellular events, to minutes and centimetres for organ-level events, presenting a challenging analytical task.

The purpose of this article is to demonstrate the HR mapping data and present an in-silico framework to quantitatively link all physiological activities contributing to the function of the small and large intestines, which we term the ‘Virtual Gut’. Relative to modelling work in cardiac and neural fields, in-silico research in the GI field is relatively rudimentary, although many studies have been reported in recent years. This article presents the key methodology of in vivo recordings of the GI tract, and follows on from, and advances, previous interdisciplinary reviews of three major GI organs, the virtual oesophagus, the virtual stomach, and the virtual intestine [7-9]. The review has a particular focus on electrophysiology, including motor control activities by smooth muscle cells and ICC,
because this is an area where modelling has been particularly productively applied to date. Brief attention is also given to other example areas of applied intestinal modelling.

2. Recording Method

HR mapping recordings are made simultaneously from a spatially-dense array of electrodes applied to the serosal and/or mucosal surfaces of the GI tract [10]. Recent advances in HR mapping devices, amplifiers, and signal processing methods have been considerable, enabling greater efficiency in experimental outputs, and deeper insights into how gastric and intestinal, slow-wave patterns contribute to motility. Our preferred method to record gastric slow-waves is to utilise the flexible printed circuit (FPC) technique to manufacture precise and efficient arrays of electrodes, typically with between 3 and 7.62 mm inter-electrode spacing. The electrode arrays can be easily configured into ‘patches’ with different configurations, depending on the orientation of the organ of interest. The electrode arrays are held together using tegaderms. Studies are conducted with the subjects under general anesthesia, with continuous monitoring of vital signs. Access to the organ of interest is gained through laparotomy or trocar insertions with the electrodes in a folded state. The electrode arrays are placed on the serosa of the GI tract and held in position with warm, saline-soaked, gauze packs placed on top of the arrays. Signals are acquired at 512 Hz using an ActiveTwo system modified for passive recordings (BioSemi, The Netherlands).

Data analysis is typically performed using the Gastrointestinal Electrical Mapping Suite (GEMS) (v1.7, FlexiMap, New Zealand) [11]. A Savitzky-Golay filter (0-1.98 Hz) is applied to the signals before down-sampling to 30 Hz. Activation times of slow-waves are identified using a falling-edge, variable-threshold (FVET) algorithm, and then partitioned using the region growing using polynomial-surface-estimate, stabilization (REGROUPS) algorithm [12,13]. Normal slow-wave patterns were defined as regular propagation in the antegrade direction of the GI tract.

An example of HR mapping data of porcine gastric slow-waves is shown in Fig. 1. An array of 29 × 6 electrodes with an inter-electrode distance of 4 mm was used to record the data from the serosal surface of the stomach (Fig. 1A). The electrograms from a column of selected electrodes are shown (Fig. 1B), which demonstrate the sequence of propagation from the most proximal electrode (top) to the most distal electrode (bottom). Based on the recording, the amplitude of the extracellular recordings (average: 0.8±0.4 mV) and velocity of slow-wave propagation (average: 7.3±2.1 mm s⁻¹) were also calculated.

3. Multiscale Simulations

Mathematical modelling uses equations and computational simulations to model complex biological problems. Detailed in silico models can often give insights into the causal relationship between the parameters over a large parameter space, which can further guide experimental investigations by identifying the most likely combinations of parameters that can yield useful data to support the hypothesis. In the case of GI physiology, mathematical models have been developed to focus on the electrophysiology of slow-wave generation by the ICC with experimental validation provided by direct recordings at the cellular level and HR mapping at the whole-organ level.

One particularly significant aspect of mathematical modelling is to develop a system of equations by following the hierarchy of biological systems across multiple, spatiotemporal scales. Such an approach is also called multi-scale modelling, which has been increasingly applied with great effect to study normal and dysrhythmic, GI slow-waves and dysmotility. Generally, in a multi-scale model of dysrhythmia, the lowest scale relates to the kinetics of the ion channels, which are then incorporated in a membrane equation (Equation 1) to simulate slow-waves generated by the ICC,
where $C_m$ denotes the membrane capacitance, $V_m$ denotes the membrane potential and $I_{ion}$ denotes the sum of all the currents through the different types of ion channels in an ICC. The ICC models are then ‘linked’ together in a spatially-averaged or continuum manner to model the propagation of slow-waves at the tissue and whole-organ scales (Equation 2). The advantage of such a setup is that perturbations to individual ion channels or structural loss of ICC can be introduced to simulate effects of diseases on GI slow-waves [16].

\[
\nabla \cdot (\sigma \nabla V_m) = A_m \left( C_m \frac{\partial V_m}{\partial t} + I_{ion} \right)
\]

where $\sigma$ denotes the conductivity and $A_m$ denotes the cell surface to volume ratio.

3.1 Effects of Ano1 Knockout (KO)

The Ano1 protein is a Ca\(^{2+}\)-activated Cl\(^-\) channel in the ICC that has been shown to coordinate the motility of the GI tract through modulating slow-waves and calcium transients [14]. A biophysically-based model of the ICC was extended to investigate how perturbations to Ano1 affect slow-waves at the cellular level and over a one-dimensional (1D) intestinal tissue model. An intrinsic frequency gradient of 24-26 cycles per minute (cpm) was assigned to the 1D model to simulate entrainment of intestinal slow-waves [16].

At the cellular level, the results showed that a knockout of the Ano1 protein was able to completely inhibit the ability of the ICC to generate slow-waves (Fig. 2A, B), as has been demonstrated experimentally [14,15]. If the ICC are coupled together in a 1D model representing a strip of tissue, the intrinsic activities entrain to a single frequency as a coherent propagating wavefront (Fig. 2C), with a velocity of 13 mm s\(^{-1}\). If the ICC in the middle of the 1D model was knocked-out, the entrainment of slow-waves was disrupted and broken into ‘plateaus’, where within each plateau the frequencies of slow-waves are entrained to the ICC with the highest intrinsic frequency. The KO ICC acted as a conduction block between adjacent plateaus (Fig. 2D).
3.2 Whole-organ Simulations

A continuum approach was used to simulate propagation of slow-waves in the whole stomach. The key concept behind the continuum approach is by modelling the activation of slow-waves in a spatially-averaged manner (as opposed to simulating slow-waves in a discrete manner at the individual cell level). In addition to utilising the ICC model to generate slow-waves [16], additional physiological factors were also considered. Gastric slow-waves demonstrate significant, inter-regional variations (Fig. 2), for example, the fundus is generally quiescent in monogastric animals. An intrinsic frequency gradient is also known to exist in the distal direction. Furthermore, a resting membrane potential gradient due to the action of ICC-derived carbon monoxide as a hyperpolarizing agent exists in the transmural as well as the distal directions, with the fundus being the most depolarised [17]. Finally, the different intrinsic, gastric, slow-wave frequencies entrain to a single frequency in the healthy stomach.

Multi-scale models have been able to unify all three aspects of gastric slow-wave heterogeneities in a single model (Fig. 3A), by prescribing parameters in the cell model to reproduce the intrinsic frequency, resting membrane potential gradients, and the conduction velocities in each region of the stomach.

![Fig. 2. Cellular model of Ano1 KO in the ICC. (A) Simulated intestinal slow-waves generated by a single ICC. (B) Ano1 KO had the effect of completely inhibiting slow-waves. (C) Simulation of entrained propagation of intestinal slow-waves in a 1D strip of muscle. (D) Simulation showing that Ano1 KO in the middle of a 1D strip of muscle disrupts the normal propagation of intestinal slow-waves.](image)

![Fig. 3. Whole-organ gastric slow-wave simulations. (A) Normal activations. (B) Gastric re-entry.](image)
stomach [18]. Recent whole-organ models have been adapted to simulate the development of gastric, slow-wave, re-entry dysrhythmia over a sustained period (Fig. 3B). Gastric re-entry was triggered in the corpus where the distance between the refractory-depolarisation of two subsequent waves is the longest, allowing more time for re-entry to develop.

4. Conclusions

Rapid progress has been made in experimental recording of in vivo gastrointestinal slow-waves, enabled by high-resolution mapping. Multi-scale models have allowed the effects of perturbations to physiological mechanisms at every biological scale to be thoroughly investigated and experimentally validated. In particular the whole-organ, dysrhythmia models will be used to investigate non-invasive, body-surface recordings, and identify enhanced methods of gastric pacing for treatment of diseases associated with slow-wave dysrhythmias.

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References


Imagine standing in the middle of a dense forest, being overwhelmed by the diversity you see. You start walking and take pictures of what appears to be a world of randomness. Later on, you notice that many pictures have a vine that hangs in a particular way, with a little fern underneath; this is similar to what I have seen in DNA sequences. I have created a tool to aid in the discovery of repetitive DNA patterns, and supplemented this tool with graphical representations of DNA to explore DNA at a megabase scale. It is my hope that these visualisations will eventually lead to new discoveries about the large-scale structure of DNA.

1. Introduction

Deoxyribonucleic acid (DNA) is the recipe book of the living world. Every living thing has DNA in it; it contains instructions to form the ingredients of biochemical reactions, with binding sites and physical structures that act as fast-responding code to tell the cells in our bodies what to do and where to go. At a molecular level, DNA is composed of four different nitrogenous bases: double and single carbon rings that are supported by a sugar/phosphate backbone. Each of the bases of DNA can be represented symbolically as one of four letters: A, C, G and T. In the physical sense, two strands of DNA are packed tightly together, coiled around each other as a double helix, aided by hydrogen bonds formed between chemically-complementary bases. When combined into a string of sequential letters, we call it a DNA sequence. The process of converting from the physical thing of DNA into a model on a computer is called DNA sequencing. (See Fig. 1.)

![Fig. 1. Three different representative models of DNA: a structural formula (left), a 3D model (middle), and a DNA sequence (right). Images are adapted from Wikimedia images from Madprime [1] and Zephyris [2].](image)

1.2 Sequencing DNA by Nanopore

The Oxford Nanopore MinION contains a consumable flow cell with thousands of small sequencing wells, each of which has a waterproof membrane over the top. This membrane is pierced by protein tunnels, which are called nanopores (see Fig. 2, [3], and [4]). An electric current is hooked up to the flow cell, which encourages DNA to move through the nanopores.
The shape of the DNA changes along its length, and changes in electrical resistance induced by the DNA structure are recorded by the sequencer and sent to a computer over a USB cable.

**Fig. 2.** The active sequencing component of the MinION sequencer, showing flow cell (top left), flow cell matrix (top right), and a representation of a DNA sequence being sequenced by a nanopore, showing the membrane (grey), DNA sequence (purple with blue / yellow / red / green bases), and nanopore complex (orange / red).

1.3 Nanoscopes and Wide-angle Lenses

The MinION sequences by passing the entirety of the template DNA strands through a sensor, so is able to observe structural changes that are more than the simple A/C/G/T sequence. It is able to see chemical changes at a sub-base level, changes on the scale of a few nanometres. We have studied nanopore sequences at the electrical signal level for investigating whether there were epigenetic signals in unamplified mitochondrial DNA [5]. We have also used a signal-level analysis to distinguish between DNA sequences that were joined *in-vitro* during sample preparation and sequences that were joined *in-silico* by the base caller [6].

Yet, at the other end of the scale, the MinION doesn't limit the length of the DNA that is put into it. Long reads from nanopore sequencing of over 100,000 bases in length have been used recently to improve a number of genomes that were previously reported as “complete”, including the human genome [7], and the genome of the small, free-living roundworm, *C. elegans* [8]. These improvements in highly-studied organisms demonstrate a substantial advantage that is gained from including long reads in a genome assembly. Our research institute has also started along the track of genome improvement, reporting a nanopore-only assembly of the rodent parasite, *Nippostrongylus brasiliensis* [9]. To better understand large-scale patterns that exist in DNA, I am exploring methods to identify and visualise structure in DNA sequences that exceed a million bases in length.

2. Motivation

One of the reasons why long-read sequencing has helped genome assembly is that it is able to sequence across highly-repetitive sequence elements, capturing the repetitive portion of a sequence together with unique and non-repetitive flanking regions. In our investigations to try to understand the reasons behind why we were unable to create a *N. brasiliensis* assembly with one contiguously-assembled sequence model (contig) per physically-contiguous chromosome, even with long reads, we found large repetitive structures in the genome that were either absent or collapsed in the existing reference genome (e.g., see Fig. 3). These structures frequently occurred at the end of assembled contigs, suggesting that they were partially responsible for the incomplete assembly. Once the discovery of these repetitive patterns was made, I developed techniques to automate further discovery, or at least...
substantially reduce the amount of effort required. These techniques also included novel visualisations of DNA which emphasise the location and nature of repetitive patterns within DNA sequences. Together, these techniques allow for a rapid assessment of large-scale DNA structure, independent of the length of the sequence.

3. Method

I have developed a freely-available method (see “Availability”) for searching for repetitive patterns in DNA. This method was inspired by the algorithm used in SATFIND [11], but is adapted to detect repetitive sequences of any length. The method, currently implemented in Perl, is still in development, but the basic method of data capture is as follows:

1. A DNA sequence is decomposed into overlapping, equal-length subsequences (kmers), recording all locations of a given kmer within that sequence.
2. For kmers that appear at least twice, the location of kmers and gap distance between successive kmers is stored.

Results are aggregated and reported per-sequence, showing median and modal gap length for any repetitions, together with additional statistics that help identify when a repeat is unexpected (e.g., proportion of sequence that was repeated, number of times a repeat of the median length was observed).

3.1 Representing DNA Patterns Graphically

Summary statistics are useful for automated discovery, but visualisation methods are useful to confirm that all discoverable patterns have been found. Using the kmer pattern information, I have adapted the traditional dotplot that is used for genome matching (e.g., see [12]) to visually represent DNA sequence patterns. While the dotplot view is useful for identifying repetitive structures, and somewhat useful for identifying other patterns, it is difficult to interpret. In an attempt to better represent the entirety of a sequence, I have also created an alternative sequence representation where the sequence is presented on the horizontal axis, and the distance between repetitive features is on the vertical axis as a log scale. This alternative “feature profile” shows tandemly-repetitive sequences appearing as ripples underneath two half-islands, and long-range reverse-complementation as arch-shaped curves (see Fig. 4).

![Feature profile (HLA-tig01415017)](image)

Fig. 4. Dot-plot representation (left) and feature profile representation (right) of a repeat-containing subsequence within the HLA region of the human genome (NA12878). Tandem-repetitive regions appear as red squares in the dot-plot representation, and as ripples with pointy tops in the feature profile representation. DNA sequence for this region was obtained from publicly-available data produced by the Nanopore-WGS consortium [7].
3.2 Displaying Repetitive Sequences

The feature profile plot is useful for large-scale structure discovery, but not so useful for understanding the specifics of that structure. Once a sequence containing repetitive elements has been found, it should be displayed in a way that emphasises (at a single-base level) the sequence patterns that are present in the sequence. If the width of a repetitive pattern is known, then that pattern can be represented in either a rectangular matrix, or represented as a spiral, with successive lines or loops containing the same number of bases. (See Fig. 5.) The rectangular matrix representation makes it easier to see deviations from a common repeat, whereas the spiral pattern reduces the emphasis on a particular start or end point of each repetitive unit.

Fig. 5. Two representations of the same 29kb assembled DNA contig from the *N. brasiliensis* genome. The rectangular matrix representation (left) arranges the DNA sequence from bottom to top, with a specific number of DNA bases on each line. The spiral representation (right) arranges the DNA sequence from centre to outside in a clockwise direction, with a specific number of bases per loop.

4. Discussion

The novel tools and approaches for pattern discovery that have been developed here are a work-in-progress, and an explanation of how or why these patterns exist is outside the scope of this work.

The tools are currently written in a mixture of Perl, R and Python code, primarily due to the ease of prototyping in those languages, particularly in the area of text manipulation (for Perl) and graphical display (for R). The high-level nature of these languages means that the current unoptimised code tends to be relatively slow, with run time taking a minute or so for a megabase-length sequence (depending on the number of repeated kmers within the sequence). This is fast enough that small genomes can be profiled in the course of a day or so, but is not ideal for high-throughput discovery (as might be carried out on individual sequenced reads).

These discovery and visualisation techniques can be used as a reasonably rapid quality-control technique for assembled contigs, for identifying unexpected breaks and fusions in assembly, and for providing insights into why an assembly might be less complete than expected.

Large-scale patterns are only observable when looking at sequences on the scale of hundreds of thousands to millions of bases. It is my expectation that new use cases will be found for genome pattern visualisation in the future following the evaluation of newer highly-contiguous genome assemblies that are being produced using long-read sequencing technologies.
5. Availability

The scripts that were used for identifying repetitive regions and generating the sequence images are freely available from my github ‘bioinfscripts’ repository: ‘https://gitlab.com/gringer/bioinfscripts/’, specifically the scripts ‘fastx-rlength.pl’, ‘repaver.r’ and ‘seqmat.r’.

References
6. So-Called Experts? Knowledge Credibility in Fiction

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By exploring how distrust in ‘data’, information and scientific research unfolds in the Australian novels *Rifling Paradise* by Jem Poster (2006), *Fall Girl* by Toni Jordan (2010) and Charles F. Finney’s *The Circus of Dr Lao* (1935), this chapter investigates the questioning of scientific evidence, information and research in relation to creative imagination. It argues that Literary Studies may play an essential role in contextualising, defining, and thus better understanding mistrust in scientific research and the threat of knowledge credibility in a ‘post-truth’ era.

1. Introduction: On the Topicality of Literary Studies

We are faced with an unparalleled information crisis: reliable and bogus information – stories adherent to facts and those not firmly grounded in history, but in fantasy and emotion – become more and more difficult to differentiate [1]. Although denial of, and mistrust in, evidence, experts and scientific research have previously existed, it now takes on a new quality. This is especially so due to the growing trend of trusting social media as a knowledge source regardless of factual content, which easily leads to imaginary stories – fiction. Literary Studies, this paper advocates, might help in contextualising, defining and thus better understanding these threats to knowledge credibility as they teach us how to analyse, evaluate and interpret texts: literary texts, cultural texts, con(-)texts. They provide historical and critical background as well as tools to critically deal with subjective, complex, imperfect information; to weigh evidence sceptically; to investigate false connections and misleading contents; and to comprehend how they relate to events and preoccupations of the period in which they were produced. Literary Studies elucidate how empirical facts are transformed into narratives with moral and emotional weight and meaning. They explore the relationship between fact and fiction; the recasting and reinvention of ‘reality’ and ‘realism’; notions of normativity; facets of textual and narrative (un)reliability; and questions of authorship and identity. All of this might be extraordinarily relevant in understanding factual tales gone wild, their cultural implications and public imaginaries.

Through the exploration of challenges for and of (scientific) truthfulness in the novels *Rifling Paradise* by Jem Poster (2006), *Fall Girl* by Toni Jordan (2010) and *The Circus of Dr Lao* by Charles F. Finney (first published in 1935), this paper clarifies how mistrust in ‘data’, information and scientific research may be connected to creative imagination and, based on a primarily thematic reading, proposes some ideas for an interdisciplinary readership of how the discussion of fictional literature may contribute to broadening our understanding of the highly topical issue of knowledge credibility, the validity of (empirical) evidence and the status of science-experts. With the aim to highlight different facets of this phenomenon, the selected novels present a small panorama of stories dealing with science as ‘sciences’ that are questionable, questioned and intertwined with acts of creative invention; stories in which the protagonists invoke and destroy the stereotype of the scientist at the same time. These novels are about performing science (as non-science) and reveal some startling assumptions about, prejudices against, and responses to, fictional scientist-protagonists. This includes fears and taboos regarding science that are reminiscent of those appearing beyond literature in our media.
These three novels manifest different dimensions of how literature raises, tests, confirms, complicates and even parodies the process of knowledge acquisition through collection of scientific specimens and the classification of organisms, or, in other words, through the assembly of data. In so doing, they contrast the principle of singularity with the principle of comprehensiveness, and playfully exploit what might be out of the natural order [2]: Rifling Paradise features a fictional naturalist striving – and struggling – to create a collection of dead animals as a data treasure trove for future research, but finally discovering fantasy in science; Fall Girl presents a fake scientist who performs science as fiction while pretending to search for an extinct animal; and The Circus of Dr Lao places a science ringmaster of unbiological beings [3] into the spotlight, in which he lectures about the scientific curiosity of his performers to an unfazed, uninterested audience that is not only too ignorant to be captured by science but also by the fantastic. Collections of naturalists – called theatres of nature by Jane Goodall – and ‘science shows’ are inherently performative [4] which also resonates within these novels, and is thus another interesting intertextual link.

2. The Rise of a Non-Scientist – Jem Poster’s Novel Rifling Paradise

Rifling Paradise is the story of Charles Redbourne, a nineteenth century English landowner who travels to Australia in order to pursue his ambition as an amateur naturalist; that is, to shoot, skin, stuff and collect specimens. In Sydney, he engages in debate with an artist, and later travels to the outback. Fever, opium and hallucinations in which the violated land haunts the protagonist, finally cause him to flee back to England.

