Issue 132 / Winter 2023

PN Physiology News

Artificial Intelligence and Big Data Special Issue

The Physiological Society

Physiology News

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Cover image: Shutterstock photo

Artificial intelligence: Friend or foe?

Dr Keith Siew
Scientific Editor, *Physiology News*

Alanna Orpen
Media and Communications Officer, The Physiological Society

This year, artificial intelligence (AI) has dominated the media as the debate oscillates between beliefs it may be the basis of a renaissance and beliefs it may cause humanity's ultimate demise!

In our special issue on AI and big data, we explore the potentials of AI and try to weigh the good, the bad and the ugly! Indeed, the film review of GATTACA by Sofija Redzic (p14-15) gives us a dystopian insight into a world in which genetic prediction almost eliminates free will. And, whilst scaremongering around new technology is a classic trope of science fiction, it reminds us to tread carefully down the unknown path of living with AI.

One area of focus, and of particular interest to The Society is how AI could transform healthcare. This summer, The Society gathered in Parliament with experts across both the AI and life science fields to tackle the challenges and discuss the integration of physiological measurements and expertise into AI tools. The event was hosted by Stephen Benn, The Viscount Stansgate, with panellists including Stephen Metcalfe MP (Chair of the All-Party Parliamentary Group on AI) and researchers Dr Richard Siow and PhD student Svitlana Surodina (King's College London, UK) who both feature in our special issue on AI. Dive into the Policy Focus (p8-9) to read the full story about the report "*From 'Black Box' to Trusted Healthcare Tools: Physiology's role in unlocking the potential of AI for health*" and The Society's work on AI and health to find out more about the report's recommendations for the Government to ensure physiology is at the heart of AI's adoption into healthcare.

Effectively managing the data that AI models are trained on will be vital in ensuring equity in healthcare. Indeed, AI provides a path for fairer, more ethical and comprehensive diagnostic tools. One group developing such a tool are Skein. Svitlana Surodina, one of the panellists from the policy event and Managing Director at Skein, has written a feature article discussing how AI could revolutionise diagnostics for Parkinson's Disease. On p25-27, she and her co-authors explain that the key to achieving this is diverse and quality data.

Using big data to develop better treatments is also the goal of work by Professor Christopher Yau and Professor Ahmed Ashour Ahmed. They are creating new DNA sequencing tools and computer programmes to study residual cancer cells. Learn more about their research on p28-31 and find out how AI could advance the future of ovarian cancer treatment and immunotherapy approaches.

We learn about the predictive power of polygenic scores from Agnieszka Gidziela (Queen Mary University of London, UK, p21-24). This feature article is filled with the fascinating history of the method and examples of how scientists use it to estimate the combined effects of many different genes on a specific trait or characteristic. Agnieszka also reveals its value for precision medicine.

While AI has the potential to improve the quality and accessibility of healthcare, it can also reproduce and exacerbate existing problems, including unreliability, misinformation, exploitation of patients and healthcare workers. To learn more about the promises and pitfalls, turn to p16 to read the feature by John Nelson (Georgia Institute of Technology, US) and Alexander Stevens (University of California, US).

We treat you to a showcase of innovative human-centred technologies on p42-45. The case studies cover how AI could improve treatment of sepsis, blood pressure monitoring and how it could even predict heart attacks eight years early. Professor Rohan Lewis (University of Southampton, UK) demonstrates the potential of machine learning to speed up image analysis and explains how the approach can help enhance the health of mothers and babies during pregnancy and across the life course.

The reaches of AI are widespread. With the popular use of large-language models, such as ChatGPT, university staff are concerned about students writing assignments. In response to this, Dr Matthew Hardy (University of Bradford, UK) has created workshops to teach students how to use AI tools responsibly and ethically. Learn more about his approach for teaching writing skills and the students' feedback (p38-39). We have more advice for lecturers on p12-13, where Professor Zoran Redzic shares his review of the book '*Survival kit for the Physiology Lecturer*' by Francisco Suárez *et al.* Recommended reading for anyone seeking a "survival kit" for exam question preparation.

Along with our articles and studies of AI, The Society's Chief Executive Dariel Burdass celebrates The Society's achievements of 2023 (p7). The celebratory note sings throughout the issue with *Physiological Reports* 10-year anniversary (p11) and rounding off with our congratulations to our new Honorary Fellows and Fellow Members on p40-41. Don't miss the wonderful snapshot of our growing network and thriving community on p32-37. The meeting reports are filled with photos and quotes from organisers and speakers. We hope these summaries inspire you to convene your own meeting for your research community.

The issue is brought to a close with our obituaries. Two moving accounts of the influence of great mentors and teachers. We hope you enjoy reading about the lives of the courageous Professor Justin Yerbury (p45) and the mesmerising Professor John Nicholls (p46-47).

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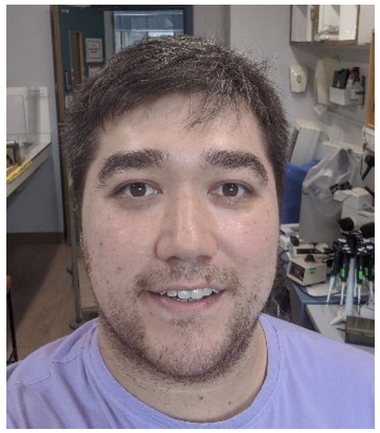
All good things come to an end



Dr Keith Siew

Scientific Editor, *Physiology News*

47 issues, 12 years and 4 terms on the editorial board later, and my time with *Physiology News* finally comes to an end. Getting to work behind the scenes to put together our community's magazine has been an honour. As one of the last bastions of a model of a learned society's magazine, run by the membership for the membership, I was always proud to be involved with shaping the future of *PN* since its revamp and relaunch in 2012. I hope you will agree that the great magazine we inherited from our predecessors (and "newsletter" even before that), has grown from strength to strength.

In my time on the board, we have seen an increase in the equitable representation of editorial board members of every sex, age, creed and ethnicity, even broadening our geographical, disciplinary, career stage and profession inclusivity. We have moved to make *PN* of sustainably sourced materials, shipped in biodegradable packaging. We have transformed the magazine into both a physical and virtual offering with now a significant portion of our readership coming from online. *PN* now has a fully restored PDF archive with the majority of past material and now all future content even assigned DOIs, forming fully citeable pieces of work. We have embraced the open culture of knowledge sharing and transitioned *PN* publishing to creative commons licensing to allow any and all to remix, reuse, redistribute and adapt this vital resource.

It has been genuinely exciting to help shine a spotlight on many important and meaningful issues covering equality, diversity and inclusivity (*PN*115; *PN*123), international perspectives from our fellow physiologists (*PN*91; *PN*112), the struggles faced by our colleagues in education (*PN*89; *PN*119; *PN*130) and delving into the difficult discussions on timely topics (*PN*98 – Ageing; *PN*113 – Chronobiology; *PN*117 – Space Physiology; *PN*121 – Medical Technology; *PN*127 – Climate Change; *PN*132 – AI & Big Data). I have much to thank the many global contributors of *PN* content over the years, it truly has been a broad education!

I can honestly say that my time on *PN* has been a joy, and like most of these things, it's the people you meet along the way that made it a fun and enriching experience. To my fellow editorial board members past and present, I extend my heartfelt gratitude for sharing your endless enthusiasm, wealth of knowledge and sense of humour. I've gained insight from each of your perspectives that have formed the writing and editor I've become today. In particular, my respect and largest thanks must go to the tirelessly devoted staff of The Society without whom the magazine would not function. From Lucy Holmes who took me under her wing to guide me through putting together my first issue as guest editor (*PN*95 – Imaging), to Julia Turan who was truly my partner in crime as we sought to make diversity, inclusivity and modernisation of the magazine our top priorities, and recently Jane Shipley, Susan Patterson, Emily Wylde and Alanna Orpen who have guided the magazine through numerous transitionary phases behind the scenes and supported me in times of personal difficulties.

To you the readership, thank you for your attention and support throughout the years. I've always enjoyed the rare opportunities where I get to meet some of you at meetings and to hear in person what the magazine means to you or to hear your excitement about an article, story or tale that resonated. I hope that I and my colleagues have kept you educated, entertained and informed as best we could, and given those in the society a much-needed soapbox when necessary.

Finally, I leave this position with sadness not only because my journey as *PN*'s Scientific Editor has come to an end, but also because I will be the last to occupy such a post. As I'm sure all are aware, learned Societies face many new challenges in the rapidly changing landscape and our Society is not immune to these pressures. And thus, it has been decided to retire the role of the scientific editor and editorial board, and to take the editing and production of *PN* entirely in-house under the direct guidance of our excellent staff. Although worry not, while one of the membership may no longer be at the helm, the editorial board will take on another form and help to inform the direction of the magazine. I wish all the very best, and hope to see *PN* continue to grow and prosper.

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Our 2023 highlights:

Together we are stronger, effective, and innovative

Dariel Burdass

Chief Executive,
The Physiological Society

As we come toward the end of the calendar year, I would like to take this opportunity to celebrate the amazing work done over the last 12 months by colleagues, Trustees and the wider membership to deliver the first year of our 2023–2027 strategy. We are one year closer to achieving our vision of a world in which physiological discovery leads to healthier lives. As my old rowing coach used to say "there is no I in team" and together we are stronger, effective, and innovative.

Firstly, I would like to say a big thank you to the Scientific Editor of *Physiology News*. Dr Keith Siew has served on and led the PN Editorial Board over the last eight years (two terms of office). I would like to thank him for his commitment and inspired ideas, which have continued to make PN a firm favourite read with members – highlighting the best of physiology and physiologists.

The Society continues to evolve to meet the demands of a sustainable future for physiology and physiologists, both financially and environmentally. We strive to enable strong networks to grow and communities to thrive. I am pleased to share just a few of our 2023 highlights, but our President David Attwell will be illustrating many more achievements in his talk at the Member Forum that have been made to raise the visibility of physiology.

Conferences

This year we launched our new two-day meeting programme – eight in total and more in the pipeline for next year – please check out our website for more details. This new format allows us to run more events to support members: they are run by members *for* members and their community.

Taking place in members' institutions, these meetings enable us to connect with the local community. This year's schedule included a meeting on "Membrane Transport" in St Andrews, "Cross-Talk of Cells in the Heart" in Liverpool and "Regenerating the Cardiovascular System" in Oxford.

We also supported a dedicated teaching meeting as part of our commitment to help this community with the changes to traditional teaching post COVID. It allowed academics to share best practice across the sector and generate ideas to implement in the future.

Publishing

Our three journals lead the discipline, promoting best practice and pushing the boundaries of scientific endeavour. In 2023 we welcomed back Kim Barret as the Editor-in-Chief of *The Journal of Physiology* (JP). Through her dedication and hard work, as well as that of the previous Editor- in-Chief Peter Kohl, and the Editorial Board, the Society's pipeline of special issues has grown with five published in 2023 and another twelve currently in progress. I am pleased to note that JP is predicted to end the year with a 18% increase in submissions and 5% increase in published content.

This year we flipped *Experimental Physiology* to Gold Open Access and we are delighted to be able to offer Society members a 10% discount on article processing charges. Many thanks to the Editor-in-Chief Damian Bailey and the Editorial Board for helping us deliver a successful flip. *Physiological Reports* has received its first journal impact factor of 2.5, which is an enormous success and tribute to not only the current Editor-in-Chief Josephine Adams and her Board but all those who have gone before since the journal's inception in 2013.

Membership

Our Training Hub launched in April this year as the home for career development, skills and training support for physiologists looking to advance their career and unlock their potential.

Our online Hub has a series of exclusive member-only resources that are tailored to the needs of physiologists. They focus on developing techniques, understanding concepts, and improving skills such as project management. We have also launched an extensive new series of video resources for early career lecturers, which have received extremely positive feedback. These online resources are supported by a programme of events and activities across the UK.

Finally – while recognising for some of our members these may be difficult times – I would like to wish you a very happy and healthy holiday season and all the best for 2024.

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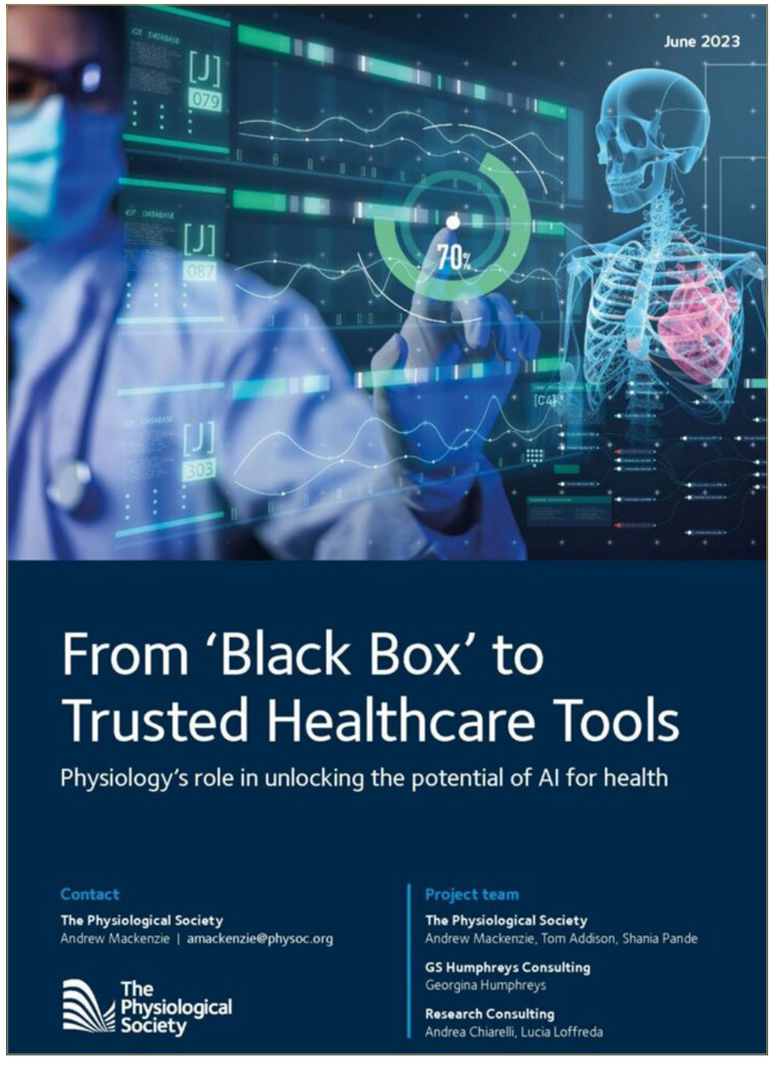
Physiology at the heart of AI safety

Andrew Mackenzie

Associate Director of Strategy and External Relations, The Physiological Society



"From ‘Black Box’ to Trusted Healthcare Tools: Physiology’s role in unlocking the potential of AI for health” underscored the importance of incorporating physiological measurements and insights into the development of AI tools.

Artificial intelligence (AI) has the potential to revolutionise healthcare by significantly improving disease detection and prevention. However, The Physiological Society is concerned that AI healthcare tools are being developed, approved, and adopted without sufficient physiological input. This should be a key priority as the Government considers the outputs of its recent AI Safety Summit at Bletchley Park.

AI will play a pivotal role in the ambition to transition the NHS from what is often more akin to a “national sickness service” to a model focused on preserving good health by leveraging innovation and technology for early disease detection. This shift will support a move towards a more integrated, whole-person approach to care and facilitate timely interventions in order to alleviate pressure on overburdened primary and secondary care, and enable individuals to enjoy healthier lives for longer.

However, the successful implementation of AI tools in healthcare is not without its challenges and risks. From inaccurate diagnoses to perpetuating existing health inequalities through biased data and access, it is crucial to carefully develop, adopt and monitor AI tools to prevent potential harm.

To explore current perspectives on the role of physiology in developing and using AI tools within the UK health system, The Physiological Society collaborated with over 30 experts across both the AI and life science fields, in June 2023, to consider the opportunities and risks. The resulting report, “From ‘Black Box’ to Trusted Healthcare Tools: Physiology’s role in unlocking the potential of AI for health” underscored the importance of incorporating physiological measurements and insights into the development of AI tools, as well as fostering a research ecosystem that leverages physiological understanding rather than dealing with siloed areas of specialism.

The limited inclusion of physiological evidence in the development of AI tools can lead to reduced trust, challenges with applicability and, at worst, to the identification of spurious correlations without sufficient physiological plausibility and ultimately harm to patients.

Our report presents a set of recommended actions for the Government, the NHS, research funders and other stakeholders to utilise physiology as a "guardrail"when developing AI in health, in order to maximise the benefits while minimising risks. Integrating physiological knowledge into relevant AI models and systems can enhance the understanding and interpretation of complex health data, ultimately leading to better-informed decision-making.

Our recommended actions highlight the critical role that physiologists and physiology play in underpinning effective AI tools by ensuring model plausibility, assessing relevant training datasets and improving the interrelationship between biomedical understanding, machine-learning systems and clinical expertise.

To harness the full potential of AI in healthcare and ensure its safe and effective implementation, we believe it would be beneficial to adopt a comprehensive approach based on the establishment of a Physiology & AI Framework, the prioritisation of physiological plausibility in research funding mechanisms and the inclusion of physiological evidence in the regulatory approval process.

Our report made three core recommendations that, together, outline a strategic roadmap for achieving these goals:

By placing physiology at the heart of AI’s adoption into healthcare we can truly unlock the potential of this fast-evolving technology to support us all to live healthier for longer.

Action 1: Establish a Physiology & AI Framework to set improved guardrails for AI in health.

To ensure that AI tools in healthcare are not only safe, but also accepted by their intended users and beneficiaries, The Physiological Society is coordinating efforts to establish a Physiology & AI Framework, working with stakeholders across healthcare services, research and AI.

The framework will set out principles for physiologically plausible technologies, improve dialogue and knowledge transfer between stakeholders and establish training programmes. This will help establish guardrails around AI and health by identifying how to integrate physiological measurements and expertise into technology development and testing, prior to deployment in healthcare settings.

Our ambition is that the framework will form the platform and evidence base on which regulators, funding organisations and policymakers make decisions on effective implementation of trustworthy AI health tools. The framework will include three key elements:

- The development and adoption of a set of principles and success criteria that describe physiologically plausible technological applications, to help lift the lid on the "black box" that is AI.
- A forum to regularly bring physiologists together with other key stakeholders, to achieve a shared understanding of physiological plausibility, opportunities and risks of AI tools in healthcare.
- A training programme for physiologists, developers and data scientists, to create a shared language and understanding to build physiologically plausible technology by design.

Action 2: Ensure that research funding mechanisms prioritise physiologically plausible AI tools.

We recommend that research funders should review the governance of funding mechanisms that concern the use of AI in healthcare. Where relevant, physiological plausibility should be included as a key decision factor in assessing the quality of grant proposals, and research teams should include physiological expertise.

Action 3: Embed physiological evidence in the regulatory approval of AI tools

We recommend that the Medicines and Healthcare Products Regulatory Agency (MHRA), in partnership with other relevant regulators, should make physiological evidence and insight a foundation of their regulatory approval process for AI tools as medical devices.

Similarly, the NHS and the National Institute for Health and Care Excellence (NICE) should update their assessment mechanisms for digital health technologies to include coverage of physiological evidence.

Through their centralised coordination function, the AI and Digital Regulations Service should ensure all collaborating regulatory organisations include physiological expertise and evidence in the assessment of relevant AI tools for healthcare.

Taken together, these recommendations provide a roadmap for developing "guardrails" when developing AI in health. This is required in order to achieve the aims of improved patient outcomes, higher trust in innovative AI technologies and a more efficient healthcare system. By placing physiology at the heart of AI’s adoption into healthcare we can truly unlock the potential of this fast-evolving technology to support us all to live healthier for longer.

Find out more about The Physiological Society’s work on AI and health at physoc.org/AIPhysiology

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News from our family of journals

Name Change Policy

Our Publications Team is pleased to announce that, in alignment with the Name Change Policy Updates from Wiley, authors publishing in both *The Journal of Physiology* and *Experimental Physiology* now have the option to include their personal pronouns as part of their manuscript when submitting with us.

Authors can add, edit or remove these pronouns at any stage upon request via our peer-review team. This is an entirely optional addition for the author, and is by no means a requirement for submission. Further guidance on the inclusion of pronouns can be found on the "Information for Authors" page for both *The Journal of Physiology* and *Experimental Physiology*.

Our journal AI policy

AI-generated content (AIGC) tools—such as ChatGPT and others based on large language models (LLMs) have grown popular in all industries, including publishing. *The Journal of Physiology* and *Experimental Physiology* require authors to fully disclose the use of any AIGC tools in the preparation of their manuscript, as per Wiley's policy. This disclosure should be placed in the Methods or Acknowledgements section, and must be transparent and detailed. Authors are responsible for both the accuracy of information provided by these tools, and for correctly referencing any supporting work on which that information depends. Tools that are solely used to improve spelling, grammar and general editing are not included in the scope of this policy.

AIGC tools cannot be considered capable of initiating an original piece of research without direction by human authors. They also cannot be accountable for a published work or for research design, which is a generally held requirement of authorship (as discussed in the previous section), nor do they have legal standing or the ability to hold or assign copyright. Therefore—in accordance with the Committee on Publication Ethics (COPE)'s position statement on AI tools—these tools cannot fulfil the role of, nor be listed as, an author of an article.

Reviewers are prohibited from using such tools, to prevent infringement upon the intellectual property and confidentiality rights of submitting authors.

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We are delighted to offer a 10% discount code for members of The Physiological Society on article processing charges for *Experimental Physiology*. Please scan the QR code and log on to retrieve your discount code. If you have any questions about the discount code, please contact *Experimental Physiology*: ephjournal@physoc.org

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Physiological Reports celebrates 10 years of basic and translational physiology

The editors of *Physiological Reports* are delighted to be celebrating 10 years since its launch as a Gold Open Access journal in 2013. Established as a joint venture between The Physiological Society and the American Physiological Society, *Physiological Reports* has gone from strength to strength under the guidance of Editors-in-Chief Sue Wray (2013–2018), Thomas Kleyman (2018–2022) and Jo Adams (2023–present), as well as the fantastic teams of Editors, whose efforts have also underpinned the success and growth of the journal over this time.

Join in with the celebrations

The 10-year anniversary celebration of the journal will run from 1 December 2023 to 30 November 2024, during which time we encourage you to get involved by reading our celebratory editorials, responding to "Calls for Papers" throughout the year, and looking out for our early career presentation awards at major physiology conferences. A new "Paper of the Year" award will also be launched to recognise the research papers of highest sound science quality published in *Physiological Reports*.

Looking back at the last decade

Physiological Reports was established to publish sound science in basic and translational physiology, and it remains a journal with broad scope and appeal. Since the beginning, the journal has handled manuscripts transferred from both The Physiological Society and the American Physiological Society, as well as Wiley supporter journals and direct submissions, and has grown in popularity. Indeed, downloads of full-text articles have increased each year. Over the past decade, *Physiological Reports* has also become a home for the international physiology community, with published papers originating from 45 countries between 2021 and 2022.

Looking ahead to the future of *Physiological Reports*

So, what is next for *Physiological Reports*? Our main priority is supporting the physiological community. First, through the publication of high-quality research and Methods articles, we also plan to enhance the publication of invited Review articles to address emerging or expanding areas of physiology. Secondly, through fostering engagement with the next generation of researchers, we are planning a new "Short Review" writing competition for early-career researchers. We anticipate a lot to look forward to over the next 10 years!

We encourage you to get involved by reading our celebratory editorials, responding to "Calls for Papers" throughout the year, and looking out for our early career presentation awards at major physiology conferences.

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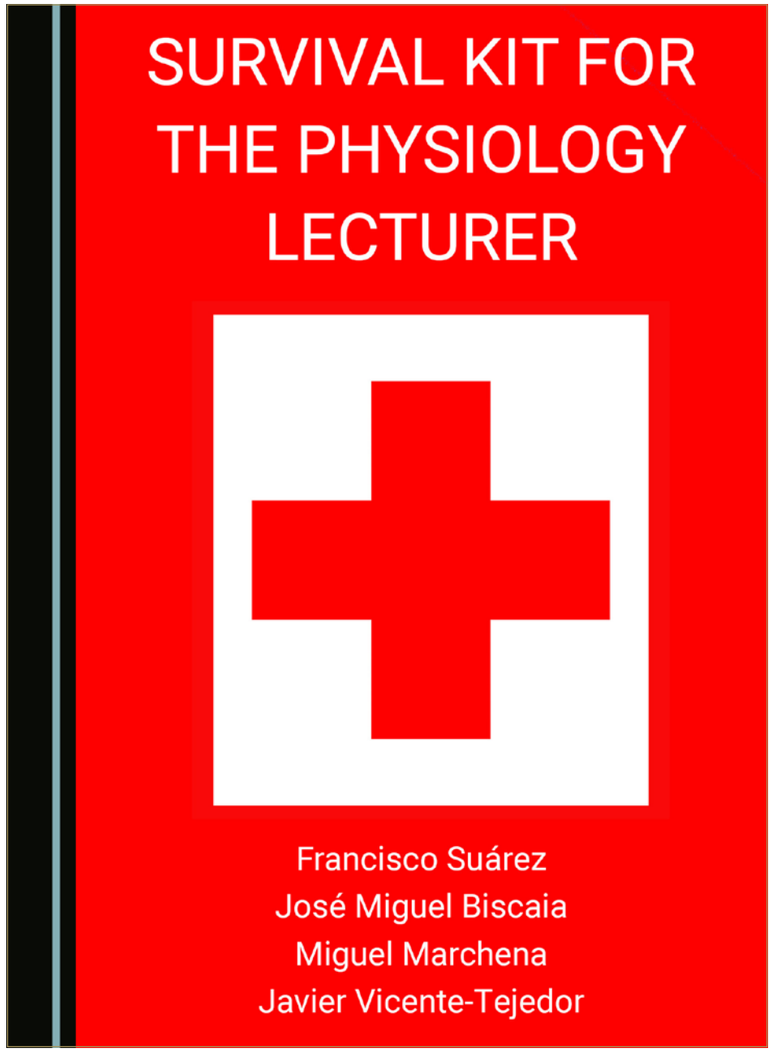
Book Review: Survival kit for the Physiology Lecturer by Francisco Suárez *et al.*

Professor Zoran Redzic

Department of Physiology, College of Medicine, Kuwait University



The value of the book lies in its extensiveness; it offers 750 pages that our community of physiology lecturers should be grateful for as a resource.

"*Just a soft reminder to send me exam questions for the coming exam by next Monday*".

Regardless of their teaching experience and seniority, most lecturers have a Pavlovian reflex that awakens anxiety every time this sentence comes up in an email. To help fellow lecturers, four physiology lecturers from Universidad Europea de Madrid and King Juan Carlos University in Madrid put together a remarkable set of physiology questions in a book. They aim to offer colleagues a "*survival kit*" for exam-question preparation.

The survival kit (i.e. this book) is a set of well-organised chapters that contain a staggering number of multiple-choice questions (MCQs) and short essay questions, covering all the main areas of human physiology. The value of the book lies in its extensiveness; it offers 750 pages that our community of physiology lecturers should be grateful for as a resource. Another feature of this book is that it is designed, as the authors say, as "*... a scaffold on which you can lean*" while preparing exams, i.e. more as inspiration for devising questions than providing questions that could be directly used in the exams. A lecturer should use this set of ideas for questions and put in extra effort and their specific expertise into making their desired structure out of the scaffolding provided, i.e. create exam questions appropriate for a particular exam in a particular course in a particular university.

The book is structured clearly, following the typical structures of physiology courses aimed at biomedical and life sciences undergraduate students. It consists of two main sections: Cell Physiology, and System Physiology, broken down further into several parts covering each section (e.g. the Cell Physiology section includes Nerve Cell Physiology, Muscle Cell Physiology, Immune Cell Physiology, to name but a few). Each part provides 15 to 30+ questions, mainly MCQs, but also short essay-based questions that cover main (key), advanced and specialised objectives (concepts) in that subchapter.

These objectives are listed at the beginning. In turn, each question is linked to a specific objective by a number in the brackets next to it. However, the authors admit in the Preface that the "*... classification is strictly subjective, and it doesn't reflect precisely whether the question is easy or difficult*". This makes it very easy to look for ideas for questions in a particular area of physiology. However, at this point the book crosses the line of oversimplification, by providing explanations for every correct answer and by linking every question to a particular concept / objective.