From childhood onwards, Charles has been fascinated by scientific enquiry based on fossil hunting and collecting trips, and published notes and articles in minor periodicals. He was, as collectors phrase it, a specialist [5]. In Australia, he aims to add significantly to his collection and contribute his quota to the sum of human knowledge [6]. All science, he explains, is grounded in facts. A collector’s cabinet is a repository of facts from which important scientific truths may be deduced, and new theories constructed. We need these collections [...] if we’re to understand the world we live in – it’s as simple as that. [7] However, Charles Redbourne does not produce or contribute to any knowledge, nor does he progress any scientific conclusions at a rate coherent to the accumulation of relevant data. The science he performs rests on shaky foundations which are doomed to collapse by the influence of critical scrutiny and other knowledge systems. For instance, his science is called into question by the representative of a different approach to nature. Eleanor, the girl he finally marries, who – as both an artist and antivivisectionist – is appalled by Charles’ daily taxidermist tasks undertaken for the sake of science. She asks, What’s it all for, anyway, this killing and skinning? [...] what kind of a fact is it, your dead lory? [...] Whatever it is you imagine you’re laying hold of – for yourself, for your precious science – it’s gone the moment you pull the trigger [8]. In contrast to Charles, Eleanor can catch something of the animal’s life in her paintings [9]. Realising this, Charles wonders not entirely playfully, whether Adam’s fall might have begun not with the eating of a fruit but earlier, with the arising of the desire to catalogue the animals and plants in his teeming paradise [10]. As a consequence, the angle of possibility through which he views the principles of natural formation widens. He cultivates a flexibility of mind and comes to understand that his expectations of his journey and his practice of science – his cataloguing – were sophisticated modes of ignorance, essentially without meaning. The protagonist in Rifling Paradise turns out to be a non-scientist. He transforms from a believer in science and a confident taxidermist into a vegan admirer of life in nature, who discovers the sublimity and a marvellous order which reveal themselves not merely in nature but in the world of thought and art. Being questioned on his trust in catalogued, evidence-based science, thus stimulates the scientist’s capacity to re-imagine reality.

Throughout his youth and adolescence the protagonist in Rifling Paradise dreamed of following in the footsteps of Darwin, whom he tries to imitate in his early collecting trips around Europe. But at the end of his journey in Australia, Charles admits that he had just been playing the role of one of the heroes of [his] childhood reading [12]. Della Gilmore, the protagonist in Toni Jordan’s 2010 novel Fall Girl also plays the role of – or rather imitates – a scientist, albeit in a different way. She impersonates an evolutionary biologist, invents a PhD and a personal webpage, contrives a sham research project to trap an extinct animal (a Tasmanian tiger) in a National Park near Melbourne, and invites a potential sponsor to a ‘field trip’, where she tells him little factoids about the life of Darwin and a bit about the theory [13]. She busies herself with measuring and photographing tracks and collecting droppings – in the way scientists do – which she had studied in a library (also making this novel a eulogy on libraries). Fall Girl imparts a misleading idea of how science is performed and tends to progress, and leads the scientists’ claim to epistemological authority and methodological autonomy – and their implicit trust in reductionism [14] – ad absurdum. Like Charles Redbourne, Della does not base her activities on a well-supported and well-tested hypothesis or set of hypotheses [15] and does not even collect ‘real data’ since all that matters is her confidence. Her ‘science’ is thoroughly flexible, provisional and uncertain.

Right from the beginning, this novel perfectly illustrates (if not surpasses) Andrea Battistini’s discovery that fictional scientists may take on the shape of a specific, literary, transcultural scamp-archetype, the picaro. Picaro-like, Della does not experience a significant process of moral education. She moves horizontally through space and vertically through society. She lives an unsedentary life that is restlessly meandering between ‘projects’ with a touch of delinquency. Reinventing herself as a scientist, she cannot be anything but a dodgy, fraudulently clever, societal outsider and isolate. In accordance with the picaresque tradition, Della’s play between self-concealment and self-revelation, masking and unmasking, bears an intrinsic performative quality [16].

However, Fall Girl does not merely set up a caricatural monument for the untrustworthy scientist-picaro, but also manifests the power of fiction in an ambivalent science con-text. Thus, according to Della, science, at least this kind of science, is more like a country craft: it is a manual skill, a dextrous one, where the clever hands of clever people make a story from bits of bone and photos of tracks and scratches on trees [17]. This definition fuses the imaginary of science and the Latin term ‘fictor’ (on which the word ‘fiction’ is based). Originally, a fictor is not merely an inventor of stories, but a sculptor creating three-dimensional artefacts with his clever hands [18]. We can conclude: in Fall Girl science is fiction.

Like Charles Redbourne in Rifling Paradise, Della explores new frontiers, seeks the nonquestions, rebels against the status quo, and has a knack for seeing things in a different light – the essential characteristics of scientists, according to Jack Oliver’s Incomplete Guide to the Art of Discovery [19]. However, rather than domesticate the unknown, both protagonists invent it. They are creative, skilled craftspeople, ‘imagineers’ reminiscent of artists. In fact, by fooling her millionaire – that is, her audience – with facts that appear to be scientifically plausible, Della behaves like a performer, staging science as a show.

Science as spectacle also unfolds in Charles Finney’s novel The Circus of Dr Lao, in which circus and related cultural spheres, such as freakshows, carnivals and ‘scientific’ museums amalgamate into a particularly productive, breeding ground for the staging of ‘scientific phenomena’.

4.  **Heterodox Knowledge and Prosaic Ignorance in The Circus of Dr Lao**
The Circus of Dr Lao by Charles Finney (1935) is a multilayered, intricate and sophisticated obscure classic presenting a modernised version of the scientific museum as a travelling circus. Although the plot of the novel is unassuming – a circus comes to a country town – Dr Lao’s show is not. Exhibiting a variety of unique creatures supposedly for their scientific interest, this circus promises: animals no man had ever seen before; beasts fierce beyond all dreams of ferocity; serpents cunning beyond all comprehension of guile; hybrids strange beyond all nightmares of fantasy [20]. Similarly to Della Gilmore and the artist in Rifling Paradise, Lao argues that [s]cience is just tagging a name to everything, which is why his own, alternative classification obeys none of the natural laws of hereditary and environmental change, pays no attention to the survival of the fittest, positively sneers at any attempt on the part of man to work out a rational life cycle, is possibly immortal, unquestionably immoral, evidences anabolism but not katabolism [21].

According to Dr Lao, his creatures have hitherto been undiscovered, and shall astonish the public from the scientific and educational point of view. While this announcement is reminiscent of the typical rhetorical pyro-techniques of hyperbolic circus advertisement, Dr Lao’s explanations of his menagerie and sideshow are rather uncommon. He expresses great vagueness in entertaining matters, combined with great precision on irrelevant biological and behavioural detail and unconventional evolutionary theory. He provides more overwhelming information than relaxing edification for his audiences. Regarding his werewolf, for instance, Dr Lao elaborates on the phenomenon of lycanthropy, anthropological (un)orthodoxy and mutable morphology as an inversion of the evolutionary laws [22]; and in the tent of his Medusa – discussing the different types of snake on her head – he hurls himself into a talk on serpentology, whereby referring to his own study of this and several other medusas [23]. He also indulges himself into a lecture on the metabolism of his Chimera, whereby complaining that science does not recognise the existence of the male chimera, because science is nothing but classification [24]. Apparently being some kind of scientist himself, Lao has adored and studied animals for more than a hundred years [25], but despite his efforts, his circus creatures have curiously remained a mystery to science.

What distinguishes this circus novel from many others [26] is less its phantasmagorical exhibits than the explicitly accentuated mistrust of the audience in the information delivered by Dr Lao. Visitors neither believe in the circus’ promise to stage the never-seen and miraculously impossible, nor in the ringmaster’s scientific explanations, prompting one visitor to ask What the hell is the Chink talking about [27]? The audience’s prosaic ignorance of the scientific and the fantastic is as grotesque as Lao’s institution. For instance, at the sight of Lao’s mermaid, a visitor declares: I hate to spend money on anything that’s so obviously a fake and complains that she does not wear a swimsuit (sic!); Lao’s sphinx comments on this: You bring the queerest people in here, Doctor Lao [28].) The audience’s reactions do not merely manifest that the circus’ science curiosities challenge old, certified knowledge, but also enshrine the failure of Dr Lao’s ‘new’, heterodox knowledge in being absorbed within the social process of certification. Lao’s scientific wonders disrupt notions of normativity and the idea of progress. We could say the novel’s theme is anti-science, presenting a scientist-protagonist who, having discovered secrets of life, does not use his intelligence and power to make the world a better place – for example, by finding ways to use this knowledge to eradicate disease and hunger – but instead to create displays for entertainment purposes [29]. The Circus of Dr Lao is also a novel about the problem of change and stability in science, and about its acceptance, which is dependent on the recipients’ ‘world view’, which is itself dependent on the cultural matrix creating and supporting that world view [30]. The circus visitors’ denial of being educated (and to wonder) in this novel acts as an indicator of the limitations of their own prevailing culture and of themselves.
5. Conclusion: Literary Non- and Con-Scientists and Science Ringmasters in the Spotlight of a ‘Post-Truth’ World

The novels *Rifling Paradise*, *Fall Girl* and *The Circus of Dr Lao* are connected by an internal logic. Limits of human knowledge and scientific objects are not the focus of interest in these texts, but the scientist-protagonists themselves, and their approach to science and scientific knowledge versus their surroundings’ ignorance, and disrespect of the importance of evidence-based information and outsmarting ambitions. These texts present us protagonists who want to be, or act as, scientists but are confronted with competing and challenging, if not subversive, ‘alternative knowledges’, with which they have to deal.

By questioning and parodying the knowledge that one derives from scientist-characters, and by featuring very ambivalent ‘scientists’, *Rifling Paradise, Fall Girl* and *The Circus of Dr Lao* mirror the ambiguous relationship between genuine scientific inquiry and pseudo-science, and thus between progress, creative inventions and ignorance. Through their scientist-protagonists who experience mistrust in their ‘data’, information and scientific research, or creatively invent them as ‘fake facts’, these novels all challenge orthodox science regarding the nature of the scientific endeavour, and are paradigmatic mediums of reflection of the constitution and conditions of scientific knowledge and its (hardly definable) truth. They present fictional scientist-protagonists who are—or become—dependent on the imagination of their vis-à-vis for reliable truths. In particular, perhaps surprisingly, in *The Circus of Dr Lao*, the objective, ‘scientific’ facts and factual information are less influential in shaping the circus audience’s opinion than emotions and personal beliefs—which is how *post-truth* is defined [31]. *Dr Lao* does not only underline that science can be a product and producer of good stories, but also highlights that, and how, ‘truths’ are troubling and problematic once they are thought of as being testable and tested by shared experience and emotional response. Stimulated by current debates, further research on the status of literature as an epistemological mode, in the growing interdisciplinary field of Knowledge Credibility Studies but also from the angle of Science in Fiction Studies, will explore these peculiarities more precisely by discussing them in the perspective of long-term trends.

In any case, Charles Redbourne, Della and Dr Lao are fictional characters engaged with science, trying to persuade others that certain—or their own—hypotheses are true, but fail to achieve the elevation of these hypotheses to the status of fact [32]. They thus can be read as a fictional counterattack to P.W. Atkins’ statement that scientists are privileged to be at the summit of knowledge, and to see further into truth than any of their contemporaries [33] as they fail to produce or present results that allow one to describe a reality in space and time which is independent of ourselves, which could be defined as a goal in science [34]. In these novels, science is, rather, a system too narrow to make place for new discoveries and/or tends to be the subject of ridicule. This can be read as an interesting social commentary on its role within the prevailing culture outlined in those novels.

By exploring the delineations of where ‘facts’ are grounded, the traditional version of scientific research ends and fiction begins, and as to how much of the former is represented in the latter, *Rifling Paradise, Fall Girl* and *The Circus of Dr Lao* do invite us to think critically about the credibility of knowledge, the status of science-experts, scientific data production and consumption (to make us more sceptical of information). But they also afford us insight into the vagaries of the human imagination and creativity by modelling ingenious synthesisers who re-imagine their realities by recasting science.

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References

40
7. The German Contribution to the Development of the Glass Micropipette Electrode

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The glass micropipette electrode was one of the simplest but most significant inventions of the 20th Century. It provided the technique that enabled us to understand how brain cells, muscle cells and gland cells work both electrically and chemically. German input into its development and use was considerable.

1. Introduction

The story begins in Davenport, Iowa, in the United States where, according to Tucker [1], Ida Henrietta Hyde was born to German immigrant parents in 1857. Ida Hyde had a difficult early life, with her father’s desertion of the family leaving her mother with five young children to support. Her mother steadily re-established herself in Chicago as an astute business woman, but the family then lost everything in the disastrous Chicago fire of 1870 with Ida having to become family breadwinner, working in a clothing factory (Fig. 1).

Fig. 1. Ida Hyde at age 14.†

Fig. 2. Hyde (ringed) at the Marine Biological Laboratory, ca. 1891.†

Her life, however, turned around after accidentally discovering, discarded in a box at the factory, Views of Nature (Ansichten der Natur) by Alexander von Humboldt. This aroused her interest in nature and science. Night school and a year at the University of Illinois, Champaign, then prepared her for several years of teaching in the Chicago public school system. While there, she was inspired by Colonel Francis Wayland Parker, a pioneer of the Progressive School Movement in the United States, who had studied at the Humboldt University in Berlin. Hyde was instrumental in establishing the Science in Schools program and in the introduction of Nature Studies to the public-school curriculum. After two subsequent years at Cornell University she graduated with a Bachelor’s degree. A scholarship to Bryn Mawr associated with an Assistant’s position then allowed her to undertake summer research at the Marine Biological Laboratory in Woods Hole, Massachusetts (Fig. 2). By 1893, her research was being noticed in Europe and she was invited to Straßburg by Professor Alexander Goette. Straßburg was a German city in the period 1871-1918 and, at that time, German university politics prevented a woman from matriculating to undertake doctoral
studies in science or mathematics [2]. Although it was suggested that it might be easier at Heidelberg, Professor Wilhelm Kühne in the Physiology Department there, made it very difficult for her [2]. Nevertheless, by 1896 she had overcome all the obstacles, passed a gruelling oral examination and become the first woman to graduate Doctor rerum naturalium (Dr. rer. nat.) (Fig. 3). She went on to do research at the German Research Table of the international Marine Biological Research Station in Naples, and from there to Bern in Switzerland and then to Harvard [2].

Fig. 3. Ida Hyde in Heidelberg 1896.††

Fig. 4. Marshall Barber 1911.††

2. Ida Hyde and the University of Kansas

In 1899 Hyde was appointed Associate Professor and founding Head of Physiology at the University of Kansas. At this same time, Marshall Barber (Fig. 4), the Professor of Bacteriology at Kansas, was developing a technique of melting glass capillary tubing and pulling it out by hand until it snapped giving sharp open tips of about one micrometre in diameter, small enough to suck in a single bacterium and to inject it into a living cell without too much damage (Fig. 5). This, of course, required mechanical micromanipulators also developed by Barber, with his techniques published in full in 1914 [3].

Fig 5. Barber’s fine glass micropipettes and micromanipulator.††

Fig. 6. Vorticella extended and contracted.††
Barber’s methods were quickly taken up by other researchers, including Hyde who, in 1921, published her invention of an electrode for extracting or inserting small quantities of fluid in living cells [4]. She could control this by the direction of flow of electric current one way or the other through mercury in the shank and then a salt solution in the tip of her glass micropipette electrode. She described how it could also be used to stimulate living cells electrically, showing that the stalk of the microscopic Vorticella would contract by differing amounts depending on the strength of electrical stimulation (Fig. 6). In a wide-ranging account of its possible uses, she also presciently suggested that her electrode could be inserted into cells to stimulate them electrically from the inside.

3. Developments in Europe

From 1921, the Hungarian, Tibor Péterfi (Fig. 7), was working at the Kaiser Wilhelm Institute at Berlin-Dahlem where Barber’s methods were also known through German Nobel Prize winning bacteriologist, Robert Koch, and Dutch botanist, Jacobus Janse. Like Hyde, Péterfi was interested in the electrical characteristics of living cells [5]. He would have known something of the high internal potassium concentration of cells such as Amoeba compared to the composition of the pond water in which they lived and, as Julius Bernstein had hypothesised, suspected that plant and animal cells might be like miniature batteries in accord with the electrochemical studies of Walther Nernst in Leipzig. Using his own microsurgical techniques and sharp glass micropipette electrodes, Péterfi managed to record tiny voltages between the inside and outside of Amoeba cells but did not believe his own findings [6] and, later, misinterpreted his results from muscle cells [7]. Meanwhile, he worked part-time for Carl Zeiss and improved the Barber micromanipulator (Fig. 8) which Zeiss then sold worldwide.

From Péterfi in Berlin, the methodology passed to Josef Gicklhorn and Karl Umrath (Fig. 9) at the German University in Prague. By 1928 they were publishing the first convincing measurements of voltages inside plant cells using glass micropipette electrodes of the Hyde-Péterfi kind [6]. Later in Graz, Austria, Umrath studied electrical voltages and messages in plant cells and nerve fibres, becoming the first person to make an intracellular recording of an action potential [8]. Ernst Florey, a graduate student of Umrath in the 1940s,
has related that Ralph Gerard (Fig. 10), Professor of Physiology at Chicago, learned the technique from Umrath on a visit to Europe and brought it back to the United States [9].

4. From the United States to the Far Corners of the World

At the University of Chicago from about 1940, Judith Graham (Fig. 11), Gerard’s doctoral student, began using glass micropipette electrodes to measure voltages in frog muscle cells and to observe the effects of electrically stimulating them, with some success and published results in 1946 [10]. Her method for hand pulling the glass pipettes was perfected by Gerhard’s subsequent doctoral student, Gilbert Ning Ling (Fig. 12) from Kunming, China, and his more accurate measurements of muscle cell voltages were published in 1949. By then, Ling’s method had been demonstrated to Alan Hodgkin of Cambridge, UK, who published preliminary results of his own measurements at a meeting of The Physiological Society in December 1948 [12]. The use of so-called Ling-Gerard electrodes quickly spread around the
world, with Gerard later being nominated for the Nobel Prize for developing them, which was unwarranted in my opinion, given the significant roles of others in their evolution.

5. New Zealand 1951

The technique quickly arrived in New Zealand where the Australian, John Carew Eccles, was working at the University of Otago in Dunedin with two talented young colleagues, Lawrence Brock, a clinician, and John Coombs, a physicist (Fig. 13). Eccles had taken over an abortive attempt by Archie McIntyre to record electrical activity in nerve cells deep inside the spinal cord [13]. This was a daring project given that it would not be possible to view these cells by the microscope, unlike cells at the surface of a muscle, and, consequently, any visual guidance of the microelectrode unfeasible. Brock developed mechanical methods for preparing consistent glass micropipettes (almost impossible by hand) and Coombs built the electrical stimulators and differential amplifiers for recording the cell voltages. Coombs's equipment is understood to have been based on or modified from designs by the gifted German electronic engineer, Jan Toennies [13]. Beginning in May 1951, and literally working day and night, they had results in July that were published in August [14].

![Fig. 12. John Coombs, Wilfred Rall, Jack Eccles and Lawrence Brock, November 1951.](image)

They showed, for the first time, beating their American competitors (J. Walter Woodbury and Harry D. Patton in Seattle), that the electrical activity of nerve cells in the central nervous system depended on chemical excitation or inhibition from one cell to the next. Electrical transmission only occurred along nerve fibres or within a single nerve cell, not from one cell to the next. In 1963 Eccles shared the Nobel Prize in Physiology or Medicine with Alan Hodgkin and Andrew Huxley for their elucidation of the mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane.

6. Conclusions

Despite their humble construction, glass micropipette electrodes – simply glass capillary tubes, melted, drawn out to open tips less than one micrometre across and filled with salt solutions – were one of the most significant technological developments of the 20th Century. When used in conjunction with non-polarisable junctions and connected to sophisticated electronic amplifiers, they enabled the verification of earlier predictions of the existence of electrical potentials across selectively permeable cell membranes and allowed the recording of trans-membrane action potentials and the investigation of quantal synaptic potentials. Through their use, the deepest mechanistic functions of the brain, from the chemistry of excitation and inhibition of nerve cells to memory and learning, as well as muscular control, sensory perception and glandular secretion and even circadian rhythms (the 2017 Nobel Prize in Physiology or Medicine) came to be understood. There was a significant German input into
their development and use, not least in contributing to the Nobel Prize winning research on
the central nervous system by Sir John Eccles begun at Dunedin in 1951.

Acknowledgments

Figures used to illustrate the article have been reproduced from the following sources:
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References
8. tsRibo-Seq: An Approach to Zoom In into Translation of Single Transcripts

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Ribo-Seq (ribosome profiling) enables global assessment of translation efficiency, yields and fidelity. However, low-abundance transcripts receive little coverage and fall outside of the Ribo-Seq detection limit. We developed a new twist of the Ribo-Seq approach, termed transcript specific Ribo-Seq (tsRibos-Seq) to specifically detect lowly abundant messenger RNAs (mRNAs). This approach yields unprecedented depth in the coverage of individual low-abundance transcripts allowing identification of slow and fast translating regions with nucleotide resolution.