Explanations of correct answers, which in some cases are not brief at all, seem unnecessary for a physiology lecturer, but makes this book potentially desirable to students, who could use it as a surrogate for textbooks. Post-pandemic, I am sure we have all encountered the rapid proliferation of websites offering physiology MCQs with (often questionable) explanations in exchange for a paid subscription. Additionally, linking every question to a particular objective is unnecessary for a competent physiologist and could potentially confuse junior colleagues, since assessing a physiological mechanism (e.g. actions of insulin / leptin on the neurons) could be used in several areas of physiology, not only in one section. Thus, if the book is aimed to be purely "*....a kit for the physiology lecturer*", then the oversimplification is superfluous. Lists of references are provided at the end of each part. This is helpful, although as they are

The survival kit (i.e. this book) is a set of well-organised chapters that contain a staggering number of multiple-choice questions (MCQs) and short essay questions, covering all the main areas of human physiology.

mainly mainstream physiology textbooks, I think they would be well known to most physiology lecturers.

The book is generally aimed more at biomedical and life science students rather than at medical students, as most questions lack genuine clinical scenarios, which, according to some research, medical students prefer (Vegi *et al.,* 2022). A review by, or help from, a medically qualified physiologist may be beneficial for the next edition. This could also improve the clarity of some answers, which the authors evidently provided bearing in mind a specific lecture, rather than a more applicable variety of broad concepts and clinical settings. For example, it is well known that the main symptoms of taking large doses of MDMA (ecstasy) are neurological (including excitation, anxiety, paranoia, headache, ataxia), cardiovascular (hypertension, palpitations) and gastrointestinal (nausea, vomiting), but the book offers "syndrome of inappropriate secretion of antidiuretic hormone" (SIADH) as the answer, which is only technically true under a very specific set of circumstances, albeit not very realistic.

The second main area for improvement in the book is to consider replacing true / false (T/F) MCQs ("which of the following is true.... Mark the correct statement.....Indicate the false statement...") and those that ask for definitions ("*choose the best definition for....*"), which this book heavily relies on, with MCQs that assess concepts. T/F MCQs are no longer seen as a reliable test by medical educationalists to distinguish between high and low performers (Downing, 1992) as there is a high chance of guessing the correct answer (Downing, 1992). They often only assess trivial knowledge (Case and Swanson, 2002) and marks could simply be awarded for knowing that an answer is incorrect (Schuwirth and van der Vleuten, 2003). The same stands true for negatively phrased questions (Coughlin and Featherstone, 2017).

A few technical improvements include potentially shortening sometimes unnecessarily long question stems (as in, one can simply ask which medical condition could be improved by a cocktail of serotonin receptor agonist and MAO inhibitors, rather than putting a paragraph-long questionable stem that would only confuse students) and removing questions that could be answered using common sense (e.g. "*After drinking a lot of beer, a person goes to the toilet; what would be the water content in his urine?*", which could realistically be answered by anybody who has ever had a couple pints).

There are a few aspects that could be amended, but overall this book is certainly a valuable acquisition for knowledgeable lecturers. It provides plenty of ideas for exam questions, so, in summary, we have to say a big "*Tanques*" to the authors and encourage students not to stress, do their best and forget the rest.

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Film Review: GATTACA, written and directed by Andrew Niccol

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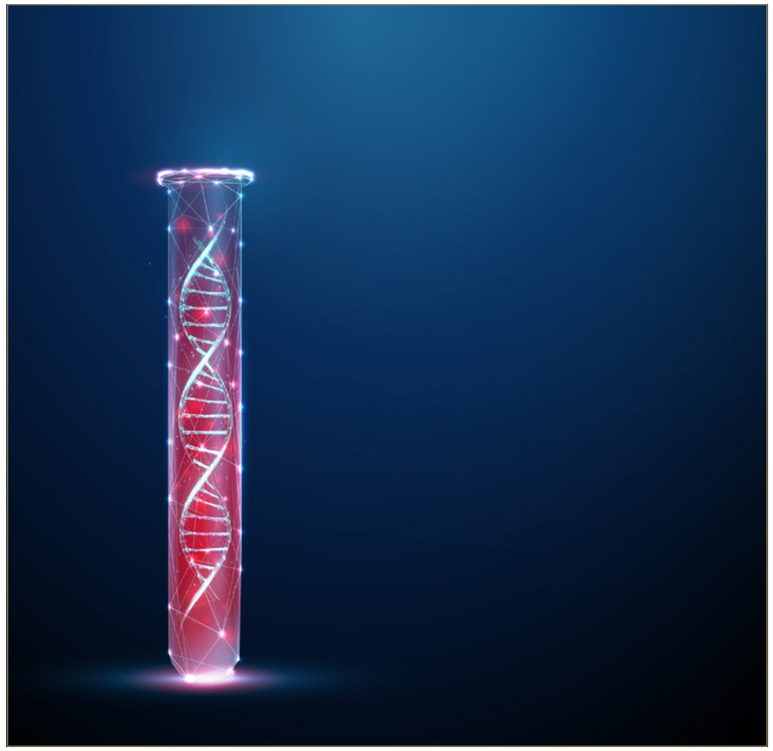

The motif in *Gattaca* of loss of human-decision making has already come true to a certain extent, with AI programs such as ChatGPT and DALL-E reducing the human component that was once required for creativity.

"Consider God's handiwork; who can straighten what He hath made crooked?"

This quote is *Gattaca*'s opening screen, based on Ecclesiastes 7: 13 in the Bible. Perhaps it may invoke a knee-jerk reaction in scientists watching. Is it not the primary goal of all life science research to help to extend the human body's lifespan past once-fatal failings? However, in this universe, society has evolved past the point of leaving things to chance.

Gattaca (1997) is set in a fictional prospective universe wherein human gene analysis has progressed far enough to let parents pick their most compatible choice from genetically analysed, multiple fertilised embryos. This unborn child's place in the class ladder is determined at conception through what its genetic code predicts it will be (allegedly) capable of. Vincent is born a "faith baby", as his parents did not use this screening. They later regret this, taking caution with their second child Anton. Anton becomes the golden child due to his superior genotype and Vincent is left embittered, nursing a dream to fly to space.

Gattaca is his path to space, an elite space exploration programme that tests the best of the genetically best to find candidates for their rigorous missions. Vincent, an "invalid" (i.e. having "imperfect" genes) must leave his old life behind and assume the physical identity of a "valid" person to enter Gattaca. The film centres around his calculated movements to evade genetic recognition in a system that checks the identity of its occupants at every Orwellian turn.

Medicine in this universe has gone beyond a tool for enabling human life to be lived fully and has morphed into the defining factor of how fully humans are allowed to live in order to best serve the collective and its goals. To quote Vincent, "[Gattaca] now have discrimination down to a science."

The black-and-white nature of sorting potential by genetic predisposition leads to an absolute block in social mobility, and from the moment of conception a human life's worth is relegated to strict categories. De-gene-erates, as the naturally conceived are termed, are at the bottom of the achievement ladder and are only shown throughout the film in low-skill jobs or as a part of the homeless population.

There is no room for self betterment or motivation in this system. All are subservient to the needs of the collective to advance further, and this machine of a society whirrs on out into the solar system (literally) without regard to the single human's wants.

Totalitarianism is defined as a "form of government that theoretically permits no individual freedom and that seeks to subordinate all aspects of individual life to the authority of the state". Perhaps that would sound familiar to a "Gattaca" universe resident.

What this societal system fails to take into account is free will, and motivation. The constant testing may account for one's genotype, but phenotypes are the intersection of that genotype with our surroundings. In Vincent's case, his motivation from his childhood is great enough to not let genetic predictions change his life's course. He outperforms his cohort, and his success contradicts the "facts" presented by (allegedly) hyper-advanced programs. It is proof that blind faith in technology is bound to be proven wrong, and that genetic information alone is simply not enough to determine, or secure, a person's future. Indeed - you could have all of the gene variants associated with being a proficient reader, but if you are never given a book or taught how to read, this potential cannot be achieved.

Only in the final moment before boarding the spaceship is Vincent's true identity revealed. The doctor testing Vincent lets him board the craft regardless, because of compassion. His son too is a "de-gene-erate". For an algorithm taking this case into account, there are no decimals between a zero and a one in binary; you either are capable, or you are not. The only thing that saved Vincent from being cast off the mission was human intervention. What will happen when Gattaca's system develops even further, so that there are no humans to intervene?

However, *"Gattaca"* was released in 1997. To draw up a comparison of how long ago that is in the tech timeline, 1997 was the first year that a specialised computer chess program beat a human player. Today, most consumer-level chess programs alone have never been beaten by a human. It is reasonable to wonder whether Gattaca's warnings still stand true after such leaps in advancement. The motif in *Gattaca* of loss of human decision-making has already come true to a certain extent, with AI programs such as ChatGPT and DALL-E reducing the human component that was once required for creativity. We also see the genetic predictions borne out through the advent of polygenic scores, which use a person's DNA to place them on a distribution of risk for certain disease-associated traits.

Maybe it is too late to divert our train off its tracks to technological totalitarianism. Or, maybe, this movie is another addition to the list of dystopian science fiction that scare their audiences about the capabilities of new technology. Either way, Gattaca has not lost its relevance, and it is worth watching to revisit the questions it raises - our tendencies toward the need for control, the future of predictive data, the dangers of totalitarian societies and the loss of the individual.

Gattaca has not lost its relevance, and it is worth watching to revisit the questions it raises - our tendencies toward the need for control, the future of predictive data, the dangers of totalitarian societies and the loss of the individual.

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Promises and pitfalls for artificial intelligence in healthcare

How AI can support or undercut quality, accessibility, and equity in health innovation, care, and management

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Artificial intelligence in healthcare: Hope and hype

Recent years have seen increasing excitement about the potential for artificial intelligence (AI) to improve the quality and accessibility of healthcare (Davenport and Kalakota, 2019). While these possibilities are real and important, AI also bears substantial potential to reproduce and exacerbate existing problems in healthcare systems. In this article, we provide a high-level overview of AI's potential applications in healthcare innovation, healthcare delivery, and healthcare management, as well as ways in which AI could contribute to healthcare problems including unreliability, misinformation, exploitation of patients and healthcare workers, and healthcare inequities. Like other emerging health technologies, AI systems are flexible; their outcomes will depend upon the interests and values that shape them. If healthcare AI is to respect and advance public values, healthcare workers, patients, and citizens must be empowered to guide AI's goals, development, and use.

Types of artificial intelligence: A thumbnail sketch

The European Union's High-Level Expert Group on Artificial Intelligence defines AI as "systems that display intelligent behaviour by analysing their environment and taking actions—with some degree of autonomy—to achieve specific goals" (High-Level Expert Group, 2019). Within this definition, there are several ways to typologise AI, including by applications, by overall level of "intelligence," and by how it works. We'll talk about applications later. On "intelligence levels," all AI systems now in existence are "artificial narrow intelligence," which is (at most) capable of performing specific and constrained tasks, such as writing or sorting images. This is often distinguished from "artificial general intelligence," a hypothetical category that could perform a wide variety of tasks (like humans), and "artificial superintelligence," which would, if achieved, vastly exceed human capabilities and possibly even human comprehension. The important thing to know is that there is little prospect of artificial general intelligence or superintelligence anytime soon (Collins, 2021). For the foreseeable future, AI will be limited to impressive performances on narrow tasks, such as generating images based on text prompts, remixing text on particular topics, or classifying images into specified categories.

More directly relevant is categorisation by how AI works. There are two big categories of AI, which can be hybridised: rule-based and machine-learning-based AI. Speaking broadly, rule-based systems identify and respond to inputs according to an (often quite complicated) "script" written by human designers. For example, a very simple rule-based patient care recommendation system might look something like the following:

IF patient is immunocompromised AND has a pneumonia diagnosis, THEN recommend patient be kept in hospital overnight.

In contrast, machine-learning-based systems iteratively develop their own scripts, in part or in whole, based on attempted applications of prior scripts and feedback on how they turned out. This process can be very intensive in data and computation time. Such generated scripts can then be "frozen" and used as-is, or permitted to continue evolving in response to novel data and feedback. A machine-learning system is given a goal and a dataset, and told to work out through trial and error the most effective way to use the dataset to achieve the goal.

Most recent AI hype has been around machine-learning systems, such as text generator ChatGPT and image generator Midjourney. Machine-learning systems are particularly powerful because they can develop and iterate upon scripts too complicated for human designers to manually construct, using datasets too large for manual review. This, in turn, allows machine-learning-based systems to mimic, and, in some cases, exceed human capabilities in tasks requiring integration of many variables or large amounts of data. For example, to manually design a detailed rule-based system for diagnosing cancer based on MRI imaging would require a great deal of time and effort. However, a machine-learning system can attempt to automate some of this process if set on a collection of preidentified cancer-positive and cancer-negative images (Wang, 2022). The system will mark some images as cancer-positive based on its existing script, check its answers, modify its script (to prioritise, deprioritise, or shift the interpretation of image features), and check whether this modification improves its accuracy. The downside of machine-learning is that a system's designers are not in complete control of what it learns. Thus, designers cannot always predict or explain how a machine-learning system will behave under all contexts of application.

Applications of artificial intelligence in healthcare

As AI is potentially applicable to any activity that involves, or that could involve, processing and analysis of data, it has myriad potential applications in healthcare. Some, such as protein folding or diagnostics, are specific to medicine; others, such as automated logistics or employee management, are not.

AI in preclinical treatment development

AI can be employed to collect, annotate, and analyse tremendous amounts of biomedical data. In so doing, it can identify connections between data points, and, sometimes, reveal previously obscured insights, such as predisposition to disease or treatment efficacy based on a combination of genes or patient-specific biomarkers (Michelhaugh and Januzzi, 2022; Wang *et al.*, 2019). Furthermore, machine-learning models trained on large datasets can often extrapolate their findings to new or proposed work, enabling scientists to perform experiments on computers at a fraction of the time and cost of traditional lab research. DeepMind's Alphafold, for instance, was trained on a pre-existing database of proteins covering about 17% of the human proteome and was found to confidently predict protein structures based on amino acid sequence alone (Jumper *et al.*, 2021). As discovering the structure of a single druggable protein is often a PhD dissertation's worth of work, DeepMind's prediction of the entire human proteome in under a year represents a triumph of machine-learning (Tunyasuvunakool *et al.*, 2021). Beyond protein folding, greater integration of AI systems into preclinical development may help scientists to repurpose existing drugs and discover new ones (Fleming 2018; Ge *et al.*, 2021; Zhou *et al.*, 2020). One study utilised AI to identify a drug currently undergoing clinical trials for breast cancer treatment as an effective inhibitor of SARS-CoV-2 cell entry (Ge *et al.*, 2021). The impressive results of AI-guided research underscore AI's potential to streamline biomedical research, reduce the cost of treatment development, and reduce the time needed to bring new treatments to patients.