1. Introduction

Translation, or protein biosynthesis, is central in converting the genetic information into physiological activity. It is the nexus node in the expression network and fine tunes proteins’ amount in the cell. Translation is highly spatially and temporally regulated which contributes to tissue specificity, cellular fate and memory formation [1,2]. Disregulation of translation leads to aberrancies in cellular homeostasis, including uncontrolled cell growth and tumorigenesis [3]. Despite its crucial importance for cellular physiology, approaches for global assessment of translation, directly in the cell, only have been developed in the last decade. Advances in the deep-sequencing technologies coupled to classic methods to map the position of translating machines, the ribosomes [4], led to development of crucial approach, ribosome profiling or Ribo-Seq [5] which allows determining with nucleotide precision the positions of translating ribosomes in vivo. This method revolutionized translation research and provides insights into what, when, where and how is translated [5]. The toolbox of Ribo-Seq is growing and Ribo-Seq-based applications advanced our understanding in translation initiation [6,7], global translation velocity [8,9], codon specific ribosomal dwell times [10,11], compartmentalized translation [12,13], interactions of nascent protein chains with other nascent chains or auxiliary proteins [14-17]. So far, the conclusions are based on highly expressed genes.

In 2010, Guo et al. monitored expression of 5,103 mRNAs using a threshold of 100 sequencing reads per transcript [18]. Recent improvements in the sequencing depth yielded quantification of 11,232 protein-coding transcripts out of the global pool of 20,301 mRNAs (ENSEMBL release 73) [10]. Yet, the half of protein-coding genes, which are lowly abundant, produces poorly covered translation profiles. In this study, we developed a twist of the Ribo-Seq approach, termed transcript-specific ribosome profiling (tsRibo-Seq), to specifically enrich the complex pool of cellular transcripts with an individual transcript of interest, which is usually lowly expressed in cells. With this approach we obtained an unprecedented coverage of a low-abundance transcript and constructing the translation profile enabled precise delineation of regions of slow and fast translation with possible function in regulating protein abundance.
2. Material and Methods

2.1. Cell Culture

Bronchial epithelial cells, CFBE41o-, were grown in MEM Earles medium supplemented with 10% fetal bovine serum and 2 mM glutamine. Three million cells were transferred to collagen- and fibronectin-coated dishes and transfected pcDNA3.1 plasmid bearing gene encoding for cystic fibrosis transmembrane conductance regulator (CFTR) protein. 24 h post transfection the medium was replaced with a fresh one and cells were incubated for another 24 h before harvesting for tsRibo-Seq or Ribo-Seq.

2.2. tsRibo-Seq

The conventional Ribo-Seq was performed as described earlier [10]. Briefly, cells were harvested in polysome lysis buffer (10 µM Tris/HCl pH 7.4, containing 5 mM MgCl₂, 100 mM KCl, 100 µg/ml cycloheximide, 2 mM DTT and 1% TritonX100), digested with RNase I (Life Technologies) and monosomes were recovered by ultracentrifugation. Ribosome protected fragments (RPFs) were purified and adapters were directly ligated to the RPFs as described earlier [18]. For the tsRibo-Seq, to enrich the CFTR transcript, an antisense oligonucleotide (or fishing probe) was designed to bind to the 3’ untranslated region (3’UTR) of CFTR gene (5’-biotin- CCCTCGAGGGCCGGATCTGCAGTACACGTTCCGAGCATCCCGCTACTG-3’). Transfected cells were lysed in polysome lysis buffer supplemented 100 nM of the fishing probe. Immediately after lysis, polysomes were mixed with streptavidin-coated, magnetic beads (Milteny μMacs Streptavidin Kit) and transferred to a μMacs column attached to a magnetic field. The beads were washed four times with 100 µl of ice-cold polysome lysis buffer supplemented with 300 mM NaCl to increase the stringency of the wash steps. Subsequently, beads were washed once with polysome lysis buffer and subjected to RNaseI digestion (1 µl 100 U/µl; Thermo Scientific) directly on the column. After 15 min, the free monosomes were eluted by adding 200 µl ice-cold polysome lysis buffer supplemented with 4 µl Superase•In. Eluted monosomes were purified from rRNA fragments and RPFs were subjected to library generation as described earlier [10,18]. Libraries were sequenced with an Illumina TruSeq SBS v3 Kit on HiSeq2000 sequencing machine. Sequencing reads were then processed as described [10]. Data are deposited within the Gene Expression Omnibus (GEO) under accession number GSE53991 (conventional Ribo-Seq from CFBE41o- cells expressing wild-type CFTR) and GSE104587 (tsRibo-Seq).

2.3. Immunodetection

Proteins in each fraction during transcript enrichment procedures were precipitated by adding five volumes of 100% acetone. Pellets were resuspended in 1x SDS-loading buffer and incubated for 10 min at 37°C prior to SDS electrophoresis and subsequent immunoblot. Antibodies against ribosomal proteins were purchased from Cell Signaling (RPL7a #2579; RPS6 #2217, RPS3 #2579), CFTR antibody 596 from CFF Therapeutics and secondary α-mouse HRP antibody (#170-5047) and α-rabbit HRP antibody (#170-5046) from BioRad. All antibodies were diluted according to manufacturer’s recommendations.

3. Results

Transcripts of many proteins with implications in disease or shaping cellular stress response are expressed at very low levels in cell. CFTR is an ATP-binding cassette (ABC) transporter [19]. Mutation-based dysfunction of CFTR causes the common, life-shortening disease, cystic fibrosis (CF) [20]. CFTR folds co-translationally [21] which is orchestrated by the translation kinetics [22] and modulated by an extensive interaction network with
chaperones [23,24]. Its folding is sensitive to alterations in translation kinetics and recent studies suggest that mutation-based local inversion of the programmed ribosome velocity at a codon largely influences protein biogenesis and channel activity [10]. CFTR is expressed at very low levels in human epithelial tissues and its translation profile is usually lowly covered in conventional Ribo-Seq settings. Thus, we sought to develop a protocol to enrich CFTR transcripts in the Ribo-Seq data set in order to extract precise information on its kinetics of translation.

3.1. Design of tsRibo-Seq Approach

Conventional Ribo-Seq protocol starts with isolation of ribosome-nascent-chain-mRNA complexes after flash-freezing the cells [8,25]. Usually, individual transcripts can be enriched by pull-down of ribosomes translating that transcript either by using specific antibodies recognizing the nascent chains of the protein of interest or by selectively targeting the mRNA. The downside of the first approach is the lack of specific antibodies to target many nascent chains. Also, if antibodies would be available, they usually need a certain length of the nascent chain to be accessible for binding outside of the ribosomal tunnel, thus, information regarding translation of the N-terminal part of the protein would be lost. Here, we overcame these limitations using sequence-specific, antisense oligonucleotides to selectively enrich the mRNA of an individual transcript (Fig. 1A).

Fig. 1. tsRibo-Seq approach to specifically enrich Ribo-Seq setting with transcripts of interest in SFBE41o- cells. A: General scheme of tsRibo-Seq approach, including cell lysis to isolate ribosome-nascent-chain-mRNA complexes, binding of the fishing probe to 3'UTR of CFTR transcript, affinity enrichment of transcript of interest, generation of RPFs followed by library generation. B: Representative immunoblots with all fractions during the transcript-specific enrichment in the tsRibo-Seq experiment. CFTR protein migrates as fully glycosylated mature (band C) and partially glycosylated form resident in the endoplasmic reticulum (band B). W1-W4 denote wash steps with high salt concentration to minimize the amount of non-specifically bound mRNAs, W5 denotes a wash with low-salt concentration buffer to set the conditions for RNasel digestion; F denotes flow-through and E, eluted CFTR nascent chains. RPS and RPL designate ribosomal proteins from the small and large ribosomal subunit, respectively, used to monitor the ribosomes bound to the CFTR nascent chains. The boxed E fraction displays an alternative representation with enhanced contrast to visualize lowly concentrated nascent chains. C: Global comparison of the expression of all transcripts detected in tsRibo-Seq compared to their expression in the Ribo-Seq experiment.
To gain insight into translation of the whole transcript, we designed the antisense oligonucleotide (or fishing probe) to specifically hybridize to the 3’ untranslated region (3’UTR) of CFTR gene, thereby using segments from the 3’UTR that are unique to CFTR transcript and do not hybridize elsewhere in the human transcriptome. This fishing probe was supplemented to the lysis buffer, in which the cells were freeze-crushed to isolate the ribosome-nascent-chain-mRNA complexes (Fig. 1A). The fishing probe was modified with biotin at its 5’ moiety, which binds to streptavidin-magnetic beads enabling the enrichment of CFTR transcripts (Fig. 1A). To reduce the amount of unspecifically bound transcripts, we washed extensively the beads (four-times) with a high-salt, polysome, lysis buffer. The RNaseI digestion to generate ribosome-protected fragments was performed directly on the beads (Fig. 1A), thereafter the generation of the sequencing library followed the classical Ribo-Seq protocol with direct ligation of the sequencing adapters [18,25]. The flow-through fraction contained high amounts of the ribosomal proteins PRL7, PRS3 and RPS6 as expected, since the majority of polysomes translated other transcripts were not retained on the beads (Fig. 1B). During the high-salt, wash steps, the amounts of ribosomal proteins in each fraction gradually decreased until none was detectable in the last steps (lanes W1-4, Fig. 1B). After digestion of polysomes to monosomes (Fig. 1A) and subsequent elution, faint bands of the ribosomal proteins from both large and small subunits were detectable (lane E, Fig. 1B), indicating that intact ribosomes were retained on the beads and eluted following RNaseI treatment. Note that the full-length CFTR (band B and C) was detectable only in the flow-through fraction (lane F, Fig. 1B). Intriguingly, within this smear, two distinct bands were visible which migrated at appr. 90 kDa and 74 kDa (Fig. 1B), suggesting that CFTR translation is non-uniform and likely at these positions the ribosomes pause.

3.2. tsRibo-Seq Libraries are Enriched in CFTR Transcript.

Compared to classic Ribo-Seq, the tsRibo-Seq revealed a 4.25-fold increase in the total expression of the CFTR transcript which is quantified by the total number of reads per kilobase per million reads of the whole library, RPKM [26]. In contrast, actin, one of the most abundant transcripts in the Ribo-Seq dataset, displayed 5.52-fold reduced expression value in the tsRibo-Seq. In general, 67% of all protein-coding transcripts detected in the Ribo-Seq approach displayed reduced expression values in the tsRibo-Seq data set with a median of 1.52-fold reduction in expression (Fig. 1C). Thereby, abundant transcripts, such as actin, were affected much stronger than the lowly abundant mRNAs. Together, our data show that CFTR transcripts can be efficiently enriched using a single biotinylated antisense oligonucleotide as a fishing probe, while the concentration of highly abundant transcripts which usually dominate the Ribo-Seq data sets, is decreased.

3.2. Insights into the CFTR Transcript Translation Landscape by tsRibo-Seq

Using the RPFs from both tsRibo-Seq and Ribo-Seq, we next deduced the translation profiles of CFTR transcript. The RPFs were calibrated to the ribosomal A-site (that is the site that accommodates the aminoacyl-tRNAs) and plotted along the CFTR nucleotide sequence as reads normalized to the depths of the library (e.g. reads per million reads of the whole library, RPM). In contrast to the profile from the Ribo-Seq, the tsRibo-Seq revealed a very good coverage of the CFTR transcript with well-defined regions exhibiting high and low ribosome occupancy (Fig. 2). High ribosomal density is indicative of reduced translation speed and might be linked to co-translational folding of the nascent chains or interactions with
auxiliary factors [27-29]. The only common position of high ribosome occupancy between both profiles was that around nucleotide 142 which is within the first membrane-spanning domain (MSD1) of CFTR (Fig. 2). Although the origin of this ribosome pausing has not yet been precisely defined, it is conceivable to propose that the high ribosome occupancy at this position likely reflects recognition by the signal recognition particle (SRP). SRP binds to the N-terminus of nascent chains when they just emerge from the ribosome. SRP-binding has been described to stall ribosomes during translation until the ribosome-mRNA complex is localized at the ER membrane and bound to the ER translocon [14,16].

Fig. 2. Translation profiles of CFTR transcript derived from the tsRibo-Seq (upper profile) and Ribo-Seq (lower profile). Each RPF is represented by one count corresponding to the position of the ribosomal A site. The schematic at the top depicts secondary structures (bars, α-helices and arrows, β-sheet structures) in the five CFTR domains which are color coded. NBD, nucleotide binding domains; MSD, membrane-spanning domains; R, regulatory domain. Disordered regions are left as white fields. *,#,●,↓,+ indicate positions of high ribosome occupancy.

tsRibo-Seq revealed far more positions with high ribosome occupancy in CFTR transcript than the Ribo-Seq profile (Fig. 2). Slow-translating regions in the first nucleotide-binding domain (NBD1; designated with #, Fig. 2) have been proposed to facilitate folding of this domain [22]. Notably, the majority of slow-translated regions are within the regulatory R domain (Fig. 2). A recent study on the impact of silent single nucleotide polymorphism (that exchanges a codon but is invariant for the amino acid) within the R domain (designated with, Fig. 2) highlights the importance of R domain in acquiring the global CFTR architecture and in establishing interactions between domains [10]. Thus, slow-translating regions within the R domain (designated with *, Fig. 2) are likely needed to orchestrate the translation speed with the co-translational acquisition of the 3D-topology. Translational pauses delineate individual domains and facilitates their independent co-translational folding while the nascent chains are still tethered at the ribosome [29]. Interestingly, we observed downstream of the MSD1, NBD1, R and MSD2 domains increased ribosome occupancies (designated with #, ↓ or +, Fig. 2) which likely guide the co-translational folding of each domain.

Overall, along with the strong signals of high ribosome occupancy the translation profile of CFTR transcript is littered with many positions of relatively high ribosome density, leaving the impression of a generally slow-translated transcript (Fig. 2). This corroborates the previously measured extremely low synthesis rate of CFTR [30], which is among the lowest synthesis rates detected for human transcripts [31,32]. Together, tsRibo-Seq provides the first high coverage of the CFTR transcript from which ribosome density and consequently translation speed can be deduced with nucleotide resolution.

4. Conclusion
With this study we add a new twist, tsRibo-Seq, to the constantly growing toolbox of Ribo-Seq applications. The tsRibo-Seq approach uses a step to enrich low-abundance mRNAs which allows for acquisition of highly covered translation profiles and delineating slow-translating regions that are likely orchestrating co-translational folding, membrane insertion
and interactions with other cellular proteins. This approach can be easily adapted to any transcript of interest. The precise information on translation rate along transcripts can be used in elucidating the effect of pathogenic mutations, more specifically those that are predicted to be dormant for folding (e.g. silent polymorphisms), but are contributory to disease penetrance and onset.

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References

9. Curvature Flow and Applications

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In this article we discuss briefly some model curvature flow and applications, before speaking in detail about advances made specific to the Helfrich model that have impact on our understanding of the blood disease spherocytosis.

1. Introduction

New advances in the field of geometric analysis have enabled exciting new applications. For example, the application of forced mean curvature flows to the modeling of fire fronts. Conventional wisdom models an evolving fire front by Huygen’s principle, which is known to be inaccurate in a variety of ways. One of these is for a wedge-shaped front. By comparing theoretical results with observed fires and experiments in fire tunnels, we have shown that by using a model that incorporates curvature, a more realistic evolution is obtained [19]. Further examples are from isothermal separation of binary alloys, where recent work on the governing equation [20] (called surface diffusion) has allowed for an improved understanding of the shape of eventual phase interfaces and applications back to mathematics itself, with flows such as the Willmore flow.

Applications of the theory produced while studying curvature flow can have impact on static questions, by taking the tools produced and applying them to stationary solutions of the flow equations. This is especially powerful in the case of human red blood cells, which is the main application focused on in the present article. Spherocytosis, the most common form of inherited anaemia in people with northern European ancestry, is a disease of the blood where blood cells assume a spherical shape. This is a serious condition that can be fatal, with the typical case requiring a lifetime of treatment.

As blood cells are self-organising, it is possible to derive an equation that the shape satisfies. In this article we give the essential ingredients to carry this out. By investigating solutions to this equation, we can, in principle, determine why blood cells are sometimes forming as spheres.

Current results are preliminary (see [2,15,22] for technical mathematical proofs), but indicate that this exciting new avenue has a lot of potential for new treatments and in the long-term, a path to a possible cure.

2. Curvature Flow

2.1 Curvature of Surfaces

In this section we give an intuitive explanation of the basic geometric objects discussed in this paper. Let Σ be a surface smoothly embedded in three-dimensional, Euclidean space. Pick an ‘inside’ and an ‘outside’ for Σ. Zoom in to a small piece of Σ at a point p. Draw an osculating circle and measure its signed radius - positive for circles on the ‘inside’ of Σ and negative for those on the ‘outside’.

The smallest possible radius is called \( r_1(p) \) and the largest is called \( r_2(p) \). These two numbers are called the principal radii of curvature (at \( p \)), and the mean curvature is given by...
their reciprocal sum:

\[ H(p) = \frac{1}{r_1(p)} + \frac{1}{r_2(p)} \]

There are two more fundamental pointwise curvature quantities associated with \( \Sigma \).

The Gauss curvature:

\[ K(p) = \frac{1}{r_1(p)} \times \frac{1}{r_2(p)} \]

and the tracefree curvature squared:

\[ |A^o|^2(p) = \frac{1}{2} \left( \frac{1}{r_1(p)} - \frac{1}{r_2(p)} \right)^2. \]

Some fundamental examples are as follows:

1. **Plane.** On a plane, all osculating circles have infinite radius. This means that they contribute nothing to any of the kinds of curvature, so we have \((p \text{ is a point on the plane})\)

\[ H(p) = K(p) = |A^o|^2(p) = 0. \]

2. **Cylinder.** On a cylinder, at any point there is an osculating circle with infinite radius (the maximum) and one with a finite radius (the minimum). The infinite radius contributes nothing to the mean curvature, and the radius of the osculating circle with finite radius is the radius of the cylinder. The centre of this circle is on the inside of the cylinder, so the principal radius of curvature corresponding to that osculating circle is \(+1/R\). That means \((p \text{ is a point on the circle})\)

\[ H(p) = \frac{1}{R}, \quad K(p) = 0, \quad |A^o|^2(p) = \frac{1}{2R^2}. \]

3. **Sphere.** On a sphere, at any point all osculating circles are great circles in the sphere, with radius equal to the radius of the sphere. So, in particular, all principal radii are equal and positive. This means that \((p \text{ is a point on the sphere})\)

\[ H(p) = \frac{1}{R} + \frac{1}{R} = \frac{2}{R}, \quad K(p) = \frac{1}{R^2}, \quad |A^o|^2(p) = 0. \]

where \(R\) is the radius of the sphere. (See Fig. 2.)

4. **Convex surfaces.** On any surface that is convex, such as an ellipsoid or paraboloid, all osculating circles lie on one side of the surface and do not intersect the surface (except to touch at the point where they are osculating). However, they need not be constant. On a paraboloid, for example, the osculating circles are on the inside of the tip and become smallest there. This means that the mean curvature is maximised at the tip on a convex paraboloid.

5. **Saddle and hyperboloid.** On a saddle or hyperboloid, at a given point there are osculating circles inside and outside, so then one of the principal radii is positive and the other negative. (See Figs. 1 and 2.)

2.2 The Laplacian

We also need to introduce a special, second-order, differential operator, \( \Delta \), on functions \( \phi : \Sigma \to \mathbb{R} \). The operator, \( \Delta \), is a kind of Laplacian which is adapted to the embedding \( f : \Sigma \to \mathbb{R}^3 \).

It has the very important property that coordinate invariance of \( \phi \) is preserved under \( \Delta \).

Setting \( g_{ij} = \left( \frac{\partial}{\partial x^i} f, \frac{\partial}{\partial x^j} f \right) \), we have
\[ \Delta \varphi = \frac{1}{\sqrt{\det g}} \sum_{i,j=1}^{2} \frac{\partial}{\partial x^i} \left( \sqrt{\det g} (g^{-1})_{ij} \frac{\partial}{\partial x^i} \varphi \right). \]

This turns the pair \((\Sigma, g)\) into a Riemannian 2-manifold, with the metric \(g\) operating on vectors \(X, Y\) in the tangent bundle (family of tangent spaces parametrised over \(\Sigma\)) via

\[ g(X,Y) = \sum_{i,j=1}^{2} g_{ij} X^i Y^j. \]

This is called the induced metric, sometimes (usually) denoted as the pullback of the standard metric on \(\mathbb{R}^3\) by \(f\).

### 2.3 Curvature Flow

We are interested in studying how a surface changes when acted upon by forces from the surrounding space. Suppose \(X_0: \Sigma \to \mathbb{R}^3\) is a surface immersed in three-dimensional Euclidean space. Consider, for \(t \in [0,T]\), the (maximal) one-parameter family of isometric immersions \(X(t): \Sigma \to \mathbb{R}^3\) satisfying

\[ \frac{d}{dt} X = \tilde{V} \]

where \(\tilde{V}\) is a vector field. The family \(X\) is a curvature flow with velocity \(\tilde{V}\).

Let us briefly state the governing equations of three of the most common curvature flows.

**Example.** Mean curvature flow:

\[ \tilde{V} = \bar{H} = \Delta X = H \nu. \]

The geometric heat equation, the mean curvature flow, was proposed by Mullins [17] to model the formation of grain boundaries in annealing metals. This is the same paper where surface diffusion is proposed for the phase interface during isothermal separation of binary alloys (see Fig. 4 (right)) and, in a related context, thermal grooving. (See Fig. 3.)