But despite being heralded as a cornucopia of biomedical insight, AI applications remain dependent on the guidance of human experts. While machine-learning models can identify patterns under mountains of genomic data, researchers must still corroborate these predictions and update models based on empirical data. For example, despite its success at predicting many protein structures, Alphafold struggles to accurately predict structures for membrane proteins (Bertoline *et al.*, 2023). Membrane proteins are integral to our understanding of disease, but they are poorly represented in Alphafold's training dataset. Thus, Alphafold has limited "experience" with membrane proteins and correspondingly weak performance. AI-derived research will only become as good as the datasets that AI is trained on. Real-world research will always be needed to guide and correct AI's missteps, as with any other modelling method.

AI in clinical treatment

Beyond preclinical research, AI has been touted as a key driver of innovation in the patient-care space, particularly for image analysis and patient monitoring (Brinker *et al.*, 2019; Dubey and Tiwari 2023; Najjar, 2023). AI can be a powerful tool for analysing clinical images such as MRIs and X-rays (Najjar, 2023), and, potentially, identifying disease markers that are either too subtle for human detection or whose relevance to disease has gone unnoticed by entire medical fields (Shen *et al.*, 2017). AI has demonstrated image-based detection speed and sensitivity meeting or exceeding human capabilities for diseases such as pneumonia and melanoma (Brinker *et al.*, 2019; Plesner *et al.*, 2023). While critical review is still necessary to verify AI diagnoses, these tools could drastically increase the throughput of disease diagnosis and enhance diagnostic sensitivity (Yu *et al.*, 2023). However, as suggested previously, AI is only as good as the data on which it is trained. Atypical presentation or user-based errors in image processing can produce erroneous results. These errors are often systematic. As discussed further below, training datasets are biased by differences in individuals' ability or willingness to share their data across racial, ethnic, or geographic lines (Johnson *et al.*, 2010).

AI is also being integrated into applications meant to reduce the rate of hospitalisation in seniors and other high-risk groups. Some healthcare professionals are looking to remote patient-monitoring devices to enable continuous monitoring without direct medical supervision or hospitalisation (Dubey and Tiwari, 2023). These tools can ensure patients receive proactive care and alleviate the burden of preventable hospitalisations by detecting anomalous indicators of disease, such as arrhythmias or elevated blood pressure, and notifying healthcare personnel. Recording patient data at scale may also facilitate early disease detection. AI models could parse large volumes of patient data to rapidly detect novel patterns calling for intervention. However, increased patient surveillance also necessitates greater scrutiny regarding how those data are used. Though physicians have an obligation to ensure that medical data are not intentionally misused, the rapid advancement of AI means the scale and variety of data collection will likely outpace the development of best practices in managing and protecting them. Thus, AI patient monitoring will complicate efforts to prevent questionable or unethical collection and use of data.

AI in epidemiology and healthcare management

Beyond improvements in disease treatment, AI may play a substantial role in large-scale tasks such as epidemiology, healthcare administration, and health resource allocation. During the COVID-19 pandemic, much work was dedicated to the development of machine-learning-based models to forecast the rise of new SARS-CoV-2 variants and prospective regional healthcare burden based on the susceptibility of local populations to severe disease (Abdulkareem and Petersen, 2021; Al-qaness *et al.*, 2020; Jiang *et al.*, 2020; Nagpal *et al.*, 2022; Zheng *et al.*, ,2020). Such enhanced surveillance could rapidly identify epidemiological trends and give researchers, medical personnel, and policymakers more time to coordinate targeted responses.

Algorithms are already ubiquitous in healthcare, and AI has already been used to handle tasks like medical workforce scheduling (Fornell, 2023). AI could also be used to guide allocation of scarce healthcare resources, a major difficulty under both normal and crisis healthcare conditions. Resource allocation has direct consequences for morbidity and mortality (Ji *et al.*, 2020), and some authors hope that AI could increase the speed and efficiency of resource allocation under crisis (Wu *et al.*, 2023). Moreover, some researchers hope that AI decision-making could help to redress inequities in healthcare by targeting resources to communities in need. However, as discussed below, existing healthcare inequities can often find their way into models and algorithms in subtle ways.

Potential problems for artificial intelligence in healthcare

Because AI has so many possible applications, it has many different potential upsides and downsides. We've already discussed many upsides. As examples of potential downsides,

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we'll explore four important problems: unreliability, misinformation, exploitation, and inequity. These do not exhaust all of the ways in which AI could contribute to health problems. However, they provide a potent set of examples to emphasise the importance of social responsibility in healthcare AI development and deployment.

Errors and accountability

Although AI systems can be very powerful, they can certainly err—sometimes in novel and unexpected ways. One well-publicised example concerns an experimental hospital AI designed to recommend whether pneumonia patients should be kept overnight. This system was trained on a historical dataset wherein patients with a history of asthma were always kept overnight for observation, and, consequently, had high recovery rates. Because of those high recovery rates, the AI system took a history of asthma as a predictor of recovery and recommended that such patients should be sent home (Christian, 2020). This is a fairly obvious error, but more subtle ones might evade detection and correction—particularly if AI is developed and deployed without input from a broad set of patients, communities, and medical professionals, or if medical professionals are not empowered to oversee, understand, and question AI decisions (Mackenzie *et al.,* 2023). Moreover, use of AI systems could both legally and psychologically diffuse responsibility for patient care and accountability for care decisions (Naik *et al.,* 2022).

AI systems are more likely to produce invalid or harmful results if applied to populations who substantially differ from those on which they were trained, or if deployed outside the scope for which they were designed. For example, machine-learning algorithms capable of identifying cancerous skin lesions are predominantly trained on white skin, and their sensitivities fall far below clinician capabilities when applied to darker skin types (Kamulegeya *et al.,* 2023). Diagnostic AI has been found to vary in performance even between different imaging machines of the same type, requiring adjustment (De Fauw *et al.,* 2018). In healthcare, measures initially developed for one purpose are often reapplied for other purposes, and not always with appropriate validation. For example, the faecal occult blood test, validated for colorectal cancer screening, is frequently reapplied in patients not appropriately prepared through dietary and medication restriction (Sharma *et al.,* 2001). This approach could lead to excessive false positives and mislead an AI system trained on a dataset including these test results. Yet much of the healthcare data available are riddled with such opportunism, heterogeneity, and inherent biases (Chin-Yee and Upshur, 2019). Dynamic, "unfrozen" AI systems can even develop new failure and error modes in response to novel data and training (DeCamp and Lindvall, 2020). In short, AI systems deployed in healthcare will require careful data and logic auditing, judicious application, and consistent expert oversight to prevent, apprehend, and correct errors (Broussard, 2023; Mackenzie *et al.,* 2023).

Misinformation

While much work is ongoing to develop and deploy AI within healthcare, population health will also be affected by AI developments outside of healthcare. Many people turn first to the internet when they get sick, and, of course, not all health information on the internet is accurate. Indeed, World Health Organization Director-General Tedros Adhanom Ghebreyesus declared in 2020 that the world faced not only the COVID-19 pandemic, but a parallel "infodemic" of COVID-19 misinformation and conspiracy theories (Zarocostas, 2020). In the future, many people may turn to AI language models like ChatGPT for health advice. Leaders in the AI search and language model space have put in a lot of work to prevent their models from repeating bad health advice (Ayers *et al.,* 2023), but, due to the structures of such models, the designers and trainers will always be one step behind new or more obscure canards (Nelson, 2023). Moreover, as AI answer services proliferate, the likelihood that one or more publicly available AI systems will be prone to giving out bad advice will increase. It should also be noted that ChatGPT's paid version has been found to provide better information about vaccine safety than ChatGPT's free version, leading to potential disparities in access to reliable health information (Deiana *et al.,* 2023).

AI could also be used to generate or spread misleading content about health, as about other topics. AI-generated images have already been used in a disinformation campaign around the August 2023 wildfire burning of Lahaina, Hawaii (Sanger and Myers, 2023). Historically, online platforms have not been held responsible for misinformation or disinformation posted by users, even when such content is promoted by recommendation algorithms (Accountable Tech, 2020; Bertolini *et al.,* 2021). It remains to be seen whether this no-responsibility approach will also apply to the outputs of language models or chatbots. Prevention of harms from AI health misinformation may require improvements in population digital and health literacy and stronger incentives for online platforms to ensure the validity of their hosted, recommended, or AI-generated content.

Facilitation or incentivisation of exploitation

AI systems require large amounts of data to train. In general, the larger and more representative the dataset available, the more powerful an AI model can become. This requirement creates a perverse incentive in healthcare recordkeeping; health data privacy is a barrier to health AI development (Bak *et al.,* 2022). Moreover, AI tools can, in some cases, be used to reidentify anonymised health data, facilitating privacy invasion (Murdoch, 2021). Debates are ongoing about both technical methods to permit health data use for AI without compromising privacy, and about the appropriate balance to be kept between these goals (Prayitno *et al.,* 2021). The European Union's General Data Protection Regulation (Regulation 2016/679) provides a good start for residents of current and former EU nations, but, as ever, efficacy will depend upon implementation.

Marketing is another area of concern. Major pharmaceutical companies have expressed interest in using AI to enhance the efficacy and cost-effectiveness of drug marketing to physicians (Sagonowsky, 2019; Wunker, 2023). Such applications may not be inherently problematic. However, during the United States' opioid abuse epidemic, direct-to-physician opioid marketing has been found to geographically associate with opioid overdose deaths (Hadland *et al.,* 2019). In 2021, consulting firm McKinsey and Company paid a settlement of 573 million USD to U.S. states over the alleged contribution of its marketing advice to the opioid epidemic (Forsythe and Bogdanich, 2021). If a major consulting firm composed of highly educated humans arguably did not take appropriate care to prevent adverse consequences from its marketing strategy, there is little reason to expect that AI systems designed to maximise return on advertising would do so. Regulatory guidance and wariness from physicians, patients, and citizens in general may be necessary to avoid manipulation, exploitation, and other harms from AI-guided business strategies and tactics.

Healthcare workers may be subject to AI-powered exploitation as well. AI could be applied to many healthcare administration tasks, from logistics and ordering to recordkeeping to management, assessment, and punishment or rewarding of healthcare workers (Reddy et al., 2018). Algorithmic workforce management, not unlike algorithmic health decision-making, carries potential for systemic errors, social biases, excessive surveillance, and worker manipulation through "nudging" (Gal et al., 2020). In 2018, Amazon had to scrap a machine-learning recruiting tool that had incorrectly inferred, based on the preponderance of male resumes submitted for developer positions, that men made better developers than women (Dastin, 2018). Algorithmic performance management of low-pay roles at Amazon has led to performance assessment and firing without appropriate attention to contextual factors and without recourse to a human boss (Soper, 2021). Uber uses behavioural "nudges" to induce drivers to work longer hours and take worse-paying assignments (Scheiber and Huang, 2017). Physicians and other powerful healthcare workers may be able to resist the imposition of such management practices, but orderlies, administrative assistants, home health aides, and other lower-ranking professionals may not be so privileged.

Exacerbation of healthcare inequities

Although many commentators hope that AI will help to reduce healthcare costs and improve healthcare accessibility (e.g. Khanna *et al.,* 2022), there are at least three ways in which AI could actually worsen healthcare inequities. First, errors and biases of the sort alluded to above are often linked to existing societal inequities. AI systems used for diagnostics perform worse for patients of demographic categories less represented in training datasets (Guo *et al.,* 2021; Kamulegeya et al., 2023; Lee *et al.,* 2021). AI systems used for healthcare management could directly reproduce past inequities in healthcare resource allocation. This is no idle speculation. One commercial algorithm widely used to identify patients for additional care in the United States has been found to systematically underestimate the care needs of Black patients due to their historically lower levels of care (Obermeyer *et al.,* 2019).

Second, advanced treatments developed using AI, or actually implementing AI – say, custom "digital twins" of individuals used to personalise diagnostics and treatment (Björnsson et al., 2020) – may, like other expensive medical innovations, be far more accessible to socioeconomic elites. Such access gaps exist even in nations with national healthcare (e.g. Kapadia *et al.,* 2022). Disparities in access to high-tech health innovations could continue to widen healthcare gaps between the rich and the poor.

Third, although AI can be used to reduce healthcare costs, under-resourced medical providers and systems will be under pressure to cut costs excessively. Resource-strapped providers might be incentivised to deploy AI systems outside their intended scope, skip important oversight, and, perhaps, even automate tasks better left partially or entirely human. In short, as with most emerging technologies, wealthy patients and the providers who serve them will be best situated to capture the upsides of AI in healthcare, while the poorest will be most vulnerable to its downsides (Bozeman, 2020).

Ensuring equity in AI for healthcare is inextricable from ensuring equity in healthcare overall. Demographic biases in AI predictions and recommendations emerge from biases in historical datasets. Moreover, in an inequitable healthcare system, advantages and disadvantages will be unfairly distributed, for old as well as for new technologies. While care can be taken to design and implement healthcare AI as ethically and appropriately as possible (World Health Organization, 2021), there is no technological fix for the socioeconomic inequities that drive health disparities (Costa-Font and Hernández-Quevedo, 2012). Substantial reforms not only to healthcare systems but to the technological, economic, and social arrangements that underpin them may be necessary to achieve good health for all (World Health Organization Council on the Economics of Health for All, 2023).

Shaping the future of artificial intelligence in healthcare

AI has the potential to contribute greatly to improving standards of care, accelerating healthcare innovation, and reducing healthcare costs. Simultaneously, it also carries potential to reduce the reliability of some healthcare work, facilitate the spread of misinformation, contribute to exploitation of patients and healthcare workers, and exacerbate healthcare inequities. Which of these, and of AI's many other potentialities, are realised will depend upon the interests, priorities, and constituencies empowered to shape the development and deployment of AI in healthcare. For technologies as for policy, the best and only – though still far from perfect – guarantee of democratic benefit is democratic governance (Pacifico Silva *et al.,* 2018).

A broad and diverse citizenry must be continually empowered to determine whether and how AI should be implemented in healthcare. Only democratic decision-making can ensure that we will anticipate and avoid adverse consequences and that we will deploy AI in ways that advance all citizens' health. Conventional democratic processes are essential (Genus and Stirling, 2018), and newer experiments in public engagement (Kaplan *et al.,* 2021) and strategic foresight (Selin *et al.,* 2023) can also be useful for aligning novel technologies with public values (Ribeiro *et al.,* 2018). The work of democracy is always piecemeal and messy. It will require that patients, healthcare workers, citizens, and communities advocate for their needs and interests, that governments work to advance them, and that those most empowered in the health innovation ecosystem – not only physicians, but administrators, technologists, and financiers – embrace both responsibility and accountability for the health of the communities they serve (Stirling, 2015; Nelson *et al.,* 2021). AI in healthcare will be what our societies make of it. It is up to us to fairly realise and distribute AI's benefits and to anticipate and prevent its harms.

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Polygenic scores and precision genetics

Polygenic scores: what they are, how they are calculated and how they can facilitate clinical outcomes

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What is a polygenic score?

A polygenic score, or polygenic index, is a mathematical tool that scientists use to estimate the combined effects of many different genes on a specific trait or characteristic. Polygenic scores were originally utilised in plant and animal breeding and transitioned to human genetics in 2007 when researchers proposed using these scores to identify individuals at an elevated risk of disease (Wray *et al.*, 2007). The practical application took shape in 2009 through a study on schizophrenia that was not only the first one to apply polygenic scores, but also introduced the term "polygenic score" (Purcell *et al.*, 2009).

Complex pathological conditions in humans tend to be associated with not one, but many genetic variants, each playing a small yet different role in increasing or decreasing risk. Polygenic scores provide a way of bringing together genetic risk scattered across the entire genome. They take findings from large gene-discovery studies and aggregate information from up to a few million genetic variants into a single score that provides a personalised index, although partial, of genetic influence on a trait. It is possible to calculate a polygenic score for any trait for which a gene-discovery study is available—physical, health-related, or psychological. A way to think about polygenic scores might be as a graded measure of risk calculated directly from DNA; not unlike a credit score provides a partial summary of your financial risk, a polygenic score provides a partial index of your genetic risk for a particular disorder or trait. Polygenic scores are a valuable tool in precision medicine as they not only help to tailor screening, prevention, and treatment strategies based on an individual's genetic risk profile but also provide a more nuanced understanding of risk and outcomes, allowing for more personalised healthcare choices, including decisions about risk management strategies.

How are polygenic scores calculated?

Polygenic scores are calculated using data from genome-wide association studies (GWAS). These are large gene-discovery studies that scan the genome (i.e. decoded DNA sequence) of several hundred thousand or even millions of people to identify genetic variants, namely the single nucleotide polymorphisms (SNPs), that are associated with a specific disease or physical or behavioural characteristic. When adequately powered, GWAS can reliably identify genetic variants that are associated with a given trait as well as how strongly each variant is associated with differences between people in that trait (i.e. the *effect size* of their association). The effect size can be positive, therefore conferring an increased risk of developing a disorder or trait, or negative therefore lowering the risk. To calculate a polygenic score, researchers combine all the genetic variants that are associated with a given trait or disorder, each weighted by its effect size. The process of creating polygenic scores using data from GWAS is illustrated in Fig.1, derived from Belsky and Harden (2019), where the participant's SNPs are given weights that signify the direction and strength of the link to a specific trait. Typically, these weights are derived from effect sizes, denoted as $\hat{b}j$, estimated in a GWAS that did not involve the research participant. Following this, the count of alleles associated with the phenotype at each SNP (j) is estimated, and this count is multiplied by the corresponding weight, $\hat{b}_j$. Ultimately, the weighted counts are added together across all SNPs to determine the participant's polygenic score. The resulting distribution of polygenic scores among participants follows a normal distribution, corresponding to the distribution of symptoms of a particular disease (Fig.2).

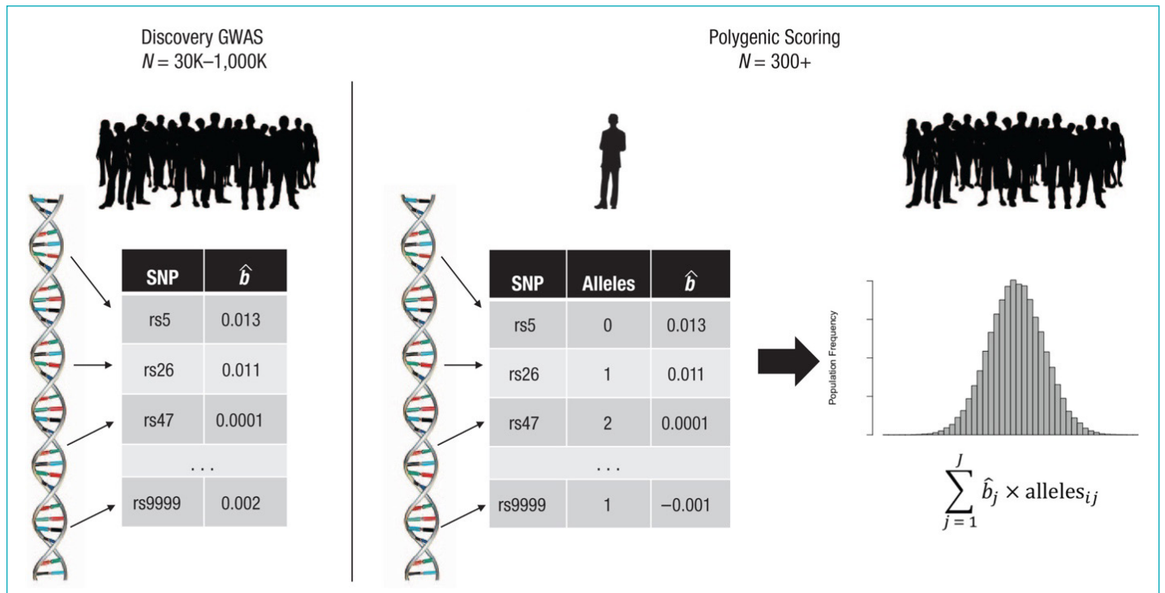

Figure 1. The process of creating polygenic scores using data from GWAS. Reproduced by kind permission from Belsky and Harden (2019).

How accurate are polygenic scores?

While lifestyle factors are important contributors to many health-related outcomes, genetics also play a significant role in determining an individual's susceptibility, hence polygenic scores offer insights beyond lifestyle factors. Genetic risk assessments can help to identify individuals at risk for certain conditions early in life, sometimes before lifestyle-related issues become apparent. This early identification allows for proactive and preventive measures. In addition, certain health conditions have a strong genetic component that may contribute to risk even in the absence of risky lifestyle behaviours. Polygenic scores help identify individuals who may be at elevated risk due to their genetic makeup. Some polygenic scores are more accurate than others in terms of predicting real-life outcomes. For cardiovascular disease, for example, studies have shown that a high polygenic score can be as effective at predicting the risk of heart problems as other lifestyle risk factors that are usually considered by medical practitioners, for example, smoking and body mass index (Inouye *et al.,* 2018).

Another condition for which polygenic scores could be of great utility is diabetes. Using polygenic scores, it might be possible to diagnose young adults with diabetes who might need insulin treatment (Padilla-Martínez *et al.,* 2020) and to differentiate between different types of diabetes (e.g. type 1 versus type 2) (Oram *et al.,* 2016). With such a high level of accuracy, greater precision in diagnosis, facilitated by polygenic scores, could result in lifestyle changes or targeted use of medication to effectively treat, or even slow down the progression of the condition before the symptoms have manifested.

Polygenic scores have been proven to be valuable not only in predicting physiological outcomes but also in shedding light on behavioural traits. However, compared to other physical traits or medical conditions, like diabetes or coronary artery disease, the prediction of behaviour and emotional problems remains relatively small, predicting less than 6% of differences between children and adolescents (Gidziela *et al.,* 2022). Although the current level of accuracy means that polygenic scores are not yet useful in correctly identifying children at risk of behaviour problems, they are currently a valuable tool in behavioural research. For example, researchers are interested in exploring whether combining polygenic scores with other environmental risk factors might lead to greater prediction accuracy.

It is important to note that while polygenic scores offer insights into potential relationships between genetics and health outcomes, they're not perfect predictors. Many factors shape our behaviour and health, including life experiences and environment. Nevertheless, polygenic scores provide a valuable tool for researchers to better understand the complex interplay between genetics, health, and behaviour, helping us uncover more about the factors that contribute to differences in traits and diseases. In essence, polygenic scores provide insightful clues, but they're not crystal-clear indicators just yet. We are on a journey of refining and improving them to enhance their accuracy for practical applications.

When talking about prediction accuracy of polygenic scores it cannot be separated from the extent to which a trait is shaped by genetics, known as its heritability. Essentially, heritability measures how much of a particular trait's variation, *i.e.* individual differences in that trait, is attributable to genetic variation. It is crucial to understand that when dealing with complex traits that are only partly influenced by genetics, such as physiological and behavioural traits, the predictive models based solely on genetic information tend to be less accurate (Plomin and Von Stumm, 2021). Most complex traits are influenced by both genetics and the environment, leading to a complex interplay.

A fascinating aspect of polygenic scores is that they're like a static snapshot of the genome; they provide a picture that doesn't change over time because the structure of the DNA does not change. This means they can be measured at any time, unlike some other biological markers that might change, for example, DNA methylation, a marker of gene expression. Nevertheless, this does not mean that polygenic scores are free from environmental effects. In fact, polygenic scores are constructed based on phenotypes that always vary as a function of both genetics and the environment. For example, scientists have observed that the polygenic prediction of educational achievement tends to strengthen as individuals progress through their educational journey, that is likely to reflect a correlation between genes and environments (Allegrini *et al.,* 2019). As children mature, they actively shape their experiences and environments, influenced in part by their genetic propensities, and these experiences, in turn, impact their academic progress.

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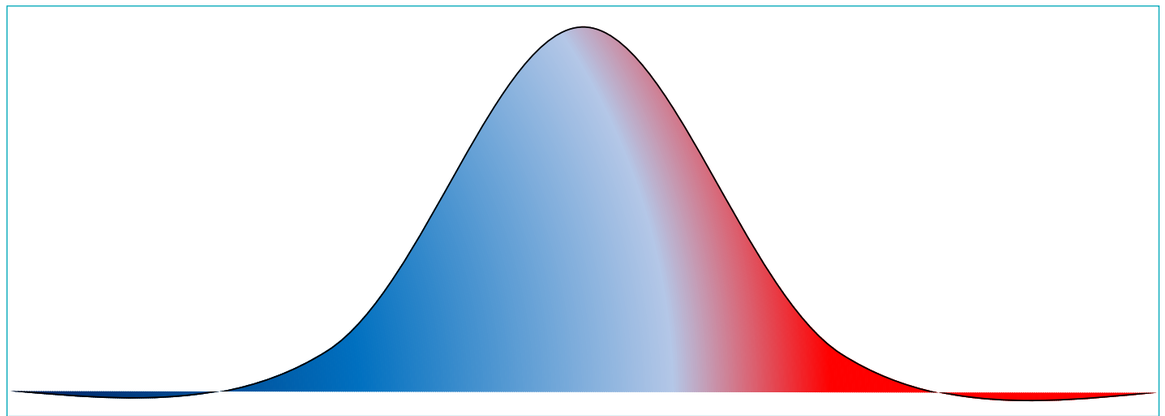

Figure 2. Distribution of polygenic scores, corresponding to the distribution of symptoms of a particular disease.

Complex pathological conditions in humans tend to be associated with not one, but many genetic variants, each playing a small yet different role in increasing or decreasing risk. Polygenic scores provide a way of bringing together genetic risk scattered across the entire genome.

What are the limitations of polygenic scores?

Polygenic scores, while a valuable tool in genetics and genomics, do have several limitations.

The precision of polygenic scores hinges on the quality and diversity of the genetic data employed in their calculation. In cases where the underlying datasets show biases or a lack of diversity, the predictive accuracy of these scores can be compromised. Such biases can happen when some populations are much more common in the data than others. When this occurs, it can lead to inaccurate risk assessments and predictions for underrepresented or marginalised groups. This limitation underscores the importance of diverse and representative genetic datasets to ensure reliable application of polygenic scores across different populations (Martin *et al.,* 2018).

Furthermore, complex traits often result from an intricate interplay between genetics and environmental exposures. Polygenic scores solely capture the genetic component of these traits and diseases, disregarding the substantial influence of environmental variables that are also relevant for disease development. While genes play a role, they are just a piece of the puzzle and miss out on these external aspects. Therefore, polygenic scores cannot be used to make definitive predictions about an individual's risk of developing a disease (Wray *et al.,* 2021).

Another limitation includes incomplete understanding of the genetic underpinnings of various traits and diseases. Polygenic scores rely on the knowledge of known genetic variants associated with a particular trait or condition. However, the genetic landscape is far from fully explored, and polygenic scores do not encompass all relevant genetic factors. The present state of genetic knowledge underscores the need for cautious interpretation and application of polygenic scores (Wray *et al.,* 2021).

In addition, use of polygenic scores in healthcare and decision-making contexts raises ethical concerns related to privacy, discrimination, and the potential for stigmatisation. Ensuring responsible and equitable use of polygenic scores is an ongoing challenge (Lewis and Green, 2021; Wray *et al.,* 2021).

There is also the question of whether whole-genome-sequencing (WGS) is required to generate polygenic scores for its use in routine medical care. WGS involves sequencing of the entire genome. While WGS provides comprehensive genetic information, it is costly and may not be necessary for generating polygenic scores. Despite the present cost of WGS being a few thousand dollars, the expenses are rapidly decreasing and are anticipated to dip below $1000 (Plomin and Simpson, 2013).

The utility of polygenic scores in routine medical care depends on the specific application. Polygenic scores may be more relevant for complex traits influenced by multiple genetic factors rather than single-gene disorders. Before polygenic scores become routine in medical care, regulatory bodies and healthcare providers need to establish guidelines for their use. This includes considerations of accuracy, clinical validity, and ethical considerations.

What are the potential applications of polygenic scores?

Polygenic scores have a number of potential applications. They can be used to identify individuals who are at an increased risk of developing a disease. This information can be used to develop preventive measures or to provide early diagnosis and treatment. Polygenic scores are a promising tool for understanding and preventing disease. However, it is important to remember that they have limitations and should not be used as the sole basis for making medical decisions.

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We will discuss specific potential applications of polygenic scores for physiologists, focusing on breast cancer, cardiovascular health and disease risk, pharmacogenetics, metabolic health, precision medicine and personalised interventions.

Polygenic scores play a significant role in breast cancer research and clinical practice. They help identify women at higher genetic risk for breast cancer, enabling tailored population screening and risk assessment for those without known genetic mutations (Yanes *et al.*, 2020). Polygenic scores also enhance risk estimation for individuals with genetic mutations, influencing decisions about preventive measures, such as prophylactic mastectomy (Yanes *et al.*, 2020). Additionally, polygenic scores distinguish between breast cancer subtypes and predict diagnostic outcomes, assisting women with treatment decisions based on their history and prognosis (Yanes *et al.*, 2020).