**Example.** Surface diffusion flow:

\[ \tilde{V} = -\Delta^\perp \bar{H} = -(\Delta H) \nu. \]

The above-mentioned surface diffusion flow was originally motivated by Mullins, but by now has found a huge number of applications. (See for example the survey by Cahn and Taylor [4].)

**Example.** Willmore flow:
The Willmore flow was originally devised by Kuwert and Schätzle [14] to make progress on problems in differential geometry, in particular, related to the Willmore functional. It decreases the curvature of a geometric object in an averaged sense as quickly as possible. (See Fig. 4 (left).) The Willmore flow is closely related to biological models, as curvature is a good

\[
\vec{V} = -\Delta \vec{H} - \langle A^0_{ij}, \vec{H} \rangle (A^0_{ij}).
\]

The Willmore flow applied to a bunny. Pictures courtesy of Crane et al. [5]. (Right three images) Isothermal separation of Ag71Cu29 after 2h, 5h, 40h at 970K. Pictures courtesy of Böhme [3].
Fig. 5. (Top) The surface model with free boundary and barriers. (Bottom) Modelled and experimental evolution of merged, oblique, fire lines. (a) Model with $\varepsilon = 1, \theta = 80^\circ$; (b) Experimental observations corresponding to the case $\theta = 80^\circ$; (c) Experimental observations corresponding to the case $\theta = 85^\circ$; (d) Model with $\varepsilon = 5, \theta = 75^\circ$; (e) Model with $\varepsilon = 0.2, \theta = 80^\circ$; (f) Model with $\varepsilon = 0.5, \theta = 85^\circ$. Below this are jump velocity profiles showing model prediction (black line) and experimental values (red circles): (a) $\varepsilon = 0.5, \theta = 85^\circ$; (b) $\varepsilon = 1, \theta = 80^\circ$. 
approximation to elastic energy, and biomembranes typically minimise their elastic energy. One long-standing problem was to understand unstable Willmore surfaces, those that in a certain sense ‘almost- minimise’ the energy functional. It is intuitive to guess that convex profile curves lead to stable surfaces, since the profile curves of Clifford tori (global minimisers) are convex. However, we proved in [6] that this is not the case, giving examples of unstable surfaces with convex profiles and unstable surfaces with nonconvex profiles. (See Fig. 6.)

Example. Mean curvature flow with a forcing term:

\[ \vec{V} = \vec{H} + \vec{F} \]

By incorporating an additional external force field into the evolution of an interface by mean curvature, we may interpret the resulting flow as the procession of a fire front where the fuel is homogeneous, the terrain is flat and uniform, and there is wind whose influence is given by \( \vec{F} \). The curvature term allows for a holistic explanation of observed fire phenomena such as the smoothing of corners and sudden jump velocities for merging fronts. (See Fig. 5 (bottom) and [19].) Enhancing the model to a curvature flow with a free boundary allows additionally for the notion of barriers to be incorporated, as depicted in Fig. 5 (top) and explained in [23].

3. Red Blood Cells and Spherocytosis

3.1 Red Blood Cells as Elastic Phospholipid Bilayers

In this section, we dive deeper into the study of the shape of human red blood cells. The human red blood cell is an example of an elastic phospholipid bilayer. (See Fig. 7 (bottom).) The phospholipids self-organise into a closed surface, held together by non-covalent forces. An actual human red blood cell is a complicated thing.

What we want to do is somehow to find a way to analyse the shape of a human red blood cell. But taking into account all of the complexities above seems intractable, at least for now, and so we make some dramatic, simplifying assumptions.

3.2 Red Blood Cells: A Mathematical Model

The basic idea is the following:

1. Human red blood cells are self-organising and will come to rest in a state of least energy.
2. The state of least energy has the lowest possible free surface energy.

In 1973 Helfrich [12] derived an expression for the free surface energy of a human red blood cell (in the idealised situation of only phospholipids). It takes as input a configuration of
a red blood cell and then outputs a number. By invoking techniques from the calculus of variations, we can find a mathematical expression for the configuration with least energy.

3.3 On Spherocytosis

We may also use this perspective to study questions related to the shape, rigidity and stability of red blood cells. Partial answers to such questions can have profound impact, for example, in the light of blood diseases such as spherocytosis.

Spherocytosis is a currently incurable and essentially untreatable disease of the blood. It is the most common form of inheritable anaemia in people of Northern European ancestry (1 in 5000).

- Red blood cells of patients shaped like spheres (spherocytes, see Fig. 7 (top))
- Spherocytes break down faster than discocytes, are more rigid, less surface area
- Worst of all: auto-hemolysis
- Can be managed through a splenectomy, a lifetime of medication, and lifestyle management

In our research, we are guided by the following question:

**Core Question:** Can the Helfrich model help us to understand why red blood cells take a different shape in patients with spherocytosis?

3.4 Mathematical Analysis and Spherocytosis

The Helfrich model combines five parameters with geometric information of the biomembrane to form the Helfrich energy. The parameters used by the Helfrich model are:

- $k_c$ and $\tilde{k}$: bending moduli; experimental evidence for $k_c$ being small and positive\(^1\)
- $c_o$: spontaneous curvature; the intrinsic preferred curvature of the cell
- $\lambda$: tensile stress
- $p$: osmotic pressure difference.

The eventual, long-term application for our research can be summarised as follows. Suppose that eventually it is possible to develop targeted drugs that nudge the values of some of these parameters in a certain direction. Since red blood cells are self-organising, if the parameters slipped outside the ‘spherocytosis range’, then the red blood cells would automatically revert to the standard discocyte shape and spherocytosis would be cured. The main difficulties here for mathematicians are to determine what the Helfrich model says about

\(^1\) Actually, the value of $\tilde{k}$ does not affect the shape of a red blood cell at all.
this ‘spherocytosis range’.

4. The Helfrich Model

Note. Many stated results are from [2]. For those that are not from this article, we give the proper reference in the statement.

Let us now give more details on the Helfrich model. The Helfrich functional or Helfrich energy is:

$$\mathcal{H}_{c_0}^{\lambda_p}(f) = \frac{k_c}{2} \int_{\Sigma} (H - c_0)^2 \, d\mu + \lambda \text{Area}(\Sigma) + p \text{Volume}(\Sigma) + \bar{k} \int_{\Sigma} K \, d\mu$$

The measure $d\mu$ adapts ‘flat’ integration to $f$, and is given by $d\mu = \sqrt{\det g} \, dL^2$, where $dL^2$ is standard Lebesgue measure on $\mathbb{R}^2$. The Helfrich model is the claim that any biomembrane minimizes the Helfrich functional. Intuitively, minimisers of a functional are quite ‘rigid’. This is expressed mathematically by the vanishing of a differential operator, $\mathcal{L}_{c_0}^{\lambda_p}$:

$$\mathcal{L}_{c_0}^{\lambda_p}(\Sigma) = 0,$$

and the positivity of another differential operator corresponding to the second derivative of $\mathcal{H}_{c_0}^{\lambda_p}$. This can be thought of as nothing more than a complicated version of the maxima/minima test for functions of one variable.

For the Helfrich functional, (note that $k_c > 0$ from earlier experimental work)

$$\mathcal{L}_{c_0}^{\lambda_p}(\Sigma) = k_c (\Delta H + H|A^0|^2) + 2k_c c_0 K - \left(\frac{k_c c_0^2}{2} + \lambda\right) H - p.$$

Our results so far include a definitive answer (in terms of the pressure difference, spontaneous curvature, and tensile stress) of when a spherocyte is a Helfrich surface. This is elementary and reduces to the analysis of a family of parabola.

**Theorem** (Classification of Spherocytes)

Suppose $f : \Sigma \rightarrow \mathbb{R}^3$ is a closed, smooth, embedded, orientable surface in the same topological class as a sphere. If $f(\Sigma) = S_r(\Sigma)$, and $f$ is crucial for the Helfrich functional, $\mathcal{H}_{c_0}^{\lambda}$, then one of the following must hold:

(a) For $c_0 = 0$:

(i) $c_0 = \lambda = p = 0$, in which case $f$ may be a sphere of any radius;

(ii) $p \lambda < 0$, in which case $f$ must be the unique critical sphere with radius $r = -\frac{2\lambda}{p}$

(b) If $c_0 \neq 0$, $u := \frac{1}{k_c c_0} + \frac{c_0}{2}$ and $v := \frac{2p}{k_c c_0}$. Then:

(iii) $v = u^2$, $u > 0$, in which case $f$ must be the unique critical sphere with radius $r = \frac{u}{2}$;

(iv) $u \geq 0$ and $v \geq 0$, in which case $f$ must be the unique critical sphere with radius $r = \frac{1}{2} \left( u + \sqrt{u^2 + v} \right)$;

(v) $u \geq 0$ and $v \in (-u^2, 0)$, in which case $f$ may be either of the two critical spheres with radii $r_\pm = \frac{1}{2} \left( u \pm \sqrt{u^2 + v} \right)$;

(vi) $u < 0$ and $v > 0$, in which case $f$ must be the unique critical sphere with radius $r = \frac{1}{2} \left( u + \sqrt{u^2 + v} \right)$. 

62
Going in the other direction is much more complicated and studying notions of stability and rigidity even more so. So far, we have only partial answers. We have work on global minimisers (using the Hopf theorem), rigidity of spherocytes (using the local-global integral method), and stability of spherocytes (using a generalised form of the maximum principle).

4.1 On “Correct” Parameter Values
While it is possible to obtain experimental values for $c_0$ for vesicles (as in Evans-Fung [8]), there currently exist no direct measurements of the spontaneous curvature of red blood cells. One may reasonably guess that $c_0 \neq 0$, as the distribution of the phospholipid types between the two leaflets of the bilayer is asymmetric.

Although the spontaneous curvature should realistically depend on position, $c_0 = c_0(x)$ where $x \in \Sigma$, one possible choice of a function is to use the mean curvature of a ‘resting shape’, as in Pozrikidis [18] and Krüger [13]. We take the view here that $c_0$ is constant. The question then becomes which constant?

Pozrikidis suggests that an appropriate choice for the spontaneous curvature of normal red blood cells is $c_0 = -0.62 \mu m^{-1}$, very similar to that reported by Deuling-Helfrich [7], where a range of values that confirm observed experimental data is given, from $-0.56 \mu m^{-1}$ to $-1.94 \mu m^{-1}$. Later the value of $-0.74 \mu m^{-1}$ was settled upon.

We have taken $c_0$ to be constant, allowing positive and negative values, for simplicity. Allowing $c_0$ to depend on position is an important topic for future work.

The bending modulus, $k_e$, can be measured experimentally, although reported values for healthy human red blood cells vary in the range $0.2 - 9.0 \times 10^{-19} J$ (see Freund [9] and Guido-Tomaiuolo [11], for example). It is reported in Guckenberger-Gekle [10] that most studies are being performed for $k_e$ between 2 and $4 \times 10^{-19} J$.

The osmotic pressure difference, $p$, for a human red blood cell has been argued by Deuling-Helfrich to be small when approaching spherocytes, but of indeterminate sign. When $p$ is relatively large, discrete rotational symmetries in addition to reflection tend to appear in equilibria, whereas for negative $p$, all discrete symmetries, including reflection symmetry, appear to be lost.

For the tensile stress, $\lambda$, Deuling-Helfrich show that $\lambda$ should be of the order $-p/k_e$, and since $k_e$ is positive, this means that $\lambda$ should have sign opposite to that of $p$. In general $p$ and $\lambda$ are expected to depend on the equilibrium configuration. It may not be reasonable to prescribe them a-priori.

One may view our results here, that focus on spherical critical points for the Helfrich functional, $\mathcal{H}^{c_0}$, as further informing the discussion on realistic values for $\lambda$ and $p$.

4.3 Energy Comparison
The question of when a critical point for the functional $\mathcal{H}^{c_0}$ is a sphere, is delicate. All of our remaining results are attempts at making headway in this direction.

Firstly, we use the uniqueness of embedded CMC surfaces (the Hopf theorem) and the isoperimetric inequality. The theorem below works by an energy comparison argument. Briefly, under the given conditions, spheres take the lowest energy out of all possible configurations. This doesn’t address the initial question (which is about critical surfaces) and also only applies in a special circumstance.

**Theorem** (Energy Comparison)
Spheres are the unique global minimisers of the energy $\mathcal{H}^{c_0}$ among closed surfaces in the same topological class as a sphere with volume fixed at $\text{Vol } \Sigma = \frac{32\pi}{3c_0^2}$, if $c_0$, $\lambda$, $p$ satisfy:
\[ 3\lambda + \frac{P}{c_0} = 0 \]  \hspace{1cm} (1)

4.4 Closeness

The previous result requires the very restrictive assumptions that the volume be fixed at a level that includes the sphere with radius \( 1/c_0 \), and the parameters of the functional satisfy (1). Relaxing these conditions can be achieved by introducing a closeness assumption.

Such a closeness assumption has been used by McCoy and Wheeler [15] in the case of zero spontaneous curvature. Our basic idea is to use the curvature flow technology developed in [16] to enhance this result to the case of non-vanishing spontaneous curvature. In [15], the functional

\[
\tilde{\mathcal{H}}_{\lambda_1, \lambda_2}(f) = \frac{1}{4} \int_{\Sigma} (H - c_0)^2 \, d\mu + \lambda_1 \text{Area} \Sigma + \lambda_2 \text{Vol} \Sigma
\]

was studied. This is quite close to our functional \( \mathcal{H}_{\lambda, p} \), with many properties common to both \( \tilde{\mathcal{H}}_{\lambda_1, \lambda_2} \) and \( \mathcal{H}_{c_0} \). The difference between the two is given by:

\[
\mathcal{H}_{\lambda, p}(f) - 2k_c \tilde{\mathcal{H}}_{\lambda_1, \lambda_2}(f) = 2k_c \pi \chi(\Sigma),
\]

which is constant.

For the case where the bilayer is topologically spherical, we have \( \chi(\Sigma) = 2 \) and

\[
\mathcal{H}_{\lambda, p}(f) - \left( 2k_c \tilde{\mathcal{H}}_{\lambda_1, \lambda_2}(f) + 4k_c \pi \right) = 0.
\]

That is, the functionals \( \mathcal{H}_{\lambda, p} \) and \( \tilde{\mathcal{H}}_{\lambda_1, \lambda_2} \), up to taking special choices of the parameters \( \lambda_1 \) and \( \lambda_2 \), differ by a constant. The variational properties of these functionals are therefore equivalent; only the numerical energy of shapes is altered.

The following theorem is known:

**Theorem** ([Theorem 1, McCoy and Wheeler])

Let \( f: \Sigma \to \mathbb{R}^3 \) be a closed, smooth, embedded, orientable surface in the same topological class as a sphere. Suppose additionally that

\[
\int_{\Sigma} |A^0|^2 \, d\mu < \varepsilon_1 \quad \text{and} \quad \lambda \geq 0,
\]

where \( \varepsilon_1 \) is an explicit universal constant. Then, if \( f \) is critical for the Helfrich functional, \( \mathcal{H}^0 \), it is a standard round sphere.

In our work, we are concerned primarily with non-zero spontaneous curvature. In addition to the classification of spherocytes and the energy comparison theorems presented earlier, we give the following which extends the theorem above for closed surfaces to the case of non-vanishing, spontaneous curvature.

**Theorem** (Closeness)

Let \( f: \Sigma \to \mathbb{R}^3 \) be a closed, smooth, embedded, orientable surface. Assume that if \( f \) is a Helfrich surface, that is, \( \mathcal{L}_{\lambda, p}(f) = 0 \), there exist universal constants, \( c_1, c_2, c_3, c_4 \), such that if
\[ \int_{\Sigma} |A^0|^2 \, d\mu \leq \min \left\{ \frac{1}{2c_1c_3}, \frac{1}{2c_0^2c_2(Area \, \Sigma)} \right\}, \]

\[ c_0^2 + 2 \frac{\lambda}{k_c} = 2c_0 u \geq 0, \]

and

\[ c_0^2 (Area \, \Sigma) < \frac{1}{c_4}, \]

then \( f(\Sigma) = S_r(\Sigma) \) is a standard round sphere.

Remarks to the closeness result. The quantity \( Q = c_0^2 (Area \, \Sigma) \) identified in the proof is dimensionless, as \( c_0 \) has the units of the mean curvature, and \( Area \, \Sigma \) has the units of \( d\mu \). Therefore \( c_0^2 (Area \, \Sigma) \) has the units of \( H^2 d\mu \) and is scale-invariant.

The constants \( c_1, c_2, c_3, c_4 \) are universal, but the area of \( \Sigma \) is not. One corollary that interprets the closeness theorem is:

**Corollary**

Let \( A_0 \in (0, \infty) \). Consider the class

\[ \mathcal{F} = \{ f : \Sigma \to \mathbb{R}^3 : f \text{ is a smooth, closed, embedded, orientable surface with} \]

\[ Area \, \Sigma < A_0 \}. \]

Suppose \( c_0^2 + 2 \frac{\lambda}{k_c} = 2c_0 u \geq 0, \) and \( c_0^2 A_0 < \frac{1}{c_4} \). There exists a constant, \( \delta > 0 \) depending only on \( A_0 \) such that any Helfrich surface \( f \in \mathcal{F} \) with \( \|A^0\|_2 < \delta \) is a standard sphere.

The closeness theorem holds for a range of the parameters \( c_0, \lambda \) and \( p \) that is larger than the range of parameters that spheres are critical for. For parameters outside this range, we therefore have a reverse energy gap phenomenon. (See [21] for a description of such phenomena.)

**Corollary**

Assume the hypothesis of the previous corollary and in addition that the parameters \( c_0, \lambda \) and \( p \) satisfy one of

(i) \( c_0 = 0 \) and \( p\lambda \geq 0 \) with one of \( p, \lambda \) non-zero;
(ii) \( c_0 \geq 0, u \geq 0 \) and \( v < -u^2 \);
(iii) \( c_0 \leq 0, u \leq 0 \) and \( v \leq 0 \).

There exists an absolute constant, \( C > 0 \), depending only on \( A_0 \), such that any Helfrich surface satisfies

\[ \int_{\Sigma} |A^0|^2 \, d\mu > C. \]

4.5 Interpretation of Stability for Spherocytes

The above results indicate rigidity of the sphere. The question of stability of the spherocytes is also important, since, in a patient with spherocytosis, the spherocytes do not regularly become singular. They are instead stable and nominally functional, despite being regularly destroyed by the spleen.

This behaviour is not typical for the Helfrich model. Indeed, we expect that generically perturbed spherocytes revert after a perturbation (if they are ever formed at all), to a standard
discocyte shape. In general, after a perturbation acts upon a biomembrane, there is no guarantee that the bilayer will return to a global minimum. It may focus instead on a stable, local minimum, or become singular.

In order to illustrate the general setting, here is a result for the model case where $c_0 = \lambda = p = 0$ and we are dealing with the Willmore functional and closed Willmore surfaces. We say that a smooth, isometrically embedded surface, $f : \Sigma \to \mathbb{R}^3$, is weakly mean convex if $H(x) \geq 0$ for all $x \in \Sigma$, and mean convex if $H(x) > 0$ for all $x \in \Sigma$. If $K \geq 0$ then weak mean convexity becomes weak convexity and mean convexity becomes convexity. Note that in higher dimensions this is typically expressed by saying that the second fundamental form is positive semi-definite or positive definite. The given definition is simpler and agrees with this for surfaces.

**Proposition (Mean convex closed Willmore surfaces)**

Consider a smoothly embedded, closed, weakly mean convex, orientable surface $f : \Sigma \to \mathbb{R}^3$. Suppose that $c_0 = \lambda = p = 0$. Then if $f$ is critical for the Helfrich functional $\mathcal{H}_{c_0}$, it must be a sphere.

The previous proposition yields a stability statement in the following sense. Let $S_r : \Sigma \to \mathbb{R}^3$ be a standard sphere centred at the origin with radius $r$. Then it is critical for the Helfrich functional with $c_0 = \lambda = p = 0$. Consider, for some smooth function $\psi : \Sigma \to \mathbb{R}$, the perturbed surface $\eta : \Sigma \to \mathbb{R}^3$, $\eta(x) = S_r(x) + \nu(x)\psi(x)$, where $\nu$ is a smooth choice of outward-pointing normal vector. Note that we assume a-priori that the perturbed map $\eta$ is an isometric embedding, which in turn restricts the function $\psi$.

Let us impose further that the perturbed surface $\eta$ is again critical for the Helfrich functional with the given parameters. We ask ourselves the question:

**Question.** Under which conditions will the perturbed surface, $\eta$, be a sphere?

All such perturbations are termed mild. Our theorem is as follows.

**Theorem (Stability theorem)**

Let $S_r : \Sigma \to \mathbb{R}^3$ be the standard embedding of a sphere with radius $r$. Consider a perturbed surface $\eta : \Sigma \to \mathbb{R}^3$, $\eta(x) = S_r(x) + \nu(x)\psi(x)$, with $\psi : \Sigma \to \mathbb{R}$ a smooth function. Assume that $\eta$ is critical for the Helfrich functional $\mathcal{H}_{c_0}$. The perturbation $\psi$ is mild in the following cases:

1. $(c_0 = 0)$ Any perturbation $\psi$ such that $\eta$ is weakly mean convex and $\lambda, p$ are such that the average of the mean curvature over the perturbed surface $\eta$ is equal to $-p/\lambda$;

2. $(c_0 \geq 0, \lambda \leq -k_c c_0^2/2, p \leq 0)$ Any perturbation $\psi$ such that $\eta$ is weakly convex;

3. $(c_0 \geq 0, \lambda \leq -k_c c_0^2/2, p \leq k_c c_0 a_0^2)$ Any perturbation $\psi$ such that is weakly mean convex and on the perturbed surface the inequality $|A^0|^2(x) \leq a_0^2$, for some $a_0 \in (0, \infty)$, holds.