Beyond breast cancer, research has shown that polygenic scores can provide insights into an individual's genetic predisposition to cardiovascular conditions like heart disease, stroke, and high blood pressure (Abraham *et al.*, 2021). By analysing specific genetic variations associated with these conditions, cardiologists can better understand why some people are more vulnerable and develop strategies for early detection and tailored prevention plans.

Polygenic scores can also be used to study drug response and pharmacogenetics– a study of how genes influence how our bodies respond to medications. Polygenic scores can help predict how a person might metabolise and respond to specific drugs (Fabbri and Serretti, 2020). This knowledge helps avoid adverse reactions and optimise treatment outcomes.

Understanding how genetics influence metabolic health is another area of interest for physiologists, because polygenic scores offer insights into an individual's risk of developing diabetes. By identifying genetic variants linked to glucose regulation and insulin sensitivity, researchers can gain a better understanding of why some individuals are more prone to metabolic disorders (Padilla-Martínez *et al.*, 2020).

Polygenic scores have the potential to contribute to the field of precision medicine. By combining genetic information with other health data, physiologists can develop personalised intervention plans that consider an individual's genetic predispositions (Wray *et al.*, 2021). For instance, they can identify individuals who are at higher risk for certain conditions and recommend targeted interventions for prevention.

With such a high level of accuracy, greater precision in diagnosis, facilitated by polygenic scores, could result in lifestyle changes or targeted use of medication to effectively treat, or even slow down the progression of the condition before the symptoms have manifested.

The future of polygenic scores to guide more personalised healthcare

It is nonetheless essential to acknowledge that polygenic scores are not flawless. They cannot definitively predict the occurrence or absence of a disease in an individual. In essence, polygenic scores offer physiologists a powerful tool to guide the development of tailored interventions, advance our understanding of human physiology, and pave the way for more personalised approaches to healthcare. However, before this is implemented in routine healthcare, the field has to overcome limitations such as representative bias (mostly European populations) in genomic datasets, understanding how to account for environmental and lifestyle factors in prediction scores, creating and/or selecting statistical models that best reflect specific patterns of a disease and tackling current ethical concerns of using unvalidated polygenic scoring processes in commercial settings, to name a few.

Polygenic scores play a significant role in breast cancer research and clinical practice. They help identify women at higher genetic risk for breast cancer, enabling tailored population screening and risk assessment for those without known genetic mutations

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AI for fairer clinical decisions

How diverse data can improve diagnostics for Parkinson's Disease

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Artificial intelligence (AI) has the potential to transform early diagnosis and subsequent treatment of neurological conditions, such as Parkinson's disease. Early diagnosis means quicker access to vital care and support that could improve an individual's quality of life and disease progression. But the applications of AI do not stop there – AI is also helping researchers to better understand the causes of Parkinson's by assessing the changes in the brain at the initial stages of the disease. These early insights could be the key to developing new and better treatments.

At Skein, we are working on an AI tool to assist clinicians with the decision-making for Parkinson's. This can be informed by patient data, but unfortunately many datasets are not representative of the population. Improving the quality and diversity of the data will provide the greatest insights for the medical community, allowing for a broader identification of a range of factors, patterns or correlations, which would ultimately improve the accuracy and reliability of diagnosis and prognosis.

AI-based tools for early-stage diagnosis and timely interventions

To enable fairer, more ethical and comprehensive AI, Skein develops a platform that helps evaluate quality, representativeness and value of data for clinical decision-making using distributed collaborative learning approaches. The goals of ensuring validity, security and compliance of patient data collection are becoming especially relevant for innovative organisations who use AI to solve the biggest challenges in preventive healthcare. Among such initiatives is AI-Mind, a European project that aims to reduce the burden of ageing brain conditions by developing novel, AI-based tools to support healthcare professionals in their early-stage diagnosis of people with mild cognitive impairment and offering timely interventions to patients.

Diverse physiological data ensure that clinical decisions are more personalised, thus providing tailored medical advice that is more likely to be effective. More importantly, by ensuring that AI tools are trained on a diverse dataset, it addresses the potential biases that may arise when considering factors like age, gender, race, and socio-economic background. This not only guarantees more equitable healthcare solutions but also ensures that historically marginalised and underserved groups receive medical attention that truly resonates with their unique physiological needs.

Parkinson's disease, a progressive neurodegenerative disorder

Parkinsons is the fastest growing neurological condition in the world, with approximately 10,000,000 individuals living with it (WHO, 2023; Parkinson's Foundation). The condition affects the nervous system, especially the

By ensuring that AI tools are trained on a diverse dataset, it addresses the potential biases that may arise when considering factors like age, gender, race, and socio-economic background.

Figure 1. Launch of The Physiological Society's policy report on AI, "From 'Black Box' to Trusted Healthcare Tools" at the Houses of Parliament in June 2023

nerves involved with movement. This means many will experience motor problems such as shaking, stiffness, and difficulty with balance and coordination (Postuma RB *et al.*, 2016). These symptoms can make it harder to walk and the changes in the brain could also affect speech and difficulties in chewing food and swallowing.

We are still trying to unravel the exact causes and risk factors of Parkinson's. So far, research has shown us that specific nerve cells in the brain are affected. These are the ones responsible for producing a chemical messenger called dopamine and coordinate our movement, mood and sleep (Latif S *et al.*, 2021). As the condition progresses, these brain cells are lost. As the number of these brain cells deplete in the brain, the levels of dopamine are reduced, which prevents the brain from communicating effectively. This is when symptoms tend to arise.

Why an early diagnosis matters

There is currently no cure for the condition, but regular medication and care can help individuals manage the symptoms and improve their quality of life (Grosset *et al.*, 2007; Islam *et al.*, 2023; WHO, 2023). As symptoms tend to worsen over time, getting an early diagnosis of Parkinson's disease is pivotal. This enables prompt interventions to manage symptoms more effectively and potentially slow down the disease progression (Parkinson's Foundation). We also see better responses to medication when treatments are started in the initial stages.

An early diagnosis provides patients with the opportunity to make informed life decisions, they can partake in clinical trials, receive comprehensive care, attend to their non-motor symptoms, as well preparing and building the emotional and psychological support. As well as benefiting the individual, an early diagnosis offers invaluable insights to researchers, aiding them in the advancement of our understanding of Parkinson's and developing potential treatments.

However, obtaining a diagnosis is not simple.

There is no single definitive test for Parkinson's disease. Instead, the diagnosis is based largely on clinical evaluation, including the examination of medical history, neuroglial assessment, imaging tests such as Dopamine Transporter Scan (DaTscan) and other multi-step, high-cost procedures.

Figure 2. Skein, data analytics team

AI offers us a way to revolutionise the early detection of Parkinson's disease.

The transformative potential of AI

AI offers us a way to revolutionise the early detection of Parkinson's disease. Machine-learning models, a subset of AI, can analyse vast amounts of data, covering everything from medical imaging to subtle variations in speech or motor patterns, which might be imperceptible to humans. By training these models on large datasets of patient records, they can identify patterns and anomalies linked to the earliest stages of the disease.

AI algorithms can analyse medical healthcare records, gait patterns, and even handwriting and voice recordings to discern the slightest tremors or changes indicative of Parkinson's. AI-enhanced neuroimaging can also detect minute changes in the brain's structure or functionality long before a clinical diagnosis would typically be possible.

Data diversity is a game changer for healthcare

While AI's analytical prowess is commendable, it is the quality and diversity of the data it analyses that plays a critical role. Although Parkinson's disease affects people around the world, its presentation, progression, and individuals' response to treatments might vary depending on regional/ethnic genetic, environmental, and lifestyle factors. That is why it is important for diagnostics and treatment to be personalised. By intentionally including diverse physiological data, especially from underrepresented populations, the medical community can better address and mitigate these disparities.

Medical research has historically been skewed towards certain populations, often Western and Caucasian. When detection and treatment strategies are based predominantly on data from a specific demographic, they might be less effective or even misleading for other groups. Diverse data ensure that the derived conclusions and interventions are universally applicable.

Figure 3. Skein, EU TARA project team

Some patients may not present with "typical" symptoms or might have unusual disease progressions. If the data are limited to a narrow population, these atypical cases might be missed or misdiagnosed. A diverse dataset can better capture the full spectrum of the disease.

Similarly, lifestyle and cultural practices can influence the progression and management of Parkinson's disease. For instance, diet, exercise habits, and exposure to environmental factors can all play a role in the disease. Diverse data can provide insights into how these factors intersect with the disease, leading to more holistic and individualised care.

Additionally, a diverse dataset allows researchers to ask a broader set of questions and identify patterns or correlations that might be less evident in a more homogeneous group. This can lead to novel insights and breakthroughs in Parkinson's detection and treatment.

AI is a societal evolution for healthcare

AI in healthcare is not merely a technological evolution; it's a societal one. That is why it is imperative to engage and discuss AI in healthcare with policymakers. As we integrate these tools more deeply into our healthcare systems, it is paramount to ensure they are safe, effective, and most importantly, equitable.

This is why we joined the preparation and launch of The Physiological Society's policy report on AI, "From 'Black Box' to Trusted Healthcare Tools" at the Houses of Parliament in June of this year. The work highlights the importance of diverse physiological data in creating next-generation AI-based prevention tools. By involving various stakeholders, from clinicians to technologists, the event provided a 360-degree view of the challenges and prospects AI holds for clinical care and the research field.

The discussions held were enlightening, touching upon the ethical, practical, and logistical aspects of AI in healthcare. The emphasis on data diversity privacy, patient autonomy, and the potential of AI to democratise healthcare was particularly salient. By working together with policymakers, we can unlock the potential of AI to revolutionise healthcare and improve patient outcomes for those living with neurological conditions to cardiovascular disease and cancer.

AI in healthcare is not merely a technological evolution; it's a societal one. That is why it is imperative to engage and discuss AI in healthcare with policymakers.

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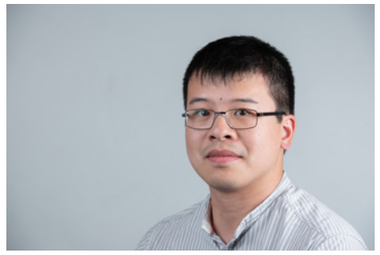
Using AI to develop better ovarian cancer treatment

Targeting residual cancer cells for future immunotherapy approaches



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Artificial intelligence (AI) promises to provide a set of transformative technologies for healthcare. From automating the reading of medical images to optimising the flow of patients through hospitals, there are numerous applications of AI that are currently being explored internationally (Acosta *et al.*, 2022).

In particular, the advent of molecular technologies that now enable us to routinely sequence our genomes and to measure the properties of single cells and molecules is providing new knowledge of the fundamental biochemical processes that govern normal and abnormal physiological behaviour. The data that arise from the use of these technologies are ripe for AI as the data quantity and richness defy manual human interpretation and necessitate the need for automated algorithmic solutions.

The convergence of molecular technologies and AI is being witnessed in their combined use in the development and implementation of advanced therapeutics for many diseases (Huang *et al.*, 2022) and particularly for cancer (Ho, 2020). While cancer outcomes have improved for many disease types over the years, predicting response to treatment for individual patients remains challenging, and it is still unclear why some cancers are prone to relapse and treatment resistance, but others are not. In this article, we will examine how AI is being used to address these issues to advance therapeutic opportunities for one of the most challenging cancers to treat – ovarian cancer.

Ovarian cancer and prognosis

Over 300,000 cases of ovarian cancer were diagnosed globally in 2020, representing 1.7% of all cancer cases and making ovarian cancer the 18th most prevalent cancer. While breast cancer is the most prevalent (12.2%) (IACR, 2023), 85% of those diagnosed with breast cancer live for 5 years or more in the UK, whereas only 45% of ovarian cancer patients can expect the same life expectancy (NHS Digital, 2023). This makes ovarian cancers one of the cancers with the poorest patient outcomes and the most lethal of all the gynaecological cancers.

While ovarian cancers are predominantly sporadic, a subset of cases have a heritable genetic component. Individuals who inherit BRCA1/2 mutations, which are better known for causing breast cancers, are also at increased risk of ovarian cancers. Furthermore, Lynch syndrome, which significantly increases the risk of colorectal cancers, also increases the risk of ovarian cancer as well.

There are many types of ovarian cancer, with the high-grade serous subtype (HGSOC) the most common, representing 70% of cases and having the poorest prognosis (and the predominant focus of this article). Ovarian cancers are difficult to recognise as they are indicated by non-specific symptoms (such as abdominal bloating, irregular periods) and late diagnosis is common, which contributes to poor survival outcomes. When it is discovered, the cancer has often already spread outside the pelvis to the lining of the abdominal cavity (peritoneum). It can also migrate to the lymph nodes in the back of the abdomen.

Current treatments

Standard first-line treatment of ovarian cancer involves a combination of surgery to physically remove cancerous tissues and platinum-based chemotherapy. Platinum-based chemotherapies are cytotoxic agents that cause DNA damage by delivering platinum-based compounds into cells, which bind to DNA, causing adducts and cross-links in the DNA. These disrupt DNA replication and synthesis, triggering DNA repair mechanisms that are unable to resolve the damage and instead trigger apoptosis (cell death). Treatment relies on the principle that cancer cells divide more rapidly than non-cancer cells and will be disproportionately affected by the chemotherapy. Nonetheless, non-cancer cells will be impacted as well, and this results in patient side-effects such as neurotoxicity.

In the last decade, first-line ovarian cancer treatments have increasingly been combined with other approaches such as anti-angiogenic therapy or poly(ADP-ribose) polymerase (PARP) inhibitors.

Anti-angiogenic therapy targets angiogenesis - the mechanism for the formation of blood vessels. During tumour growth, cancer cells continuously secrete many related factors that promote angiogenesis, such that new vascular networks are continuously generated in the tumour tissues for the rapid proliferation of cancer cells. Anti-angiogenic therapies block key components of the angiogenesis pathway, such as vascular endothelial growth factor A (VEGF-A), to limit vessel formation and reduce tumour formation.

PARP inhibitors are targeted treatments for ovarian cancers that have mutations in the homologous recombinational repair (HRR) pathway, which is responsible for resolving double-strand DNA breaks. PARP inhibitors block the function of the PARP enzyme, which is involved in the repair of single-strand DNA breaks. During DNA replication, these unrepaired single-strand DNA breaks are converted into double-strand breaks that cancer cells with deficient HRR function cannot repair, which then triggers cell death.