4. $(c_0 \geq 0, p \leq -k_c \left(c_0 a_0^2 + \frac{1}{2c_0} \left(\frac{c_0^2}{2} + \frac{\lambda}{k_c}\right)^2\right))$ Any perturbation $\psi$ such that on the perturbed surface the inequality $|A^0|^2 \leq a_0^2$, for some $a_0 \in (0, \infty)$, holds.

4.6 Stability and ZhongCan-Helfrich

The above notion of stability, via classification of mild perturbations, is not a-priori closely related to the classical notion of positivity of the second variation of energy. However, earlier studies can be cast in some cases into this framework, as we briefly now explain.

In ZhongCan-Helfrich [25] it is shown that given a sufficiently large pressure, $p$, spherocytes may be deformed into one of a family of surfaces associated with $l$-th order spherical
harmonics. In particular, these critical shapes are not standard round spheres. However, some of them do appear to be convex (and also mean convex) (e.g., Figure 6 in [7]). Further, they have, for sufficiently large pressure, lower Helfrich energy than a sphere. This gives us an interesting non-existence result for mild perturbations of spheres.

In the language we use here, this reads:

**Theorem** ([ZhongCan-Helfrich])

Let \( S_r : \Sigma \rightarrow \mathbb{R}^3 \) be the standard embedding of a sphere with radius \( r \). Assume that the pressure \( p \) is sufficiently large. There exist smooth perturbations \( \psi : \Sigma \rightarrow \mathbb{R} \) with the following properties:

- The perturbed surface \( \eta : \Sigma \rightarrow \mathbb{R}^3, \eta(x) = S_r(x) + v(x)\psi(x) \) is critical for the Helfrich functional \( \mathcal{H}_0 \);
- The perturbed surface, \( \eta \), is not congruent to any round sphere, and so the perturbation \( \psi \) is not mild;
- The perturbed surface is convex.

In particular, this shows that our stability theorem could not hold with large pressure. It is interesting to note that only alternative (i) allows for \( p \) to be positive, so long as \( \lambda \) is negative and the average curvature condition is satisfied.

4.7 Stability and Notions of Convexity

Our stability theorem highlights the crucial role that convexity plays in the analysis of stability. We observe that weak convexity (that each of the principal curvatures is non-negative at every point) is a much stronger condition than weak mean convexity (that the sum of the principal curvatures is non-negative at every point). Since the value of \( a_0 \) may be quite large depending upon the osmotic pressure difference \( p \), it may be that in practice perturbations of spherocytes fall into or near to categories (iii) and (iv) of the stability theorem.

Due to this focus on convexity and mean convexity, we suspect that many Helfrich surfaces are mean convex, irrespective of any stability concerns, that is, without using any knowledge about the solution being a-priori ‘close’ to a sphere in some sense. While we are far from confirming this, we are able to upgrade (in some cases) weak mean convexity to strong mean convexity.

**Theorem** (Weak to strong mean convexity)

Suppose that \( c_0 > 0, |A^0|^2 \leq a_0^2, \lambda \geq k_c \left( a_0^2 - \frac{c_0^2}{2} \right) \), and \( p < -c_0kca_0^2 \). Consider a smoothly embedded, closed, weakly mean convex surface \( f : \Sigma \rightarrow \mathbb{R}^3 \). Then if \( f \) is critical for the Helfrich functional, \( \mathcal{H}^{c_0} \), it must be strictly mean convex.

5. Concluding Remarks

In this article we have discussed modern applications of curvature flow and geometric analysis with a focus on spherocytosis and the Helfrich model. The Helfrich model, in the first instance, takes five parameters and gives a preferred shape for the biomembrane. One basic question that can be asked with a view toward spherocytosis is: Which parameter values yield spherocytes?

This question is answered in Theorem 1, yielding a critical set of parameters in which blood cells take the shape of spheres. While some parameters are fixed and cannot be changed, others can possibly be altered, for example, through targeted drug delivery.

To apply this result we now need to find a method to measure the parameters in patients with spherocytosis, and then investigate means of modifying these parameters away from the critical set.
There is a long road ahead of us. As discussed in Section 4.1, the experimental determination of parameters from a given sample is still a matter of active investigation. The next step in our view is to further investigate in this direction.

The remaining mathematical analysis of the Helfrich functional presented in this article is to discover further properties of the critical set, and to discover new information about the parameter space outside the critical set identified in Theorem 1. This is very difficult to approach directly, as we do not have any idea which particular shapes may be preferred. Only biconcave disks and spheres are known geometries in this model setting. (Other shapes such as sickle cells are not modeled purely by the Helfrich energy, so we do not expect to see them here.) That is why we approach this issue in an indirect fashion, by, for example, studying questions of stability, and convexity.

Questions of stability in particular have other important applications. In a healthy patient, the blood cell is very stable in the sense that small perturbations caused by blood flow do not break the biomembrane or cause it to reorganise into a new structure. The critical set identified earlier is very large and some regions are expected to be unrealistic. Therefore, it is reasonable to remove the regions of the critical set where the blood cell is unstable. Further, if the sphere itself is stable outside the critical set, this will be a region that we should definitely avoid when looking to modify parameters, since we would expect that it is much more difficult to move out of a stable region than into an unstable region. This would hopefully lead into a stable region for the biconcave disk, although this is currently an open question. Our efforts with advanced mathematical analysis on questions of stability and convexity are therefore expected to be impactful once we move into experimentation.

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References

10. Empathic Concern for Disability and Accessibility

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This paper reports a series of studies on empathic concern for disability and accessibility (ECDA). The first study interviewed various stakeholders about accessibility. Empathy was identified as the key feature to creating an accessible environment. Subsequently, an assessment tool was developed to measure ECDA, and applied in cross-cultural and intervention studies. ECDA can be assessed reliably, mediated by gender and culture, and is sensitive to change as a result of mindfulness meditation.

1. Introduction

When you encounter a victim of circumstances, such as a wheelchair user struggling to enter an inaccessible public building, you would empathise with the person. In addition to the empathic understanding, you may have a desire to help and enhance the welfare of the distressed person. The empathic thoughts and feelings, coupled with the desire to alleviate the suffering, lead to compassion [1], or empathic concern for a specific situation [2]. In this case, you may offer to help, so that the wheelchair user can enter into the building. Such an act of compassion, particularly as it is extended to non-relatives, has been considered as a unique human attribute [3-5]. This component of human nature has recently been a focus of attention for scientific research, particularly with a view to increasing widespread prosocial behaviour. This paper explains how I conceived the idea of developing a scale to measure ECDA from a foregoing qualitative interview study, how far the scale has been developed by examining its reliability and validity, and how I am planning to apply the scale for future research.

2. A Qualitative Interview Study about Accessibility

An interview study [6] was designed to gain insights into the factors influencing accessibility to sport and recreation activity for people with long-term mobility impairment from multiple perspectives. To achieve this aim, not only people with mobility impairment, but also service providers, and service planners and funders were interviewed in five locations across New Zealand. The interview data from a total of 53 interviewees underwent thematic analysis and resulted in six themes depicted in Fig. 1.

Under the theme of built environment at the community level, we coded a service provider’s comment, “It gets frustrating when you see a building that fits the budget versus something that’s fit for purpose.” and a comment by a person with disability, “They put a hoist in for the spa … which is okay for people who can stand and weight bear, but [it’s not suitable] for people [like me] who can’t [stand to transfer from a wheelchair on
to a hoist chair]. These two quotes represented a view on accessibility features as expensive ‘add-ons’ and a failure in mental simulation from the perspective of service consumers. The former case indicated a lack of empathy with common humanity at the emotional level, and the second case exemplified a deficit of empathy in terms of perspective taking, embodied cognition, or metalisng skill at the cognitive level. In both cases ECDA is insufficient. It would be important to develop a scale to measure ECDA, to quantify the current status of ECDA and to examine the effect of potential intervention programs aiming to enhance ECDA.

3. Development of a Scale to Assess ECDA

In accordance with the standard procedure for psychometric scale development, the assessment of ECDA [7] is designed to measure the degree of how much bystanders empathise with people who are disabled due to a lack of accessibility to public space, and the degree of how much the bystanders want to help the disabled people. The purpose is to develop a series of stimuli, each of which depicts a person with impairment in a public space where the demand of the environment either exceeds (inaccessible) or doesn’t exceed (accessible) the physical capability (see Fig. 2) to be used to evaluate the effect of gender, culture, and intervention.

A total of 100 vignettes representing 50 examples of persons with impairments in accessible (i.e., non-disabling) and 50 in inaccessible (i.e., disabling) environments were collected from internet websites and by taking appropriate photographs. Content validity, or meaningfulness to university student viewers in both New Zealand and Japan, was generated from qualitative inquiry by a panel of the three research staff members in New Zealand and

Fig. 2. Exemplary items of Empathic Concern for Disability and Accessibility for accessible (above) and inaccessible (below) conditions in English (left) and Japanese (right).
three members in Japan. As a result, the panel decided that (1) impairments were limited to impairment in mobility and vision; (2) a person with impairment was not present in the photographs; (3) a person with impairment was described in written words; (4) the format of measurement was a four-point Likert scale with response anchors of 1: Not at all, 2: A little, 3: Moderately and 4: Very much, to the question: “Please watch a series of slides on the screen and circle a number to describe the extent you would like to help the person right after watching each slide”.

After a pilot trial, a total of 100 items was considered too long, and the number of items was reduced to 60 (30 pairs of accessible and inaccessible conditions) by excluding 40 items that were ambiguous, repetitive, or culturally irrelevant. The 60 items of the ECDA were administered to convenience samples of 127 (76 males, 51 females) Japanese, and 104 (48 males, 56 females) New Zealand sport science major undergraduate students.

Excellent internal consistency was demonstrated in by Cronbach’s alphas reliability estimation with the Japanese sample (α = 0.955) and the NZ sample (α = 0.925) and by split-half reliability with the Japanese sample (α = 0.935; 0.948) and the NZ sample (α = 0.875; 0.918). Construct validity was examined by exploratory factor analysis which yielded four factors: F1: obvious inaccessible situations; F2: obvious accessible situations; F3: complex inaccessible situations; F4: complex accessible situations. The four-factor solution accounted for 49.46% of the total variance in the Japanese sample, and 39.53% of the total variance in the New Zealand sample. All factor correlations were low (r < 0.70) in both samples good discriminant validity. Confirmatory factor analysis was inappropriate due to a violation of normality assumption. Thus, the final 60-item ECDA scale evidenced an excellent reliability in terms of internal consistency, adequate construct validity, and good discriminant validity.

4. **Effects of Gender and Culture on the ECDA**

The Japanese and New Zealand data, that had been used to examine the reliability and validity of the ECDA, were also analysed to test the effects of gender and culture on the ECDA in Japan and New Zealand [8]. The analysis yielded that (1) in both accessible and inaccessible conditions the Japanese males expressed a higher level of helping intention than did the Japanese females, and the New Zealand males were less willing to help than were the New Zealand females, and that (2) irrespective of gender, the Japanese were more willing to help in the accessible condition, and the New Zealanders were more willing to help in the inaccessible condition.

The results support the female-gender hypothesis of prosocial behaviour in the New Zealand sample, but not in the Japanese sample. Consistent with the social stereotypes in Western cultures whereby women display concern for the socially disadvantaged [9], New Zealand female students were more willing to help people with impairments than were New Zealand male students. On the contrary, the Japanese male students were more willing to help people with impairment than were Japanese female students, contrary to the Western stereotypes. The Japanese students’ greater willingness to help in accessible compared with inaccessible situations may be explained by a possibility that the singularity effect [10], or the willingness to help a single concrete victim, as depicted in the ECDA, is more pronounced in the individualistic culture of New Zealand than in the collectivistic culture of Japan.

5. **Effects of Guided Mindfulness Meditation on the ECDA**

The purpose is to examine the effect of a guided compassion meditation compared to a control sitting meditation on the ECDA. The compassion meditation is also called love kindness [metta] [11] or befriending [12] meditation in which a meditation guide leads meditators to be kind to yourself and love yourself and with a wish that you are free from suffering and in peace (i.e., self-compassion), and to extend compassion to close, neutral, and
distant people, including enemies, and ultimately all sentient beings in the universe. In the sitting meditation, meditators are guided to focus on breathing, physical sensations, sounds, thoughts and feelings [13].

A total of 60 Japanese female university students participated in this study as part of two regular weekly lectures. The 60 students consisted of Class A and Class B with each class comprised of 30 students. Throughout the two lectures, 20 students from Class A and 23 students from Class B completed the study. A 2 X 2 comparative trial design was implemented to compare meditation types (sitting meditation vs. compassion meditation) and two time-points (pre- vs. post-meditation) with Class A exposed to sitting meditation and Class B to compassion meditation. A statistical analysis revealed that the Class B students in the compassion meditation group maintained the level of the ECDA in the inaccessible condition, whereas the Class A students in the sitting meditation decreased the ECDA in the inaccessible condition. The finding of decreased ECDA after the sitting meditation may be due to the meditation guide to focus the meditators attention to physical sensations, which can be painful and uncomfortable for novice meditators. By contrast, the meditators in the compassion meditation group first briefly attended to breathing and associated body movement, and then soon shifted the focus to compassionate thoughts for self and others, which could dissociate the physical discomfort and pain from the conscious experience and memory [14]. The results suggest that compassion meditation helps to maintain the level of ECDA by countering desensitization to compassion fatigue [15].

6. Conclusion

A qualitative interview study about disability and accessibility prompted a need to develop a scale to measure ECDA that can be used to examine individual differences and intervention effects. According to the standard procedure for scale development, prototype vignettes were constructed, reviewed, revised, and administered to pilot samples. The final version of the ECDA scale demonstrated initial support for internal consistency and construct validity. Validation studies evidenced sensitivity to detecting gender and cultural differences and the effect of mindfulness meditation. Further validation studies are planned to investigate the effect of mega disability sports events on ECDA, and the nature of enhanced ECDA as deepened insight and enhanced critical thinking.

Acknowledgments

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11. Ambulatory Gastric Mucosal Slow Wave Recording for Chronic Experimental Studies

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Abnormal bioelectric slow wave activity has been implicated in major functional motility disorders but its correlation to symptoms is still unclear. In this study we used an ambulatory system to record slow waves from three patients for five days. The results of the study will allow for investigation of pathophysiology, correlation of electrophysiology data to patient symptoms and to determine the effects of post-prandial and nocturnal slow wave patterns.

1. Introduction

The pacemaker cells of the gut, known as the interstitial cells of Cajal (ICC), are responsible for generating bioelectric slow wave activity, which coordinates gastric motility [1]. Patients suffering from functional motility disorders such as gastroparesis and chronic unexplained nausea and vomiting have shown a reduced ICC count and complex dysrhythmic slow wave patterns [2]. These patients typically have delayed emptying of the stomach and/or symptomatically suffer from nausea, vomiting, abdominal pain, bloating, early satiety and weight loss [3]. Clinical management of these disorders is difficult and typically involves prokinetic drugs along with nutritional support and pain management.

In recent years, a therapy utilizing high-frequency gastric electrical stimulation (GES) (Enterra®, Medtronic, MN, USA), has been adopted by some clinical and research centers for severe gastroparetic patients who fail conservative treatment [4]. Here, pacing leads are sutured into the gastric serosa, and the stimulator is implanted in a subcutaneous pocket in the abdominal wall. Some research centers utilizing GES have additionally introduced a screening phase whereby temporary GES (tGES) is performed via endoscopic implantation at the mucosal surface of the stomach for 5 days to evaluate symptom improvement and to guide permanent implantation [5]. tGES can also be performed percutaneously but is currently not approved for patients use in the USA [6].

The clinicopathological correlation of gastric dysrhythmias remains uncertain. It is anticipated that long term ambulatory recordings of the slow wave information will provide a renewed understanding of the underlying electrophysiology and pathophysiology, which may assist in improving therapy via electrical stimulation. The slow wave information prior to and post GES has not been investigated in significant detail. Thus, tGES provides an opportunity to record the slow wave information over 5 days in awake patients, to assist in understanding chronic slow wave behaviour and how it correlates with symptoms. In this study, we assessed the feasibility of using a commercial wearable ambulatory recording system to obtain long-term multi-point slow wave recordings in patients undergoing tGES.

2. Methods

2.1 Experimental Methods
Patients diagnosed with gastroparesis confirmed by scintigraphy, who were undergoing tGES at the University of Louisville Hospital gave informed consent to take part in this study (n=3). While under procedural sedation via fentanyl and midazolam, three bipolar temporary cardiac pacing wires (Model 6416, Medtronic, MN, USA) were inserted through the nasopharynx and guided endoscopically to the mucosa, where they were attached via endoclips to the corpus, mid-corpus and antrum (Fig. 1). A pair of the attached electrodes are connected to the GES device to deliver electrical impulses, while three of the remaining electrodes were connected to the recording module.

The recording module is powered by a rechargeable Lithium ion battery (450 mAh), with functionality for electrophysiology measurements along with tri-axial micro-electromechanical system (MEMS) accelerometer, gyroscope, magnetometer and temperature measurements. For this study, from each patient, three sensors were utilized to record the unipolar slow wave data, and accelerometer data was collected for the duration of tGES. The portable recording module measured 64.5 x 33 x 13.5 mm and weighed 30g without leads, making it suitable for long-term wearable use.

Patients were asked to record their food intake and symptoms in a diary, every 4 to 5 hours, using a 5-point Likert scale, where 0 represents absent symptoms and 4 represents maximum severity.

2.2 Accelerometer Recordings

Three axis accelerometer data were acquired at 30 Hz, which provided the opportunity to measure when the patient was mobile. A differential sum vector magnitude (dSVM) was calculated as in (1) to capture large-scale movements,

\[
d_{SVM}(t) = \sqrt{(A_x(t+1) - A_x(t))^2 + (A_y(t+1) - A_y(t))^2 + (A_z(t+1) - A_z(t))^2} \tag{1}
\]

where \(A_x(t)\), \(A_y(t)\) and \(A_z(t)\) are the time varying accelerometer data in the x, y and z axes, relative to the ambulatory system. Fig. 2A shows the dSVM for 2 hours, during which the patient was mobile.

An envelope of the dSVM signal was then computed using the root mean square in a 30 sec moving window (Fig. 2B). To detect movement, a moving estimate of the standard deviation was computed within a 30 min window, as a time-varying threshold. If the envelope of the dSVM was above the standard deviation estimate, it was considered as movement (Fig. 2C). These periods were used to exclude slow wave data during that time period, as frequency and amplitudes of slow waves would be misleading.

2.2 Mucosal Slow Waves

The slow wave data were filtered using a similar framework as described previously [7], where baseline and high-frequency noise were removed. The baseline of the signal was estimated using a Savitzky-Golay (SG) filter with a window size of 1 min and a second-order
polynomial, which was subsequently subtracted from the raw signal. In these mucosal recordings, ECG artefacts were more substantial than in traditional serosal recordings, and the use of a traditional filter would potentially alter the slow wave morphology, as the dominant ECG frequency overlaps with the slow wave spectrum [8]. Thus, a wavelet denoising filter was adopted. The slow wave data were decomposed using a symlet wavelet with five vanishing points up to the fifth level of decomposition. The details were soft thresholded using a heuristic Stien unbiased risk estimate threshold, after which they were reconstructed [9]. Fig. 3 shows a slow wave signal of 2 min, prior to and post wavelet filtering, where the ECG artefacts have been eliminated.

The dominant frequency and amplitude of the slow wave signal was then calculated in 5-minute segments with a 75% overlap of the moving window, for 5 days. A fast Fourier transform was calculated for each segment, with the frequency with the highest power denoted as the dominant frequency. The amplitude was calculated based on the difference of the maximum and minimum values in the window segment. To account for spurious amplitude deflection, the amplitude was calculated in 1 min moving window segments within the 5 min window. Any frequency values beyond 15 cpm and amplitude values greater than 10 mV were considered to be outside of plausible physiological range, and were thus discarded [10,11]. ANOVA was performed on the frequency and amplitude estimates of the slow wave to assess for significance across patients.

3. Results

3.1 Ambulatory Recording System

Data were successfully recorded in three patients. The rechargeable Lithium-ion battery in the recording device lasted for five days without recharging. The mean compressed file size for the recording period was 354 Mb. The patients had a good tolerance to the recording module and were able to wear it comfortably for the duration of the study.