Despite the availability of these treatments for patients diagnosed with late-stage ovarian cancers, over 70% will have a recurrence with a median time to relapse of 18-24 months. Relapsed disease is generally incurable, and the objective of further therapy is to control the condition and manage symptoms, prolong the need for further treatment, and maintain quality of life for the patient.

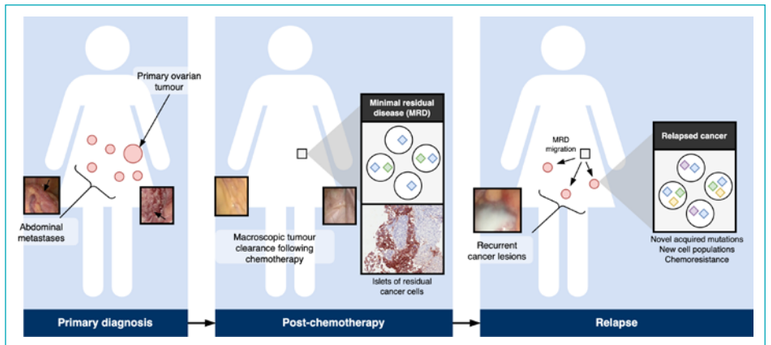

Figure 1. **Ovarian Cancer.** At primary diagnosis, high-grade serous ovarian cancers are typically characterised by advanced disease due to late presentation with primary ovary tumours and abdominal metastases. First-line chemotherapy, in combination with maintenance therapy, can provide macroscopic clearance of the tumour. However, haematoxylin and eosin (H&E) staining of tissues will reveal microscopic residual disease formed of islets of cancer cells distributed across previously affected regions. Relapsed cancer occurs due to the expansion and migration of the minimal residual disease cancer cells and ongoing mutations can lead to changes in the tumour characteristics and the emergence of chemotherapy resistance.

Residual cells, the seeds to cancer cell repopulation

High-resolution studies of post-operative tissues reveal that microscopic deposits of ovarian cancer cells (minimal residual disease, MRD) can remain after surgery and chemotherapy (Hellner *et al.*, 2016). These residual cells are the seeds by which the cancer cell population can repopulate and, having already survived a course of treatment, they are likely to be resistant to further applications of the same treatments (Fig.1).

Many biological mechanisms have been attributed to treatment resistance in ovarian cancer. Underpinning these is the genetic diversity of ovarian cancers (Fig.2). Whole-genome sequencing has revealed that HGSOCs contain anywhere between 5,000 and 50,000 single nucleotide mutations as well as a complex landscape of chromosomal rearrangements and DNA copy number changes (Cancer Genome Atlas Research Network, 2011). The characterisation of these mutational processes has led to the identification of mutational signatures (Macintyre *et al.*, 2018) and pathways leading to different evolutionary states

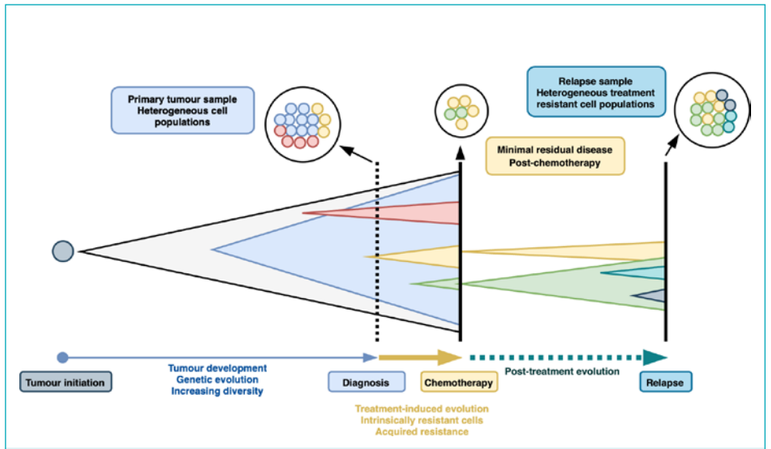

Figure 2. **Genetic evolution of ovarian cancer.** After tumour initiation, ovarian cancers evolve as the tumour develops with new lineages of cancer cell populations emerging. At diagnosis, a primary tumour sample will contain a heterogeneous mixture of genetically related cancer cell types. Chemotherapy will cause the eradication of chemo-sensitive cancer cell populations and promote the relative survival of cell types that harbour intrinsic resistance mechanisms. Further evolution is stimulated, leading to new lineages of cancer cells with their own specific genetic characteristics and chemo-resistant cell populations may also emerge.

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AI algorithms are used to identify the target signatures but can also be used to design and optimise the design of the mRNA vaccine itself to maximise stability and specificity of the treatment.

and trajectories (Lahtinen *et al.*, 2023). Mutations lead to alterations in normal cellular programming that promote the growth of the cancer and may confer resilience to treatments. For example, cancers that acquire reversion mutations that restore HRR function can become resistant to PARP inhibitors. The mutational processes driving ovarian cancers are continual; new mutations are acquired over time and as the cancer grows. This presents a challenging dynamic target for treatments and explains why standard treatments can eventually be overcome by cancer cells.

Non-genetic mechanisms could also contribute to treatment resistance. We proposed a model whereby the phenotypic behaviour of HGSOC cells is a mixture of five signatures, which we identified through single-cell sequencing of the cell-of-origin (the fallopian tube epithelium) of ovarian cancers (Hu *et al.*, 2020). We have also observed that MRD cells harbour an adipocyte-like gene expression signature (Artibani *et al.*, 2021). Using a cell culture model, MRD-mimic cells were found to be dependent on fatty acid oxidation for survival and displayed resistance to cytotoxic agents. Treatment-induced cell plasticity can therefore push ovarian cancers towards phenotypic states that confer greater resistance to therapies.

Interactions between ovarian cancer cells and adjacent stromal and immune cells within the tumour microenvironment (TME) also provide a further source of resistance pathways. For example, ovarian cancers have been associated with increased levels of cancer-associated fibroblasts (CAFs) that can obstruct the transportation of chemotherapeutic agents and impair chemotherapeutic efficacy by creating physical barriers and microvascular compression, while ovarian cancers classified as having a high level of epithelial-to-mesenchymal transition expression markers have been found to have a particularly poor prognosis and were associated with high frequency of immunosuppressive macrophages (Hu *et al.*, 2021).

Creating new DNA sequencing tools

To examine the exact properties of treatment-resistant cancer cells, we must collect them immediately following treatment. However, retrieving and analysing post-treatment ovarian cancer specimens is difficult. Sample retrieval requires invasive procedures and, due to the microscopic nature of residual disease, only a small amount of biological material may be available. This can present challenges for subsequent analysis. If we wait until the disease relapses, more diseased tissue would be available but, as the cancer evolves over time, the properties of the cancer may have changed in the time between primary treatment and relapse.

Small islets of residual disease may contain fewer than 100 cells but standard whole-genome sequencing typically requires large quantities of DNA obtained from tens of thousands of cells. We developed DigiPico (Carrami *et al.*, 2020), a sequencing protocol specifically designed to enable us to sequence the picograms of DNA available from residual disease samples. In addition to the experimental techniques, it was also necessary to develop an AI algorithm, called MutLX, to process the sequencing data to reliably differentiate true mutations from artefacts. MutLX adapts its behaviour, adjusting to the noise and sequencing characteristics of each sequenced sample. The result is that we are now able to examine the genetic properties of microscopic residual disease cell populations and investigate resistance mechanisms in ovarian cancer.

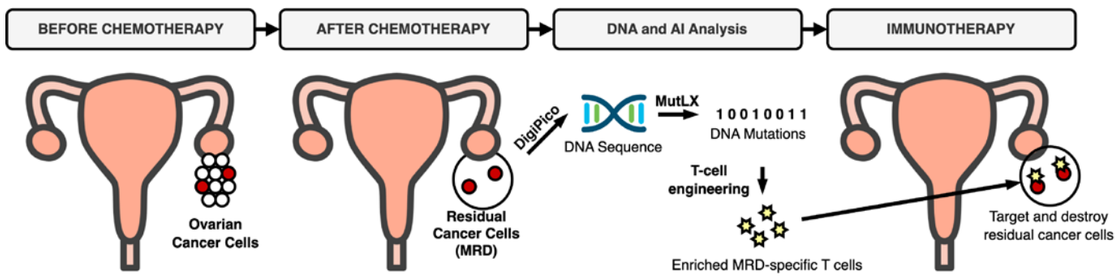

Figure 3. **Adoptive T-cell therapy supported by artificial intelligence for targeting minimal residual disease in ovarian cancer.** The use of DigiPico and MutLX to sequence and analyse MRD disease samples enables the selection of enrichment of the patient's own MRD-specific T-cells to be produced in the laboratory. These can then be infused back into the patient to target and specifically destroy residual disease, preventing relapse and intervening before cancer evolution changes the properties of the cancer.

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The future of ovarian cancer treatment

AI technologies will change the way ovarian cancer is diagnosed and treated within the next 10-15 years. The most immediate impacts will likely emerge first in diagnostic tools. As different types of clinical, molecular, and imaging technologies become available, data arising from these will need to be integrated via AI to support clinicians with treatment planning and selection. Later, what is perhaps most exciting is that AI might become integrated into the production of patient-specific treatments as well.

For example, adoptive T-cell therapies attempt to enhance a patient's own immune system's ability to attack and eradicate their tumour with T-cells (Morotti *et al.*, 2021). These therapies involve removing a patient's or donor's T-cells, growing and/or modifying them in a laboratory, and reinfusing them back into the patient (Fig.3). One challenge with these therapies is the phenomenon known as "T-cell exhaustion".

Mutations carried by cancer cells appear foreign to our immune system, which reacts by initiating a T-cell response to eliminate the cancer. However, if the immune system is persistently unable to clear the cancer, T-cell exhaustion can occur, in which the immune system switches from attacking the cancer to co-existing with it and T-cells become underactive. Boosting the cancer-specific T-cell response through adoptive T-cell therapy is an obvious approach to addressing this issue. Using DigiPico and MutLX, we can now sequence and identify mutations specific to residual cancer cells, and therefore identify the corresponding cancer-specific T-cell subpopulation. By expanding and enriching this subpopulation in the laboratory and then reimplanting these T-cells into the patient, the hope is that the residual cancer could be fully eradicated, preventing relapse. Importantly, by intervening at the MRD stage, the disease can be tackled before further cancer evolution takes place, which might alter the properties of the disease.

Modern vaccine technologies have also been developed as cancer therapeutics (Lin *et al.*, 2022). Messenger RNA-based cancer vaccines deliver short RNA fragments into the body, which instruct cells that take up the vaccine to produce tumour-associated proteins that stimulate an immune response against the patient's cancer. AI algorithms are used to identify the target signatures but can also be used to design and optimise the design of the mRNA vaccine itself to maximise stability and specificity of the treatment.

MutLX adapts its behaviour, adjusting to the noise and sequencing characteristics of each sequenced sample. The result is that we are now able to examine the genetic properties of microscopic residual disease cell populations and investigate resistance mechanisms in ovarian cancer.

These examples suggest the tantalising possibility of combining AI to aid in the more accurate diagnosis and prognosis of a patient's cancer with AI that helps to create bespoke therapeutics to address the condition in the future. However, this use of AI also presents new regulatory challenges. For instance, if every ovarian cancer patient receives therapy that is uniquely tailored to their cancer at the molecular level, how do we evaluate the effectiveness of the therapy if there is only one person who receives that exact therapeutic? These and other issues such as the potential for bias to exist in AI systems or that AI may be overconfident about its own predictions necessitate the need for detailed thinking and planning in determining the overall benefit of AI-enabled therapeutic pathways. Nonetheless, after decades in which the long-term outcomes of ovarian cancer patients have not significantly changed, the possibility of new approaches to treating this condition is an enormously exciting opportunity.

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Two-day scientific meetings

A further three two-day meetings organised by our members at their institutes took place in August and September this year. These meetings bring your communities together to hear and discuss the latest research in the field. A vital element is also networking with both early career and established researchers to forge new collaborations.

University of St Andrews, UK

Meeting Report

Membrane Transport 2023: Recent Research into Ion Channels, Transporters and Epithelial Physiology

24 – 25 August 2023, University of St Andrews, UK

Early Career Researcher Poster Competition Winner
Dr Amy Dorward, University of St Andrews, UK

Early Career Oral Communication Prize Winners
Dr Florian Sure, University Erlangen-Nürnberg, Germany

Rene Lawong, Bonn-Rhein-Sieg University of Applied Sciences, Germany

Early Career Poster Prize Winners
Dr Amy Dorward, University of St Andrews, UK

Mayuree Rodrat, University of Bristol, UK

Nattanan Sajjaboontawee, University of York, UK

We began the second half of our 2023 events programme in August with a trip to the University of St Andrews for the *Membrane Transport 2023: Recent Research into Ion Channels, Transporters and Epithelial Physiology* meeting. This meeting was organised by Dr Morag Mansley (University of St Andrews, UK), Professor Mike Althaus (Bonn-Rhein-Sieg University of Applied Sciences, Germany) and Dr Stephen Keely (Royal College of Surgeons in Ireland, Dublin, Ireland).

Across the two days, the 85 attendees enjoyed the latest research in epithelial transport physiology and broadened their knowledge of the various emerging techniques in the field of membrane transport.

Alongside the 15 invited speaker talks, eight presenters from a number of international institutions showcased their work as oral communications and the 34 abstracts presented as posters made for a vibrant, engaging poster session at the end of day one. The scientific programme was wrapped up with an inspiring keynote lecture by Professor Volker Vallon (UC San Diego, US) entitled "The kidneys' inner workings and needs: Lessons from inhibiting a glucose transporter".

Epithelial physiology was not the only thing on display. The conference dinner taking place in Lower College Hall highlighted the striking, older buildings offered by the university followed by the attendees' enthusiasm and impressive dancing at the ceilidh.

The organisers and two attendees share their highlights below.