3.2 Experimental Analysis
Fig. 4 shows three segments of mucosal slow wave activity, from three channels, from within the five-day duration from a patient. The overall slow wave frequency and amplitude was $3.0\pm0.96$ cpm and $1.43\pm1.75$ mV. Fig. 5A shows a boxplot of dominant slow wave frequency across patients, while Fig. 5B shows the slow wave amplitude across patients. There was a significant difference in slow wave frequency across all patients ($p < 0.05$), while the slow wave amplitude of Patient 1 was different to those of Patients 2 and 3. The mean slow wave frequency for Patients 1, 2 and 3 were $2.97\pm1.14$ cpm, $2.84\pm0.55$ cpm and $3.26\pm0.89$ cpm, while the mean slow wave amplitudes for Patients 1, 2 and 3 were $1.68\pm1.81$ mV, $1.73\pm1.69$ and $1.06\pm1.65$ mV. The results indicate that the slow wave amplitude was highly variable in comparison to the slow wave frequency. Previous GI HR in-vivo studies have shown in gastroparetic patients that although slow wave frequency maybe in the normal range, slow wave amplitudes are variable [12], up to twice that of normal activity, and similar results may be evident here.

4. Discussion

This study introduced a novel wearable recording system to enable the ambulatory telemetric assessment of gastric slow wave physiology, along with a framework to analyse the data. This is the first reported study of recording gastric mucosal slow waves over an extended period of time in humans. This technology will be valuable in defining a chronic understanding of gastrointestinal electrophysiology. It will also provide the opportunity to personalize therapy based on the behaviour of slow wave activity in the gut.

In this pilot study, patient data were used to develop the methods required to analyze the data in an efficient and reliable manner. Initial results have indicated that slow wave amplitude was more variable than frequency in the recorded patients. These results are concordant with a previous intraoperative study in a similar patient group which showed the presence of gastric dysrhythmias, along with large amplitude variation [12,2]. Further development of analysis techniques using time delays in signals to assess propagation patterns will aid in the correlation of slow wave data with dysrhythmic propagation patterns, clinical symptoms, and will serve as a future therapeutic bio-marker [13,14]. Metrics were also computed to determine if the patient was mobile using accelerometers. In future, this information can be used to determine...
the type of activity the patient was performing. This would assist in correlating and understanding the effects of various physical activity on gastric slow waves.

Slow waves have been recorded from the mucosal surface in animals and humans using low and high-resolution electrical techniques [10,11], and during GES [4]. However, these recordings were typically for short periods of time (less than 10-20 min). Wireless and ambulatory systems have also been developed for serosal and cutaneous gastric slow waves [15,16], but this is the first reported study for ambulatory mucosal slow wave recordings in patients over an extended period of time. This ambulatory recording module will allow us to investigate the effect of electrical stimulation on slow waves, as well as to assess the postprandial and nocturnal patterns of slow wave activity.

In conclusion, we have recorded continuous mucosal slow wave activity for five days, from gastroparetic patients, during high-frequency tGES (temporary Enterra stimulator). In future, this framework would be valuable to assess the slow wave activity, alongside patient symptoms for clinicopathological correlation, and to provide an objective biomarker to inform clinical treatment, for example, whether to progress to a permanent stimulation.

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References
12. Superconductor Sandwiches: Strongly Interacting States in Thin-Film Multilayers

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We can now make, atom upon atom, thin-films of disparate solids. These multi-layer solids exhibit fascinating new properties that result from interactions between the layers. Here we present a particular such case, recently discovered in so-called ‘superconductor sandwiches’, which provides a significant new perspectives on the enigmatic physics of high-temperature superconductors.

1. Introduction

One of the themes from this 2017 Alexander von Humboldt Kolleg on “Our changing world in the South Pacific”, was that of ‘interconnectedness’. This theme of interconnectedness was seen in the relationships between increasing green-house gas concentrations, southern-ocean clouds and life on pacific islands, between ‘the humanities’ and ‘the sciences’, and between collaborations made through the von Humboldt programme and community.

The idea of interconnectedness also plays out strongly in the physics of solids we study. The language solid-state physicists use may be different, but the ideas are similar; the properties of the solids we study are highly contingent on one another, so that altering one aspect of the material, may change all its properties [1,2]. Our goal here is to understand the physics of this interconnectedness.

Superconductors are a key class of solids that we study [3]. Electrical current can move through a superconductor with zero loss. They are the pinnacle of efficiency and the closest thing we have to a ‘perpetual motion’ machine on earth1. Usually, however, superconductor scientists are urged to pursue more sensible ends and so superconductors have been put to more practical uses [4]; e.g. coiled to make compact, powerful magnets. These magnets are used, for example, in MRI machines or electric generators. In a different vein, superconductors have become the primary platform for quantum computing – a result of their rich, surprisingly interconnected2 and deeply quantum mechanical physics [2].

New Zealand leads the way in the industrialization of the best performing superconductors. These are called cuprate high-temperature superconductors3 (HTSs) and were discovered in 1986 [3]. Following intensive research and incremental development, NZ now hosts a successful, fully-independent manufacturer of HTS superconducting magnets

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1 Imagine making a loop of superconductor, then start a current spinning around the loop. Because there is zero electrical resistance in a superconductor, that current will keep flowing around and around for as long as one cares to wait. Note however, when you try to do ‘work’ with this current you will introduce dissipation and a loss of current – which is ultimately due to the conservation of energy principle.

2 For example, the Bardeen-Cooper-Schrieffer theory of superconductivity was developed into the Higgs mechanism of elementary particle mass generation.

3 The name comes from them all containing CuO2 layers which become superconducting at comparatively high temperatures. Unfortunately, when scientists try to come up with snazzy names for their discoveries, the results are often even worse.
(“HTS-110”) [5], has developed the world’s first HTS magnetic resonance imaging system (MRI, as one would find in hospitals), and is integral to several international HTS power systems projects (motors, generators etc.). The ongoing industrialization research and development is led by the Robinson Research Institute, based in Wellington, NZ.

Despite the ongoing industrialization of superconductor technology, and intensive research into HTSs, there still remain important research questions [2,3,6]. For example, we cannot predict and purposefully engineer a new superconductor because we do not know exactly why HTSs are superconductors. The science of HTSs involves many interacting electronic ‘states’ and it has proved difficult to ascertain how exactly they are interconnected.

Our latest fundamental research in this field involves the interaction between an HTS and a magnetic material (a ‘manganite’) in thin-film multilayers – colloquially called ‘superconductor sandwiches’ [7,8]. We study these superconductor sandwiches for several reasons: (i) one can control and create useful material properties; (ii) they are a novel way to understand the physics of HTS; and (iii) the physics of the inter-layer interactions and the resulting ‘emergent’ properties are of fundamental interest in themselves.

Here we present a particular case whereby a HTS sandwiched between a particular manganite adopts startling new, ‘emergent’ properties [7]. Understanding the interactions that cause these properties will give us a significant new perspective on the enigmatic physics of HTSs.

2. Sample preparation and methods

We grow thin films of the high temperature superconductor (HTS) and magnetic material (‘manganite’) using a technique called pulsed laser deposition [8]. This technique is akin to spray-painting, where the spray is created by shooting laser pulses at the solid one wants to grow (the HTS or manganite in our case). With this technique, we grow nano-meter thin layers that are yet still as well-ordered (‘crystalline’) as they would be in a high-quality crystal. We then grow layers of alternating material simply (!) by changing the spray can, so to speak. The high-quality of the layers and interfaces between them, and the thinness of the layers, mean that we create new hybrid, interconnected solids.

The thin-film multilayers we present here are made from 20 nm of (Pr0.5La0.2Ca0.3)MnO3 (PLCMO, the manganite), 7 nm of YBa2Cu3O7 (YBCO the superconductor and all-round best performing HTS), followed by another 20 nm of the manganite PCLMO [7]. The physical phenomena we report however are reproduced for alternate combinations of film thicknesses and manganite – we discuss later what we believe the salient physical parameters are. These nano-meter thin ‘superconductor sandwiches’ are grown on inert crystalline substrates.

To highlight some of the physics of these superconductor sandwiches, we present here (i) electrical resistance measurements in zero and high-magnetic fields, and (ii) the optical properties for light from the far-far infrared through to the ultra-violet. The latter were measured by a technique called ‘ellipsometry’, and our results here, particularly for the far-far infrared light, are a technical achievement owed mostly to Dr. Marsik [9].

3. Results

3.1 Electrical resistance

Fig. 1 shows the electrical resistance, \( R \), for the superconductor-sandwich versus temperature, \( T \), for various magnetic fields indicated in the legend [7].

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4 They are rather, on the whole, serendipitously discovered.

5 Optical properties include such things as absorption and refraction. Here we present the optical properties rather by way of the dielectric function and ‘optical conductivity’ – quantities that can be converted mathematically into the absorption or refraction etc.
Let us first focus on the zero magnetic field case (the black curve in Fig. 1). At temperatures above $T = 80$ K the data reveal nothing unusual and reflect the metallic-like response for the normal state of YBCO as the other layers of the sandwich are insulating. The properties of the YBCO and PLCMO are not interconnected at these higher temperatures, at least as far as the electrical resistance is concerned. At low temperatures however, $R$ turns up sharply. Such an up-turn normally indicates the solid is an insulator, but in the superconductor sandwiches it's an unusual and unconventional insulating state.

Let us now look at the effect of a magnetic field. Most surprisingly, a moderate magnetic-field reverses this insulating state and restores a conventional-looking superconducting state! Considering the past 100 years’ worth of research on superconductors, almost universally a magnetic field is seen to degrade the properties of a superconducting state – eventually destroying it [3]. In our system, the opposite appears to be true – solely due to an interaction between the interconnected manganite and HTS.

Our next task therefore is to understand how the layers in the superconductor sandwich interact to produce this new behaviour. An important part of this pursuit is to understand the novel, and unusual, insulating state at zero magnetic field. For this we can gain much insight by measuring the optical properties.

### 3.2 Optical properties.

Fig. 2 shows the optical properties of the superconductor sandwich in zero magnetic field. The data are the real-part of the optical conductivity, $\sigma_1$, vs. the wavevector. The optical properties are characterized by the real-part of the optical conductivity – for various temperatures and from far-infrared light ($10$ cm$^{-1}$) through to visible light ($10,000+$ cm$^{-1}$). Also shown is the properties for the manganite by itself (blue and grey lines).

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6 At intermediate magnetic fields – half way through the transition from the resistive to zero-resistance state – there are pronounced intrinsic fluctuation effects. These lead to large jumps in the $R$ vs. $T$ curves, as seen for example in the data taken at a $3T$ magnetic field.

7 We know of only three other examples, and that our case involves unique physics to these [7].
wavenumber/energy of the light. The various peaks signify the absorption of light (at that energy) due to various physical processes: (i) inter-band transitions at high energy (around 10,000 cm\(^{-1}\)); (ii) vibrations of the solid in the ‘far infrared’ (the three peaks around 500 cm\(^{-1}\)); and (iii) the overall offset from zero \(\sigma_1\) signifies how conducting/insulating the solid is, the smaller the offset, the more insulating it is.

It is rather a fourth prominent feature that is most interesting to us here however. This is the large peak that occurs at low temperatures and low light energies around 10 cm\(^{-1}\). The evolution of this peak is highlighted in Fig. 3 which shows \(\sigma_1\) as well as the real-part of the dielectric function, \(\varepsilon_1\). As the peak in \(\sigma_1\) is getting larger at lower temperatures, there is a large downturn of \(\varepsilon_1\). These two observations tell us that a ‘condensation’ is occurring - electrons in the solid are moving from higher energy states into a low energy state that can absorb light at 10 cm\(^{-1}\). A similar process occurs in a conventional superconducting transition, except that in the conventional case no peak forms in \(\sigma_1\).

All these data can be understood as a transition into a superconducting state that is confined in space, as depicted in Fig. 4. The condensation is shown by the down-turn in \(\varepsilon_1\), the confinement by the peak in \(\sigma_1\) (at the risk of over-simplification). Because the superconducting state is confined, electrical current cannot flow from one end of the solid to the other. This results in the high-resistance state shown by the black curve of Fig. 1.

The open symbols in Fig. 3 show modelling of the data with an effective medium model. In this model, superconducting regions typical of YBCO are separated by vanishingly thin insulating regions (black lines in Fig. 4). The model describes the data well and helps to confirm our phenomenological understanding of this unusual zero-field insulating-state, but is too simple to help us understand its cause. For that, we now turn to a discussion of the wider data we have collected.

4. Discussion
Why do we have such unconventional properties in these superconductor sandwiches? The first indication is given by the sensitivity of the effects we see to the composition of the manganite. For example, in going from (Pr\textsubscript{0.5}La\textsubscript{0.2}Ca\textsubscript{0.3})MnO\textsubscript{3} to (La\textsubscript{0.7}Ca\textsubscript{0.3})MnO\textsubscript{3} these effects disappear. However, these unconventional properties remain in going from (Pr\textsubscript{0.5}La\textsubscript{0.2}Ca\textsubscript{0.3})MnO\textsubscript{3} to (Nd\textsubscript{0.7}Sr\textsubscript{0.1}Ca\textsubscript{0.2})MnO\textsubscript{3}, for example [7,8,10]. Clearly, the properties of the manganite layers play an important role and are interconnected with the properties of the YBCO superconductor.

By a process of elimination, the key property of the manganite causing our unconventional behaviour appears to be a charge-ordering [11]. This is where electronic charge accumulates in a pattern that is different to the pattern of the atoms. We have since observed robust charge-order in the manganite – and, particularly prominent charge-order in the YBCO of our superconductor sandwiches [12]. The layers thus appear to be interacting via charge-order. That the superconducting properties are also so radically altered by the charge-order, would thus show that the long-studied HTS superconducting state is in fact deeply intertwined with a charge-ordered state [7,13].

5. Outlook

We are continuing to develop the hypothesis laid out above to arrive at further testable predictions, and of course to carry out measurements to test them. Our approach of studying thin film-multilayers appears to be a fruitful way to further our understanding of high-temperature superconductivity – for example, in revealing a deep connection between charge-order and superconductivity. These hybrid, interconnected materials are also scientifically interesting in themselves and their tuneable, exotic properties may be useful in novel devices.

The science presented here can also be seen as part of strong track record of fundamental research into HTSs in New Zealand. This research has underpinned NZ’s world-leading work to industrialization HTSs. The science presented here might also be seen through the lens of interconnectedness discussed during the Kolleg. The whole is sometimes more than the sum of its parts as a result of complex interactions between those parts. In making our thin-film multilayers we have created solids which have richer physics and properties than the (already rich) properties of their constituent components.

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References


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8 Or, more correctly the ions – which are atoms with more or fewer electrons associated with them.
9 ‘Proximity effects’ between superconducting and non-superconducting materials can take various forms. Some more well-known examples include; (i) a superconducting state induced in the non-superconducting material, or (ii) the non-superconducting material can be used to ‘pin’ magnetic vorticies in the superconducting material. The ‘proximity effect’ we discuss here is qualitatively distinct from these previously observed cases.
DMY Sommerville, who worked in Wellington from 1915 to 1934, was one of the early pioneers of higher dimensional geometry. Here we examine one aspect of his work, the relationships between the numbers of faces of different dimensions of a polyhedron, and some recent developments on this topic.

A polyhedron is commonly understood to be a three-dimensional solid with flat polygonal faces and straight edges which meet at sharp corners or vertices. (We will only consider the case of convex bodies here. We refer the reader to [5] and [13] for the general theory, and their higher dimensional analogues.) They have of course been known since antiquity. There is some evidence that ancient Egyptians could calculate the volumes of pyramids. A more comprehensive study of geometry began in ancient Greece; this included the regular polyhedra, which we now call the Platonic solids.

Surprisingly, it was not until the eighteenth century that any relation between the number of faces of different dimensions was discovered. This is Euler’s relation, which asserts that

\[ v - e + f = 2, \]

where \( v \) denotes the number of vertices, \( e \) denotes the number of edges and \( f \) the number of (two-dimensional) faces of a given polyhedron.

It is easy to see that any polyhedron has at least four vertices; anything with fewer vertices would be at most two-dimensional. Stacking a shallow pyramid onto one face will give us a new polyhedron with exactly one more vertex; thus we obtain examples with any number of vertices higher than four. Likewise we must have \( f \geq 4 \), and slicing off a small section close to one vertex gives us a polyhedron with exactly one more face. Thus we obtain examples with any higher number of faces than four. This is not quite true for \( e \); there is no polyhedron with seven edges. A tetrahedron has six edges, and is the only polyhedron with either four vertices or four faces. Any other polyhedron must have at least five vertices and five faces, so Euler’s relation forces \( e \geq 8 \).

Early in the twentieth century, Steinitz [5, Sec. 10.3] characterised the possible values of \( v, e, f \) for which there is a polyhedron with \( v \) vertices, \( e \) edges and \( f \) faces. He showed that this is possible if, and only if, Euler’s relation is satisfied and \( 2e \geq 3v \). Necessity of the latter condition follows from the fact that every vertex belongs to at least three edges, whilst every edge contains exactly two vertices.

In general, Euler’s relation is the only relation between \( v, e, f \) which is satisfied by all polyhedra [5, Chap. 8]. However new relations emerge if we restrict our attention to particular classes of polyhedra.

Consider first the special case when every face is a triangle. Since any edge belongs to exactly two faces, this forces \( 2e = 3f \). Substituting into Euler’s relation then allows us to express any two of \( v, e \) and \( f \) in terms of the third: for such polyhedra \( e = 3v - 6 \) and \( f = 2v - 4 \).

Suppose instead that our polyhedron is simple, meaning that every vertex belongs to exactly three edges (or exactly three faces). Since any edge contains exactly two vertices, we see that \( 2e = 3v \). Manipulating Euler’s relation again, we can express \( e \) and...
\(v\) in terms of \(f\): \(v = 2f - 4\) and \(e = 3f - 6\).

Formally, a polyhedron can be defined as the convex hull of a finite set. Alternatively, a polyhedron can also be defined as a bounded set whose members \(x\) satisfy a system of linear inequalities \(Ax \leq b\), where \(A\) is a matrix with three columns, and \(b\) is a column vector with the same number of rows as \(A\) (this number must be at least \(f\)).

In the nineteenth century, it came to be realised that such definitions make sense in higher dimensions, and that there is genuine geometry beyond three dimensions. As Sommerville wrote in 1929: *It is scarcely necessary to apologise for writing a book on \(n\)-dimensional geometry* [12, Preface]. Accordingly, a polytope is now defined as the convex hull of a finite set in \(R^d\), for any \(d\). Equivalently, a polytope may also be defined as a bounded set whose members \(x\) satisfy a system of linear inequalities \(Ax \leq b\), where \(A\) and \(b\) are any matrix and column vector of appropriate size. The latter has particular applicability when we recognise it as the feasible region of a linear programming problem.

It is now conventional to denote the number of \(m\)-dimensional faces of a polytope \(P\) by \(f_m(P)\), or simply \(f_m\) if \(P\) is clear from the context. Thus \(f_0\) is the number of vertices, \(f_1\) is the number of edges, and so on. For a \(d\)-dimensional polytope, the only \(d\)-dimensional face is \(P\) itself, so \(f_d = 1\). We call the \(d\)-tuple \((f_0, f_1, f_2, f_3, \ldots, f_{d-1})\) the \(f\)-vector of a given polytope. For convenience, one also sets \(f_{-1} = 1\). Euler’s relation for three-dimensional polyhedra can then be written as \(f_0 - f_1 + f_2 - f_3 = 1\). It turns out that the corresponding result is also valid in all dimensions: for any \(d\)-dimensional polytope, the identity
\[
f_0 - f_1 + f_2 - f_3 + \cdots + (-1)^{d-1}f_{d-1} + (-1)^d f_d = 1
\]
always holds. This is called the Euler-Poincaré relation.

A proper face of a \(d\)-polytope has dimension at most \(d - 1\); any face with this maximal dimension is called a facet. As in three dimensions, any \(d\)-polytope must have at least \(d + 1\) vertices and at least \(d + 1\) facets; and for both, any value greater than \(d + 1\) is possible. A simplex is any \(d\)-polytope with exactly \(d + 1\) vertices (equivalently, with exactly \(d + 1\) facets). As before, there are gaps in the possible number of edges. In dimension four, a simplex has 10 edges, but no polytope has 11 or 12 edges. In dimension five, a simplex has 15 edges, but nothing has 16, 17 or 18 edges. We will discuss this in more detail shortly.

The aforementioned result of Steinitz thus characterises the ordered triples which can be \(f\)-vectors of three-dimensional polytopes. Extending this to higher dimensions remains a difficult problem. To this day, a complete characterisation of the \(f\)-vectors of four-dimensional polytopes remains unknown. Some substantial partial results are known. The set of all possible values of pairs \((f_0, f_1)\) of four-dimensional polytopes was determined by Grünbaum [5, Chap. 10]. An interesting feature of this is the gap at \((8, 17)\). That is to say, there is no four-dimensional polytope with eight vertices and 17 edges, although there are examples with \((f_0, f_1) = (7, 17), (8, 16)\) and \((8, 18)\), respectively. By duality, the set of all possible values of \((f_2, f_3)\) is also known. Grünbaum also determined all possible values of \((f_0, f_2)\). Later Barnette and Reay [2] determined all possible values of \((f_0, f_2)\), and by duality all possible values of \((f_1, f_3)\). Then Barnette [3] determined all possible values of \((f_1, f_2)\), completing our knowledge of the two-dimensional projections of \(f\)-vectors of 4-polytopes. Note that by the Euler-Poincaré relation, knowledge of any three components of the \(f\)-vector of a 4-polytope determines the entire \(f\)-vector.

Quite recently, all possible values of \((f_0, f_1)\) of 5-polytopes were determined, independently in [7] and [10].
In higher dimensions also, the Euler-Poincaré relation is the only relation between the components of the $f$-vector which is satisfied by all polytopes [5, Chap. 8]. Dehn [4] was the first to realise that, as in three dimensions, other relations emerge if we restrict our attention to particular classes. A $d$-polytope is called simple if every vertex belongs to exactly $d$ edges (equivalently, to exactly $d$ facets). It is called simplicial if every facet is a $(d - 1)$-dimensional simplex. Dehn noted that the $f$-vector of every four-dimensional simplicial polytope satisfies $f_2 = 2f_3$ and hence $f_3 = f_1 - f_0$. In five dimensions, he showed that the $f$-vector of every simplicial polytope satisfies the three identities

$$f_2 = 4f_1 - 10f_0 + 20, \quad f_3 = 5f_1 - 15f_0 + 30, \quad f_4 = 2f_1 - 6f_0 + 12.$$ 

In both dimensions, the numbers of vertices and edges alone determine the numbers of higher dimensional faces, for any simplicial polytope.

Sommerville established the corresponding results in higher dimensions [11]. In particular, the numbers of vertices, edges and 2-faces determine the numbers of higher dimensional faces of any simplicial polytope of dimension 6 or 7. The general result is as follows.

**Theorem 1.** For any $d$-dimensional simplicial polytope with $f$-vector $f$, and any $m$ in the range $-1, 0, \ldots, d - 2$, we have

$$f_m = \sum_{j=m}^{d-1} (-1)^{d-1+j} \binom{j+1}{m+1} f_j.$$ 

These results are now known as the Dehn-Sommerville equations.

Corresponding results for simple polytopes follow by duality. We will not say any more about relations between components of $f$-vectors. Instead we concentrate on the possible values that the $f$-vectors and their components can take, in particular on the restrictions placed on the other components by knowing the value of $f_0$.

Precise upper bounds for $f_m$ ($1 \leq m < d$), in terms of $f_0$, were obtained in 1970 by McMullen and Shephard. (See [13, Chap. 8].) They showed that for every $m$, the upper bound for $f_m$ is attained by the so called cyclic polytope [5, §4.7] with the appropriate number of vertices. Since cyclic polytopes are simplicial, the upper bound question for general polytopes has the same solution as the upper bound question for simplicial polytopes.

Barnette [1] established precise lower bounds for simplicial polytopes. For the case $m = 1$, he showed that any simplicial $d$-polytope with $v$ vertices has at least $dv - \binom{d+1}{2}$ edges, and that there exist simplicial polytopes, namely the stacked polytopes, with precisely this many edges. Kalai’s Rigidity Theorem [6] asserts that this lower bound is still correct under the weaker assumption that every two-dimensional face is a triangle. But until recently little was known about lower bounds for non-simplicial polytopes.

We now present some new results about such lower bounds for general polytopes. Mostly we consider the issue of determining $f_1$ in terms of $f_0$. It is of course interesting also to bound the values of $f_m$ for $2 \leq m < d$. We discuss this at the end of the paper.

For convenience, we denote by $E(v,d)$ the set of numbers $\{e :$ there is a $d$-polytope with $v$ vertices and $e$ edges$, \}$, and define, following Grünbaum’s notation [5, p 184],

$$\phi(v, d) = \binom{d+1}{2} + \binom{d}{2} - \binom{2d+1 - v}{2} = \binom{v}{2} - 2 \binom{v-d}{2}.$$ 

91
Grünebaum conjectured [5, p 183] that $\phi(v, d) = \min E(v, d)$ for $d < v \leq 2d$, and proved it in the cases $d < v \leq d + 4$.

This has recently been proved in full, i.e., for all $v \leq 2d$ [9, Theorem 7], as has the corresponding result for $2d + 1$ vertices.

**Theorem 2.** Let $P$ be a $d$-dimensional polytope with $v \leq 2d$ vertices. Then $P$ has at least $\phi(v, d)$ edges, and there is a unique polytope with $v$ vertices and precisely $\phi(v, d)$ edges. Furthermore, $\min E(2d + 1, d) = d^2 + d − 1$ for every $d \neq 4$, and the polytope with this minimal number of edges is unique when $d \geq 5$.

**Sketch proof.** For $v \leq 2d$, the proof proceeds by induction on $d$. Let $F$ be any facet of $P$, put $v = d + k$, where $k \leq d$, and let $n$ be the number of vertices in $P \setminus F$. If $n = 1$, then $P$ is a pyramid over $F$, and we apply the obvious identity $f_1(P) = f_1(F) + f_0(F)$. Otherwise, we apply the non-obvious but easily verified identity

$$\phi(d + k − n, d − 1) + nd - \binom{n}{2} = \phi(d + k, d) + (k − n)(n − 2).$$

This establishes the lower bound, since $(k − n)(n − 2) \geq 0$, and there are at least $nd - \binom{n}{2}$ edges in $P$ which are not contained in $F$.

The uniqueness statement requires more work, whose details we omit. Let us just mention that for $v = 2d$, the minimising polytope is the prism, which can be realised as the convex hull of two congruent $(d − 1)$-dimensional simplices, lying in parallel hyperplanes. And when $v = d + k$, with $k < d$, the minimising polytope is a $k$-fold pyramid over a $(d − k)$-dimensional prism.

The case $v = 2d + 1$ was established in [9, §4], with a longer argument. It was well known in the cases $d = 2$ or $3$, and Grünebaum [5, p 193] noted that $\min E(9, 4) = 18$.

Precise upper bounds for the numbers of edges are easier to obtain. Steinitz’ result ensures that $\max E(v, 3) = 3v − 6$, and in higher dimensions the cyclic polytopes show that $\max E(v, d) = \binom{v}{2}$.

Having evaluated $\min E(v, d)$ and $\max E(v, d)$, at least for $v \leq 2d + 1$, we could be more ambitious and attempt to determine $E(v, d)$ exactly, not just its maximum and minimum. Is it an entire interval of integers or are there gaps?

For $v = d + 1$, the only polytope to consider is the simplex, so $E(d + 1, d) = \{\binom{d + 1}{2}\}$.

For $v = d + 2$, the situation is described in detail by Grünebaum [5, §6.1]. It is easy to check that $E(5, 3) = [8, 9]$. For $d \geq 4$, we have $\binom{v}{2} − \min E(d + 2, d) = 2 \binom{v − d}{2} = 2$, so there are three feasible values for $e$, and there exist polytopes exemplifying each one. Thus $E(d + 2, d)$ is a complete interval.

For $d = 3$, Steinitz essentially proved that $E(6, 3) = [9, 12]$. For $d \geq 4$, if $k$ is an integer between $d − 3$ and $d + 3$, it is not hard to find a $(d − 3)$-fold pyramid over a three- dimensional polyhedron which has $d + 3$ vertices and $k + \frac{3}{2}d(d + 3)$ edges. Thus $E(d + 3, d)$ is also a complete interval.

However $E(d + 4, d)$ is not a complete interval, because the value $\phi(d + 4, d) + 1$ is absent when $d \geq 4$ [9, Theorem 20]. This is the only gap, and in fact

$$E(d + 4, d) = \{\phi(d + 4, d)\} \cup \left[\phi(d + 4, d) + 2, \binom{d + 4}{2}\right]$$
whenever \( d \geq 4 \). Likewise, \( E(d + 5, d) \) has a single gap, when \( d \geq 5 \):

\[
E(d + 5, d) = \{\phi(d + 5, d)\} \cup \left[\phi(d + 5, d) + 2, \left(\frac{d + 5}{2}\right)\right].
\]

For a larger number of vertices, these gaps get longer [9, Theorem 19].

**Theorem 3.** If \( 5 \leq k \leq d \), then a \( d \)-polytope with \( v = d + k \) vertices, and with more than the minimum number \( \phi(v, d) \) of edges, must have at least \( \phi(v, d) + k - 3 \) edges.

As a simple application of these results, we show that there is no ten-dimensional polytope with 80 edges. When \( d = 10 \) and \( v \leq 20 \), we have \( \phi(v, 10) = 100 - \frac{1}{2}(21 - v)(20 - v) \). Thus any polytope with 15 or more vertices has at least \( \phi(15, 10) = 85 \) edges. A polytope with 13 or fewer vertices can have at most 78 edges. Since \( \phi(14, 10) + 1 = 80 \), no polytope with 14 vertices can have 80 edges either. However all numbers close to 80 can be realised, since \( E(13, 10) \cup E(14, 10) \cup E(15, 10) = [70, 79] \cup [81, 105] \).

The following encapsulates what we know about gaps between the sets \( E(v, d) \) and \( E(v + 1, d) \) [9, Proposition 21].

**Theorem 4.** If \( d = n^2 - j \), where \( 1 \leq j \leq n - 4 \), then there is no \( d \)-polytope with between \( \phi(d + n + 1, d) + j + 1 \) and \( \phi(d + n + 1, d) + n - 3 \) edges.

We finish with the promised remarks about higher dimensional faces. The function \( \phi \) was actually called \( \phi_1 \) in [5]. More generally, Grünbaum defined a function

\[
\phi_m(v, d) = \left(\frac{d + 1}{m + 1}\right) + \left(\frac{d}{m + 1}\right) - \left(\frac{2d + 1 - v}{m + 1}\right)
\]

for each \( m \leq d \), and conjectured that this is equal to the minimum of \( \{f_m(P) : P \text{ is a } d - \text{polytope with } v \text{ vertices}\} \), if \( v \leq 2d \). He proved this in the case \( v \leq d + 4 \), which includes the case \( d = 4 \). In [9, §6], it is proved that Grünbaum’s conjecture holds under the additional assumption \( m^2 + dm - (d - 1)^2 > 0 \).

We now illustrate some ad hoc arguments which confirm Grünbaum’s conjecture in dimension five as well. We need only consider the case \( v > d + 4 \), i.e., \( d = 5 \) and \( v = 10 \). So let \( P \) be a five-dimensional polytope with 10 vertices, \( f_1 \) edges, \( f_2 \) two-dimensional faces, \( f_3 \) ridges (three-dimensional faces) and \( f_4 \) facets. Theorem 2 gives the desired conclusion for \( f_1 \), and the inequality \( m^2 + 5m - 16 > 0 \) ensures it for \( f_3 \) and \( f_4 \). So we are left with the case \( m = 2 \), i.e., we need to show that \( f_2 \geq \phi_2(10, 5) = 30 \). The unique minimiser for \( f_1 \) given by Theorem 2 is the prism, which has \( f_2 = 30 \). If \( P \) is not a prism, Theorem 3 tells us that \( f_1 \geq 27 \). We now consider three cases, depending on how many facets \( P \) has.

The case \( f_4 \leq 6 \) is easily dismissed; any such five-dimensional polytope must be a simplex, which has only 6 vertices. If \( f_4 = 7 \), we use the characterisation of \( d \)-polytopes with \( d + 2 \) facets enunciated by McMullen [8, p 352]. This is dual to the characterisation of polytopes with \( d + 2 \) vertices mentioned earlier. When \( d = 5 \) and \( v = 10 \), it ensures that \( P \) is a pyramid over the Minkowski sum of two triangles, and a straightforward enumeration gives \( f_2 = 33 \).

Now assume \( f_4 \geq 8 \). The Euler-Poincaré relation guarantees \( f_1 + f_3 = f_2 + f_4 + 8 \). Since every facet contains at least two ridges, and every ridge belongs to exactly two facets, we must have \( 5f_4 \leq 2f_3 \). It follows that
\[ f_2 = (f_1 - 8) + (f_3 - f_4) \geq 19 + 1.5f_4 \geq 31 > \phi_2(10,5), \]

as required.

To date, the smallest cases of Grünbaum’s conjecture which remain unresolved are \( d = 6, m = 2 \) and \( v = 11 \) or 12.

References
14. Observations of Environmental Changes in the Antarctic Region

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In different ways, “colonial settlement” and “global warming” have had quite different consequences for the Antarctic environment. Some of these consequences are discussed. Measures taken in recent years to restore the environment in both the Antarctic and Sub-Antarctic-island regions are outlined. Unfortunately, the ongoing adverse effects of “global warming” on the continent and its surrounding waters, continue and details of this are illustrated.

1. Introduction

The Antarctic region which includes both the continent itself as well as the Sub-Antarctic islands, the maintenance for which nowadays various countries carry the responsibility, has suffered during the last two centuries as the result of “colonial” exploration. But more recently, it has come to be realised that the wildlife of the region is threatened on account of the effects of global warming. This paper discusses some aspects of these changes which are proving to be detrimental to the Antarctic region.

2. Exploration in the Antarctic Region

For centuries there was a belief that a vast continent existed in the far south of the globe to “balance” the known northern lands of Europe, Asia and North Africa [1]. While many early explorers ventured south of the Equator, it was Captain James Cook in the Resolution, a vessel of 462 tons, accompanied by Captain Tobias Furneaux in the Adventure (336 tons), who were the first to cross the Antarctic Circle, reaching 67°15’ S by 39°35’ E, on 17th January, 1773, before being stopped by ice. Cook again crossed the Antarctic Circle on 20th December, 1773 and for a third time, reaching 71°10’ S by 106°54’ W, on 30th January, 1774. From these most southerly journeys ever accomplished at the time, Cook convinced himself that “if land lay farther south, it was practically inaccessible and of no economic value.” [2].

If only Cook’s observations and reports had been taken seriously! Many expeditions throughout the 19th Century were motivated by economic gain, with sealers and whalers from
Europe and America slaughtering thousands of animals for furs and oil (Fig. 1). Much exploration to the region had as its primary goal, the discovery of further islands, populated by seal and penguin communities which were then slaughtered almost to extinction [4].

3. “Colonization” and its Adverse Effects

During the mid-19th Century, there was an attempt to establish a settlement at Port Ross, Auckland Island by the Southern Whale Fishing Company, a British Company with business interests in agriculture and fishing, mainly whaling [5]. The company was granted a Royal Charter with founder, Charles Enderby appointed as the resident Chief Commissioner and Lieutenant Governor of the new colony. The settlement began in December, 1849, with the colonists arriving in three ships, into Erebus Cove, Port Ross. In January, 1850 the settlement was officially named Hardwicke, after the Earl of Hardwicke, the Governor of the British Company. Attempts were made to grow crops and to farm livestock but the poor quality soils and harsh climate, together with the difficulties of mustering livestock on account of the dense undergrowth, lead to a complete failure of the venture. Whaling was also attempted but this too proved to be a disaster. The settlement was abandoned in August, 1852 and all that remains of this colonization attempt is a cemetery where Hardwicke was established, (Fig. 2).

But subsequent slaughter of wildlife by other colonialists continued. For example, Fig. 3 shows the remains of a steam digester used to extract oil from King and Royal Penguins (Aptenodytes patagonicus and Eudyptes schlegeli, respectively) herded like sheep into pens as they returned from their fishing at seas on Macquarie Island. As many as 150,000 birds were slaughtered per season [6].

Sealers landing on formerly pristine islands brought with them predators of the native birds and animals, most notably rats and cats, so that by the 20th Century, many native populations of the Antarctic region were declining. Human impacts on the region have been summarised as follows [7]:

- harvesting some Antarctic species to the verge of extinction for economic benefit;
- killing and disturbing other species;
- contaminating soils; and
- discharging sewage to the sea and leaving rubbish, cairns and tracks in even the most remote parts.
4. Changing Attitudes

The 20th Century brought a change of attitudes towards the Antarctic region with, for example, the establishment of the Commission for the Preservation of Antarctic Marine Living Resources (CCAMLR) in 1982 [8]. Countries who share the region have begun to focus on preservation rather than destruction. Led partly by initiatives of the New Zealand Department of Conservation (DOC), Sub-Antarctic islands (e.g., Campbell Island) have been cleared of all ferals (cats and rats) as the result of most enlightened poisoning programmes using aerially dropped rat baits (120 tonnes in all), targeting the most remote cliffs and ridges (Fig. 4).

Two quite amazing consequences for the wildlife of Campbell Island followed this programme. Firstly, the Campbell Island Teal which has been shown to be a distinct species, *Anas nesiots* [10] and once thought to have become extinct, was initially found on Dent Island in 1972. Following a captive breeding programme on Codfish Island, New Zealand, birds were released back on to Campbell Island from 2004 to 2006 [9], where they are now surviving in the wild (Fig. 5). Secondly, the Campbell Island Snipe (*Oenocorypha aucklandica perseverance*) (Fig. 6), also thought to have become extinct, was found on Jacquemart Island in 1997, and this bird has since recolonised the main island although precisely how this flightless bird found its way across to Campbell Island from Jacquemart Island remains a mystery.

A quite separate eradication programme involving the removal of rabbits, rats and mice from Macquarie Island by the Australian Antarctic Division [11], has resulted in the return of this island to something like its original condition, with seals and birds flourishing (Figs. 7 and 8).
and 8) and original vegetation, such as tussock and Macquarie Island cabbage plants, re-establishing themselves on degraded areas of the landscape [11].

5. Global Warming

Global warming is most obvious in the Antarctic region from the behaviour of glaciers and the occasional formation of extensive crevices in the ice shelf, as, for example, occurred in the Larsen C ice shelf in December, 2016 [12]. Ironically, one consequence of this is the decrease in salinity of the seas surrounding the Antarctic continent [13] and therefore an increase in the freezing point of Antarctic waters.

The most noticeable effect of this on the Antarctic environment is an increase in the extent of sea ice, even during mid-summer, which was felt most seriously during the 2013 Australian Scientific Expedition to East Antarctica [14] when the small Russian ice breaker, Akademik Shokalskiy, became trapped in pack ice, leading to an extensive international rescue of its occupants. More recently, during a tourist expedition, also on the Akademik Shokalskiy, in which the author and his wife were participants, entitled “In the Wake of Mawson” [15], one aim of which was to make a zodiac landing in Commonwealth Bay and to hike to Mawson’s Hut, it proved impossible to approach Commonwealth Bay on account of the extent of the ice. Indeed, the nearest to the continent itself that this particular expedition came, was about 60 km off the continent near Davis Bay, at which point the Akademik Shokalskiy could go no further.

A more serious problem which is a direct result of the more extensive sea-ice cover, from the point of view of Antarctic wildlife, is the plight of the Adelie penguin (Pygoscelis adelie) which has a large colony near France’s Dumont d’Urville research station in East Antarctica. The extent of the sea-ice in the region means that adults must travel much further to fish for food, leaving eggs or chicks to the predators or surviving chicks to starve. Indeed, in this region during January, 2017, amongst the 18,000 pairs of Adelie penguins near the French research station, only two chicks survived the season. Four years earlier, about 20,200 pairs produced no surviving chicks [16].

6. Conclusions

There is no doubt that following the eradication programmes on the sub-Antarctic islands, the environmental changes in the region are for the better. Unfortunately, there remain adverse effects on wildlife as a consequence of global warming.

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15. Tribute to Dr Heinrich Pfeiffer

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This article pays tribute to Dr Heinrich Pfeiffer (1927-2016), long-standing Secretary General of the Alexander von Humboldt Foundation. He played a pivotal role in setting up the Alexander von Humboldt Foundation’s links with Australia and New Zealand.

1. Introduction

Dr Heinrich Pfeiffer, who was born on 27 January, 1927 and died on 22 December, 2016, was Secretary General of the Alexander von Humboldt Foundation (Alexander von Humboldt-Stiftung) for 38 years (Fig. 1). He commenced this role in 1956, just three years after the post-World War II re-founding of the Stiftung. Over this period, he had a profound impact on the development of the Alexander von Humboldt Foundation as we know it today, and on its standing both in Germany and internationally. From 1964 Dr Pfeiffer was also the Stiftung’s Managing Director. Following his retirement in 1994, he continued to be actively involved in the Foundation as an Honorary Member of its Board of Trustees until his death at the age of 89 years.

2. Fellows’ Tributes to Dr Pfeiffer

The June 2017 Humboldt Conference Limits of Knowledge in Krakow was held in memory of Dr Pfeiffer. Originally, he was to have attended as part of the celebrations for his ninetieth birthday. The Australian Association of von Humboldt Fellows was pleased that two of its members were able to attend the Krakow conference, Professor Hans-Albert Bachor AM FAA and Dr Michael Hall. In particular, Dr Hall had the opportunity to preface his conference paper on the limits of knowledge in quantum mechanics with remarks recalling the truly outstanding support that Dr Pfeiffer gave to Australian scholars and Australian-German initiatives. When the members of the Australian Association were informed of the sad news of Dr Pfeiffer’s death in early 2017, the Association received messages of tribute – Dr Pfeiffer is remembered ‘down under’ and in New Zealand with affection and warmth and deep gratitude. He was an outstanding ambassador for the Alexander von Humboldt Foundation and for his country.

One colleague wrote, “Dr Pfeiffer dedicated many years to the welfare of the Alexander von Humboldt Foundation and will be fondly remembered”. Another Humboldtian noted, “He was always easy to talk to and helpful with advice”. A further tribute included, “He was a wonderful energetic invigorating person”. Others recalled his presence at Humboldt Foundation meetings in Australia or the visit in the year of his retirement as Secretary General.
of the *Stiftung*, when Monash University presented him with an honorary doctorate. This was one of many such awards that he received (Fig. 2).

3. **Monash University’s Honorary Doctorate**

In its citation for the degree of Doctor of Laws *honoris causa*, Monash University paid tribute to Dr Pfeiffer’s “tireless engagement” saying, “it is difficult to imagine the Humboldt Foundation without Dr Pfeiffer. It is thanks to him above all that the Foundation, despite its many and varied activities …, has never become an anonymous administrative machine. Dr Pfeiffer’s warm personal involvement, his willingness to help whenever difficulties arise, embody in the very best sense the Humboldt Foundation’s commitment to the personal and individual sponsorship of its research fellows, as the members of the worldwide ‘Humboldt family’ can testify”. Those who knew Dr Pfeiffer would concur wholeheartedly.

The University’s doctoral citation continued: “Dr Pfeiffer has done more than any other single person in Germany to further and strengthen international academic cooperation and research. In honouring him … we honour his life’s work, not only as Secretary General of the Alexander von Humboldt Foundation but equally as a good European and citizen of the world” [1].

In his response as he delivered the graduation address, Dr Pfeiffer said that the award was “a recognition of the achievements of all the co-workers, friends and supporters of the Alexander von Humboldt Foundation”. He continued, “By serving, not by reigning … I have fostered the academic cause. I have tried to do what is helpful to sponsor scholars on an individual basis” [2].

On the occasion of the Monash University honorary doctorate, the Australian Association of von Humboldt Fellows arranged a dinner after the graduation ceremony and, by chance, the private dining room where the Fellows gathered with the guest of honour had wallpaper in the distinctive green then adopted by the *Stiftung*. Dr Pfeiffer was very impressed indeed and reluctant to accept it was a coincidence.

4. **Dr Pfeiffer’s Personal Interest in Humboldtians**

Australian Association Fellow Dr Paul Lennox was awarded a Ludwig Leichhardt Fellowship by the *Stiftung* – this award symbolises in a special way the bonds of friendship between Australia and Germany. It was granted to Dr Lennox as an Australian geologist, with geology a field to which Leichhardt also contributed. Dr Lennox recounts that Dr Pfeiffer queried him about Leichhardt when they first met about 1991 in Frankfurt. This prompted Dr Lennox to research the story of Leichhardt and his scientific explorations and, at subsequent meetings, Dr Pfeiffer followed with interest Dr Lennox’s research both in geology and into Leichhardt. Further, when Dr Pfeiffer visited the University of New South Wales in the presence of a Nobel Laureate, Dr Lennox made a bee-line to Dr Pfeiffer and not to his companion which bemused the Nobel Laureate! Dr Lennox wrote on hearing of Dr Pfeiffer’s
death that he had been touched by Dr Pfeiffer’s personal interest in him, despite the hundreds of fellows dealt with over the years, and noted in his tribute, “That takes a special ability”.

5. German Tributes to Dr Pfeiffer

   Stiftung President Professor Helmut Schwarz (Fig. 3), in a memorial address in January 2017, described Dr Pfeiffer as a “bridge-builder”. He said, “Heinrich Pfeiffer’s countless acts of support and friendship are legendary; they were founded on a cosmopolitan attitude that has become rare, on respect for foreign cultures, on an almost insatiable curiosity about people, that is, on all the virtues that the young Alexander von Humboldt described in the words: ‘Friendship is a language spoken by the heart.’” In his address, Professor Schwarz recalled that Walter Scheel, who was Bundespräsident when I had my Fellow’s visit to Villa Hammerschmidt in Bonn, referred affectionately to Dr Pfeiffer as “Mr Humboldt” [3].

When the Stiftung informed the Humboldt family of Dr Pfeiffer’s death last December, its accolade included the following, “Under Dr Pfeiffer’s leadership, the Foundation developed into one of the most recognised organisations in the area of German cultural relations and education policy. Heinrich Pfeiffer built up a network of trust among the individuals sponsored and supported by the Foundation. This network has made major contributions to international understanding and continues to shape the Foundation to this very day. The deep attachment felt by our alumni throughout the world, with whom he maintained diverse relations and friendships right up to his death, has clearly manifested itself time and again ... and has served to enhance the Foundation's standing around the world. The Alexander von Humboldt Foundation is profoundly grateful to Dr Heinrich Pfeiffer for his many years of service which he rendered with heart and soul” [4]. That is just how so many Australian and New Zealand Fellows remember him.

6. Preparing to be General Secretary
What perhaps is less known about Dr Pfeiffer is his personal history prior to joining the Alexander von Humboldt Foundation. Dr Pfeiffer was conscripted towards the end of World War II and trained as a pilot. Following his release from a prisoner of war camp, he completed studies in philosophy, history and education, and a doctorate in philosophy. He spent some years in school and higher education teaching before taking a position in the German section of the Fulbright Commission, which was giving scholarships to German students to go to America. From here, he was recruited to the Alexander von Humboldt Foundation – thus began his life’s work.

7. Conclusion
At the time of Dr Pfeiffer’s retirement, the German newspaper, Die Zeit, published an article entitled ‘Eine Erfolgsgeschichte des Wissenschaftsmanagers Heinrich Pfeiffer: Humboldts Seele’ – ‘The Success Story of Academic Manager Heinrich Pfeiffer: Humboldt’s Soul’ [5]. Here he is acknowledged for acquiring the Stiftung’s grounds, buildings and monies – this acknowledgment sounds better in the original German with the alliteration of “Grundstücke, Gebäude und Geld”! Commenting on a certain mischieviness of Dr Pfeiffer and the arching of his bushy eyebrows during the interview, Die Zeit recounts that he was not yet 30 years old, when he started “his life’s work”. Dr Pfeiffer stated himself during the interview, “I was given a field, uncultivated and without weeds”. This, he transformed into a flourishing garden where scientists and scholars, irrespective of academic discipline and nationality, could undertake research through international exchanges, advancing knowledge, understanding and cultural development, crossing borders and ideologies, and establishing a worldwide network of Humboldtians.

As Australian and New Zealand Alexander von Humboldt Fellows, we expressed our profound gratitude to Dr Pfeiffer in Wellington at the closing of the 2017 biennial colloquium of our Associations – this article records that poignant moment. Vale Heinrich Pfeiffer!

Acknowledgments
This article is adapted from a tribute that I paid to Dr Pfeiffer at the biennial meeting of the Australian and New Zealand Associations of von Humboldt Fellows in Wellington on 19 November 2017. I am grateful to the Alexander von Humboldt Foundation for access to the resources and photographs which underpin this article.

References
Biographical Notes of Presenting Authors

Christopher M. Kellett received the Bachelor of Science in Electrical Engineering and Mathematics from the University of California, Riverside in 1997 and the Master of Science and Doctor of Philosophy in Electrical and Computer Engineering from the University of California, Santa Barbara in 2000 and 2002, respectively. He subsequently held research positions with the Centre Automatique et Systèmes at École des Mines de Paris (France), the Department of Electrical and Electronic Engineering at the University of Melbourne (Australia), and the Hamilton Institute at the National University of Ireland, Maynooth. Since 2006, he has been with the School of Electrical Engineering and Computing at the University of Newcastle, Australia, where he is currently a Professor.

Professor Kellett is an Associate Editor for IEEE Transactions on Automatic Control, IEEE CSS Letters, the European Journal on Control, and Mathematics of Control, Signals and Systems. He has been the recipient of an Australian Research Council Future Fellowship (2011-2015), an Alexander von Humboldt Research Fellowship (2012-2013), the 2012 IET Control Theory and its Applications Premium Award, and the inaugural IFAC Foundation Award (2017). Professor Kellett’s research interests are broadly in the area of systems and control theory and applications, with specific emphases on stability and robustness properties for nonlinear systems, high speed model predictive control, applications in electricity distribution networks, and applications in social systems such as carbon pricing.

Jeroen Schillewaert M.Sc Eng (2003), M.Sc. Math (2005), Ph.D. (2009) (all at Ghent University Belgium), was a Postdoctoral Fellow at the University of Canterbury, NZ (2009-2010), then Visiting Assistant Professor in Brussels (2010-2012). In this period, he was awarded an Oberwolfach Leibniz Fellowship and then joined the University of California at San Diego as a Visiting Assistant Professor (2012-2013). Upon winning a Marie Curie Intra European Fellowship he moved to Imperial College London (2013-2015). At the end of his period there he took up a von Humboldt Fellowship to work at the University of Münster (Germany, 2015). After a brief period as a foreign exchange quant at Goldman Sachs London, he is now a Lecturer at the University of Auckland since March 2017.

Peng Du B.E. (Hons), Ph.D. (University of Auckland) is a Senior Lecturer at the Department of Engineering Science and Auckland Bioengineering Institute at the University of Auckland, New Zealand. The focus of his research is on experimental recording and mathematical modelling of gastrointestinal electrophysiology. In particular, he is interested in using experimental data to reinforce multi-scale simulations of gastrointestinal electrophysiology. He is also collaborating with the Fraunhofer Institute IZM in Berlin on developing the next generation of high-resolution recording electrodes. In 2012 Peng won the Vice Chancellor's Prize for Best Doctoral Thesis. Later that year, Peng was awarded a Marsden Fast Start Grant, and a Rutherford Foundation NZ Post-doctoral Fellowship. In 2013, he received a University of Auckland Early Career Excellence Award. In 2015, he was awarded one of the prestigious Rutherford Discovery Fellowships.

David Eccles B.Sc., Bbmed.Sc. (Hons), Ph.D. (VUW), began his post-doctoral research career as a Computational Biologist for Next-Generation Sequencing at the Max-Planck-Institut für molekulare Biomedizin, Münster, Germany. He returned to New Zealand in 2012 and is currently working as a freelance bioinformatician and Postdoctoral Fellow at the Malaghan Institute of Medical Research, Wellington, New Zealand. In 2014 he became part of the first wave of 150 research labs to try out a new sequencing technology, the Oxford
Nanopore MinION, and has been trying to encourage other researchers to use long-read “observational” sequencing ever since. He is an advocate for free and open source software (FOSS) and open research practices, aiming to help create a society where the sharing of technology, ideas, and knowledge is a universally accepted practice. Doctor Eccles’ current work includes mitochondrial cDNA-Seq, 3D printing, plasmid sequencing, and river water metagenomic analysis. He is a father of three German-speaking children, an Early Career Researcher member of the Royal Society Te Apārangi, and an eLife Ambassador for open science, transparency and bioethics.

**Anna-Sophie Jürgens** Dr. phil. (LMU Munich), Magister (LMU Munich), is a Feodor Lynen Postdoctoral Fellow (Humboldt Foundation) at the Humanities Research Centre of the Australian National University (2017-2019). She studied Comparative Literature, Russian and French Philology in Munich, Germany, and St. Petersburg, Russia, and wrote her dissertation (published as a monograph in 2016) on circus in (Australian) fiction. She was awarded both an undergraduate and a Ph.D. scholarship from the German National Merit Foundation (Studienstiftung des deutschen Volkes) and in 2017 was honoured with a Fellowship by the National Library of Australia, supporting her postdoctoral project on the representations and dynamics of scientists in Australian fiction. Dr Jürgens’ interests in scholarship include the aesthetics and poetologies of knowledge, science in fiction, especially fictional non- and conscientists, modern and contemporary circus fiction, and the history of (violent) clowns. In 2018 she organised the conference “Imagineers in Circus & Science”, ANU’s first interdisciplinary conference on the relationships between scientific research and creative imagination. More information about her monograph, edited collections, book chapters & papers, as well as circus and art projects can be found on academia.edu: [https://anu-au.academia.edu/AnnaSophieJ%C3%BCrgens/](https://anu-au.academia.edu/AnnaSophieJ%C3%BCrgens/).

**Allan H. Bretag** B.Sc. (Hons), Ph.D. (Adelaide) was a Postdoctoral Fellow at the I. Physiologishes Institut der Universität des Saarlandes in Homburg/Saar, Germany in 1972-1973, supported by the Alexander von Humboldt-Stiftung. To undertake his Fellowship he took Leave-of-Absence from a Physiology Lectureship in the School of Pharmacy at the South Australian Institute of Technology (SAIT) begun in 1970. Following his return, he continued at SAIT (from 1990, the University of South Australia) until his retirement in 2005. On Sabbatical Leave in 1977-1978, he worked at the Claude Bernard University in Lyon, France, Cambridge University, UK, and Cincinnati University, USA. He was appointed Honorary Visiting Research Fellow in the Physiology Department at The University of Adelaide from 1988 to 2007. His community contributions have included membership of numerous state, national and international Committees and Boards involved with Neuromuscular and Neurological Disorders. He was President of the Muscular Dystrophy Association of South Australia from 1975-1985 (continuing as its Director of Research), President of the IXth International Congress on Neuromuscular Diseases (Adelaide, 1998), President of the World Alliance of Neuromuscular Disorder Association (The Hague) from 2007-2015 and is a Member of the Executive Board of the Asian and Oceanian Myology Center (Tokyo). Professor Bretag’s research interests range from chloride ion channels in cell membranes, through muscle diseases to the history of science. He remains an Adjunct Professor in the School of Pharmacy and Medical Sciences at the University of South Australia and is a Distinguished Fellow of the Australian Association of von Humboldt Fellows.

**Zoya Ignatova**, M.Sc. and Ph.D. (Univ. Hamburg Germany), was a Postdoctoral Fellow with Lila Gierasch at the University of Massachusetts, Amherst, USA from 2003-2005. Upon her
return to Germany, she took a group leader position at the Max Planck Institute of Biochemistry in Martinsried by Munich. In 2008 she took a position as a Professor in Biochemistry (W2) and moved to the University of Potsdam. In 2015 she ‘returned’ to Hamburg, taking the position of Professor in Biochemistry and Molecular Biology (W3) at the University of Hamburg. She is also currently a Managing Director of the Institute of Biochemistry and Molecular Biology.

Glen Wheeler B.Compt.Sc., B.Math.(Adv) (Hons) with Distinction, Ph.D. (2010, UoW), was a Deutscherakademischeraustauschdienst (DAAD) Fellow and Alexander-von-Humboldt (AvH) Fellow at the Freie Universität Berlin and Otto-von-Geuricke Universität Magdeburg from 2008-2012. Returning to Australia in December 2012, he has been based for six years at the University of Wollongong and is currently on a continuing Lecturer appointment. During this time he has held a variety of Visiting Fellow positions, including at the Max Planck Institut Golm, the ETH Zürich, MSC Tsinghua, Stanford, and the Korea Institute for Advanced Study. Dr Wheeler’s research interests centre around geometric partial differential equations, with in particular pioneering work in higher-order curvature flow. He has attained competitive grant funding of various forms, including an ARC Discovery Project, and has in 2017 been presented with the biennial Peter Schwerdtfeger Award by the Australian Association of Alexander von Humboldt Fellows.

Motohide Miyahara B.A. (Ritsumeikan), M.Ed. (Tokyo), M.A. (Antioch), M.S. (UCLA), Ph.D. (UCLA), was a Postdoctoral Fellow at the Free University Berlin, Germany from 1994-95 with the Alexander von Humboldt-Stiftung. He conducted a research project to investigate co-occurring developmental disorders of hyperactivity and motor incoordination in children. During the fellowship he assisted a host professor who organised an international conference and at the conference he met a professor from the University of Otago in New Zealand who later offered him a lectureship. Since 1996 he has been working in the School of Physical Education, Sport and Exercise Sciences in the University of Otago, teaching the courses related to lifespan human development and disability, while running the Movement Development Clinic, a teaching and research laboratory where university students learn to teach children with unique learning needs. In 2002, he took advantage of his sabbatical leave and worked for collaborative research projects on children with attention deficit hyperactivity disorder at the University of Western Australia and Curtin University of Technology. In 2006 he was nominated as a Gambrinus Scholar at the University of Dortmund, Germany, and engaged in teaching and research and a university-wide lecture. In 2009 and 2014, he spent sabbatical leaves at the National Institute of Physiological Science in Japan where he learned to conduct neuroimaging research, using functional magnetic resonance imaging in neuroscience studies. Since 2013 he has been investigating the behavioural and neural mechanism of empathy and prosocial behavior in the context of disability and accessibility.

Niranchan Paskaranandavadiel B.E., M.E. (First Class Hons), Ph.D., (University of Auckland), is a Research Fellow at the Gastrointestinal Motility Research Group at the Auckland Bioengineering Institute and Department of Surgery at the University of Auckland. He is a member of Institute of Electrical and Electronics Engineers, Australasian Neurogastroenterology and Motility Association, and American Physiological Society. His research goal is to develop novel and innovative experimental techniques to understand electrical disorders in the gut, which will aid in the development of innovative therapies and healthcare technologies that will augment patient care and treatment.
Benjamin P.P. Mallett  B.Sc. (Hons), Ph.D. (Victoria University of Wellington), was awarded the Swiss Government Excellence Scholarship to undertake postdoctoral research at Fribourg University in 2013. In 2016 he returned to New Zealand and is currently a Rutherford Postdoctoral Research Fellow at the University of Auckland, and based in the Photon Factory there. Ben Mallett’s research interests orbit around novel physics in solids and using spectroscopy to understand it. He enjoys working in collaboration with scientists across the country and across the world, and looks forward to a future sabbatical in Germany! Ben is an active member of the Faculty of Science Post-doctoral Society at the University of Auckland, which supports fellow early-career researchers, and he is regularly involved in science outreach activities.

David T. Yost, B.Sc. (Hons) (Melb), M.Sc. (ANU), Ph.D. (Edinburgh), is a mathematician. Most of his research has been in functional analysis, but more recently, he has been working in convex geometry. Returning to Australia after his Ph.D., his first position was a Research Fellowship at La Trobe University, followed by a Queen Elizabeth Fellowship and then a Research Fellowship at the Australian National University. After that he moved to the Free University of Berlin, first as a Humboldt Fellow, and then for one semester as a visiting Professor. He then spent several years as a visitor, with some casual teaching work, at the University of Milan and Milan Polytechnic (Italy), the University of Lyon (France), Chulalongkorn University (Thailand) and the University of Extremadura (Spain). In 1999 he was appointed to King Saud University, in Riyadh, where he worked for four years. He came to the University of Ballarat, now Federation University, in 2003. He served as Deputy Head of the School of Information Technology and Mathematical Sciences from 2007 to 2009, and in 2010-2011 as Acting Director of the Centre for Informatics and Applied Optimisation. Since 2013 he has been a Council Member of the Australian Mathematical Society.

Trevor R. Finlayson  B.Sc. (Q’ld, 1965), Ph.D. (Monash, 1969), D.Sc. (Melb, 2015) is an Honorary Principal Fellow at the University of Melbourne. Following a period as a Research Associate at the Central Electricity Research Laboratories, Leatherhead, Surrey, England, (1969-1972) where he researched type II superconducting materials of potential application to an A.C. transmission cable, he was recruited to the academic staff of Monash University, specifically to create and teach a course in Materials Science for undergraduate students. He was promoted to Senior Lecturer in 1979 and to Associate Professor in 1991. His research focus throughout his academic career has been concerned with structural instabilities in crystalline solids and their influence on material properties. He was awarded an Alexander von Humboldt Fellowship in 1977 for collaborative research on superconducting materials, at the Institut für Edelmetalle und Metallchemie in Schwäbisch Gmünd and on two subsequent periods of Outside Studies Programme in Germany, (1998 and 2004), at Ludwig Maximillians Universität, München and RWTH-Universität, Aachen, he conducted collaborative research with Professor Dr. Uwe Klemradt on the dynamical behaviour of shape-memory materials. Since retirement from Monash University in February, 2007, he has continued research as an Honorary Principal Fellow, University of Melbourne, where his current projects are concerned with aspects of martensitic transformations in metal alloys and the ceramic, magnesia-partially-stabilised zirconia (Mg-PSZ), using mainly neutron scattering techniques. The ideas for his chapter in this eBook came from a trip to Antarctic regions with Heritage Expeditions aboard the Russian Icebreaker, Akademik Shokalskiy, during the summer of 2017. He is a Member of the Australian Institute of Physics and an Honorary Member of Materials Australia. His extra-mural interests include choral music as a chorister at Christ Church, South Yarra, and cricket as an Umpire on the Cricket Victoria Premier Panel. He is currently
Gabrielle L. McMullen AM, B.Sc. (Hons), Ph.D. (Monash), FRACI, was a Postdoctoral Fellow at the Chemisches Institut of the University of Freiburg, Germany from 1977-1981, initially supported by the Alexander von Humboldt-Stiftung and then the Deutsche Forschungsgemeinschaft. Upon her return to Australia in 1981, she worked for 14 years in the Department of Biochemistry and Molecular Biology at Monash University and as Dean of Mannix College, the University’s Catholic residence. In 1995 she moved to Australian Catholic University as Rector of its Ballarat campus from which she was appointed in 2000 to the national role initially of Pro- and then Deputy Vice-Chancellor (Academic). Her community contributions have encompassed membership of education, health, social services and theological boards and from 2011-2017 she was a Trustee of Mary Aikenhead Ministries. Her current roles include member of the Australian Catholic Council for Pastoral Research, the Governing Body of the Missionary Sisters of Service, the Divine Word University Council and the University of Divinity Council, Trustee of the Opening the Doors Foundation, and inaugural Chair of Diocese of Sale Catholic Education Ltd. Professor McMullen’s research interests include Catholic identity and mission, and the history of science. She is a Member of the Order of Australia, a Fellow of the Royal Australian Chemical Institute and is the current President of the Australian Association of von Humboldt Fellows.