Dr Morag Mansley

University of St Andrews, UK

As part of the organising committee, we were delighted to have been selected to arrange one of the first two-day meetings from The Physiological Society. We saw this as a unique opportunity to bring the Epithelia and Membrane Transport community together post-COVID with a smaller, focused meeting. We set out with the goal of promoting our Theme to the next generation of physiologists in our field. We are really grateful for the additional sponsorship we sought out and were awarded from industry partners, as well as the School of Medicine at the University of St Andrews, as this allowed a lower registration rate for undergraduate and postgraduate students. We aimed high with our invited speakers as we wanted to ensure the meeting was attractive to physiologists in the UK, but also Europe and beyond. In the end, the programme was excellent and we are grateful, not only for the invited speakers, but those selected from submitted abstracts – the quality of presentations throughout was extremely high. Our poster session was really well attended and we opted to have a full two-hour session; this allowed for great discussion. Our Taste of Scotland dinner and ceilidh in the historic Upper and Lower Colleges of the university was a highlight of the meeting. The Events team from the Society were fantastic throughout, the organisation was smooth and they were happy to hold extra meetings in the run-up to the event to ensure everything was on track. Overall, I felt the meeting was a great success – we heard really exciting recent work from the Epithelia and Membrane Transport field, old and new colleagues had many in-depth discussions that the in-person event really catered for, and we were left with the recurring question – when is the next meeting?!

Meeting organisers (from left to right) Professor Mike Althaus, Dr Morag Mansley and Dr Stephen Keely

Professor Mike Althaus

Bonn-Rhein-Sieg University of Applied Sciences, Germany

It was a great pleasure to co-organise the Membrane Transport 2023 meeting with Dr Morag Mansley and Dr Stephen Keely. With four scientific sessions, "Recent developments in epithelial transport physiology", "New insights into structure and function of ion channels and transporters", "The transport physiologist's toolbox in 2023" and "Dysfunction of ion channels and transporters in diseases", we brought together excellent international speakers investigating a wide range of ion channels and transporters across many organs and tissues. As such, the meeting stimulated cross-disciplinary exchange of ideas and techniques. With the support from our sponsors (Nanion, Mund Scientific Instruments, Fisher Scientific, Sarstedt, Harvard Biosciences and the University of St Andrews) and The Physiological Society, we were able to make this a highly attractive meeting for early career researchers. Their oral and poster presentations greatly contributed to the success of this conference. I thoroughly enjoyed the friendly and positive atmosphere during the two days in St Andrews and I hope we can repeat this experience with our vibrant "Epithelia and Membrane Transport" community in the future. See you in 2025?

Congratulations to our early career award winners!

Dr Stephen Keely

Royal College of Surgeons in Ireland, Dublin, Ireland

It was an absolute privilege to have been a co-organiser for the Membrane Transport 2023 meeting in St Andrews. Overall, with its excellent programme of international speakers, fantastic venue, and thoroughly enjoyable social activities, the meeting could only be considered to be a great success. The standard of the oral and poster presentations was very high and the emphasis on early career researchers was appreciated by all. Support from The Physiological Society, both before and during the meeting, was second to none and there was great enthusiasm among participants for there to be a similar epithelia-themed meeting in 2025.

Professor Volker Vallon of University of California San Diego delivered the keynote lecture "The kidneys' inner workings and needs -Lessons from inhibiting a glucose transporter"

Professor Bonnie L. Blazer-Yost

Indiana University–Purdue University Indianapolis, US

The Membrane Transport meeting was an absolute delight. It was so nice to attend a meeting where every talk was interesting and pertinent to my research scope. Meetings of this size are ideal for senior scientists to reconnect with colleagues and for trainees to network with people in their field. I think the organisers did a great job of including both senior and junior scientists and covering a range of topics, tissues and techniques. I would love to see this meeting happen on a routine basis. I would certainly attend and would encourage my trainees to do so as well.

Dr Amy Dorward

University of St Andrews, UK, Early Career Researcher Poster Competition Winner

From kidneys to a ceilidh, Membrane Transport 2023 was the most enjoyable and engaging meeting I've attended this year. The programme of varied and cutting-edge research in the fields of epithelial and membrane transporters, put together by the fantastic organisers, showed such support for early career researchers. The focused two-day meeting meant I learned a lot, had the opportunity to present my own research, and met some potential collaborators in the process. Thank you!

https://doi.org/10.36866/pn.132.32

https://doi.org/10.36866/pn.132.32

Meeting Report

Cross-Talk of Cells in the Heart: Novel Mechanisms of Disease and Arrhythmias

11 – 12 September 2023, University of Liverpool, UK

(From left to right) Dr Katja Rietdorf (session chair), Dr Daniel Johnson (meeting organiser) and Dr Calum McMullen

Seventy-one speakers, chairs, organisers and cardiac physiologists joined us in Liverpool in September. This meeting was a platform for the discussion of cutting-edge advances in the field of cardiac arrhythmia and disease, with a specific focus on cross-talk of different cell types in the heart and how these interactions may contribute to an arrhythmogenic phenotype.

The organisers, Dr Nordine Helassa (University of Liverpool, UK) and Dr Daniel Johnson (The Open University, UK) convened an exciting programme, which included 22 oral communication presentations, many of which were given by early career researchers.

This meeting was supported by the British Heart Foundation, Mapping Lab, Stratech Scientific, Cairn Research and Foresee Biosystems.

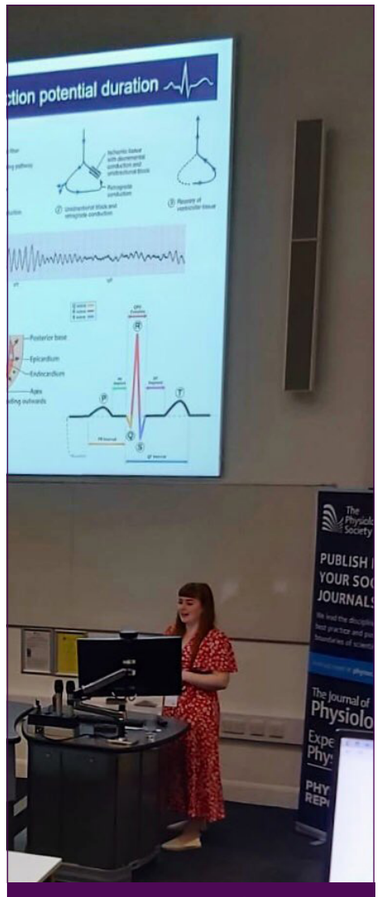
Dr Julian Wagner

University of Frankfurt, Germany

It truly was a fantastic meeting combining various experts who work on the same issue: intercellular crosstalk of the heart. My personal highlight was to realise that so many groups work on a similar topic as I do. Hence I had a great scientific exchange and was able to initiate new collaborations.

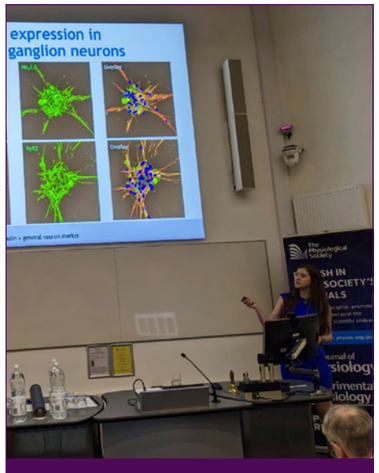
Early Career Poster Prize Winners
Kirsty Wadmore, University of Liverpool, UK

Leena Patel, University of Birmingham, UK



Dr Erin Boland (University of Glasgow, UK) presenting her research

Welcome and Introduction: Programme organisers, Dr Daniel Johnson and Dr Nordine Helassa



Dr Molly O'Reilly (Amsterdam UMC, The Netherlands) presenting her research

https://doi.org/10.36866/pn.132.34

Meeting Report

Regenerating the Cardiovascular System: Mending Broken Hearts and Beyond

13 – 14 September 2023, University of Oxford, UK

Early Career Researcher Oral Competition winner, Dr Eline Huethorst (University of Glasgow, UK) being presented the award by meeting organiser, Dr Caroline Pellet-Many (Royal Veterinary College, London, UK)

Early Career Researcher Oral Competition runner up, Dr Konstantinos Lekkos (University of Oxford, UK) with Dr Caroline Pellet-Many (Royal Veterinary College, London, UK)

Forty-seven speakers, chairs, organisers and cardiac regeneration researchers joined us in Oxford immediately after the Liverpool meeting. This meeting highlighted the recent developments in the field of cardiac regeneration and development, with an emphasis on findings from animal models with natural ability for heart regeneration, including the zebrafish and neonatal mouse.

The organisers, Dr Mathilda Mommersteeg (University of Oxford, UK), Dr Caroline Pellet-Many (The Royal Veterinary College, London, UK) and Professor Paul Riley (University of Oxford, UK) convened a wide-reaching programme, which included 12 oral communication presentations, many of which were given by early career researchers.

This meeting was supported by the British Heart Foundation Oxbridge Centre of Regenerative Medicine.

Dr Eline Huethorst

University of Glasgow, UK; Early Career Researcher Oral Competition Winner

I really enjoyed going to The Physiological Society meeting on "Regenerating the Cardiovascular System: Mending Broken Hearts and Beyond", because it was an intimate and interactive meeting with many experts in the field. The excellent talks led to interesting discussions that gave me new insights into cardiac regeneration that could benefit my own research projects. Furthermore, I am extremely honoured that the committee selected my talk for the Best Oral Communication Award. I am looking forward to the next one.

Early Career Oral Communication Prize Winners
Dr Eline Huethorst, University of Glasgow, UK

Dr Konstantinos Lekkos, University of Oxford, UK

Programme organiser Professor Paul Riley (University of Oxford, UK) presenting at the meeting

If you have been inspired to convene your own meeting for your research community, the first call for our 2025 meetings is open now until 1 March 2024. The second call will close on 1 September 2024. There will be up to 11 meetings in 2025. To find out more please visit: https://www.physoc.org/our-events/meeting-workshop-support

https://doi.org/10.36866/pn.132.35

Meeting Report

Drowning Prevention and Treatment Online Summit

11 – 13 October 2023, Online worldwide

Physiologists are vital in this action against drowning; only by understanding the physiological mechanisms of the drowning process, can we build life-saving interventions.

The Society was delighted to partner with the International Drowning Researchers' Alliance (IDRA) in October to host an important online summit on drowning prevention and treatment. It brought together experts in drowning prevention from both a theory and practice perspective, to ensure that research is converted into action, with the aim of saving lives worldwide.

The online summit was organised by Professor Mike Tipton (University of Portsmouth, UK), a founding member of IDRA, and also Dr Paddy Morgan (North Bristol NHS Trust, UK), Dr Jenny Smith (University of Chichester, UK) and Adrian Mayhew (Surf Life Saving GB, UK). IDRA is an international scientific network devoted to all aspects of the use of quantitative and technical methods in drowning research to promote safety in and around water environments.

Professor Tipton commented, "This was a vital meeting between researchers exploring all aspects of drowning prevention and treatment and the people who are out there saving lives. Only by bringing together these experts do we stand a chance at stemming this global problem. This meeting offered a real opportunity to share recent research into the physiological and clinical aspects of drowning and convert that knowledge into life-saving action."

Drowning remains a global pandemic, claiming the lives of more than 236,000 people per year. More than 90% of those drowning deaths occur in low- and middle-income countries, and the drowning threat is set to get worse with climate change and rising sea levels. It has been estimated that between 80% and 90% of all drownings are preventable, highlighting the need for greater education, discussion, and research into drowning in order to curb this threat.

Bringing together physiologists and life-saving experts from around the world who work in both clinical and community settings to share current knowledge and thinking across many aspects of drowning is essential in addressing this global problem. Physiologists are vital in this action against drowning; only by understanding the physiological mechanisms of the drowning process, can we build life-saving interventions.

More than 300 people registered from 38 countries, and each day of the summit attracted more than 150 attendees to hear the day's 12 presentations from experts from organisations including Lifeguards Without Borders (US), The Royal Society for the Prevention of Accidents (UK), Surf Life Saving GB (UK) and National Ambulance Resilience Unit (UK). The online programme was tailormade to be inclusive of time zones and enabled presenters from all over the world to showcase their research.

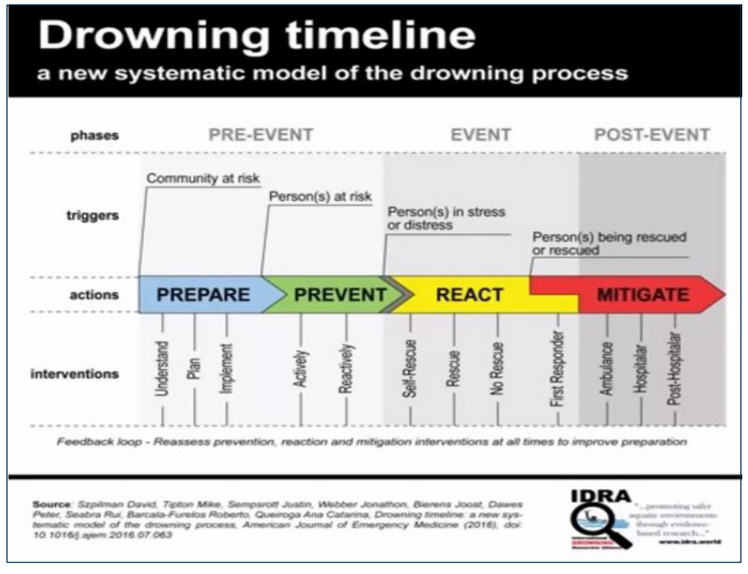
Dr Victoria Laxton, Transport Research Laboratory, UK said on social media,

"Great experience speaking at 'Drowning Prevention and Treatment' global webinar this morning. I hope you all enjoyed my talk on the fatigue lessons we could learn from the bus industry!"

Topics covered included drowning prevention strategies and impact, community involvement and preparedness, innovations in drowning risk assessment and rescue, and international perspectives, including climate change.

Kai Valonen from Safety Investigation Authority Finland commented, *"Thank you for the opportunity to talk about our recent study on drownings in Finland. I'm glad if Safety Investigation Authority in Finland can contribute to the global drowning prevention challenge".*

If you missed it, those talks that speakers have agreed to be uploaded will be available on The Society's website at www.physoc.org/.



https://doi.org/10.36866/pn.132.36

Meeting Preview

Physiology in Focus 2024

Tuesday 2 July - Thursday 4 July 2024, Northumbria University, Newcastle upon Tyne, UK

The Physiological Society and The Scandinavian Physiological Society are delighted to be hosting a joint conference in July next year in Newcastle upon Tyne, *Physiology in Focus 2024.*

Dr David Kennedy

Society Rep, Newcastle University, UK

"We are looking forward to welcoming physiologists from The Physiological Society and the Scandinavian Physiological Society to Newcastle. This vibrant city is home to two outstanding universities with researchers working on all topics in physiology. The city is compact with world-renowned nightlife so you can be guaranteed many opportunities for informal networking in the city's bars and restaurants. We are also only a short metro ride from Whitley Bay along the beautiful Northumbrian Coast. My colleagues and I look forward to welcoming you to the city."

As always, the scientific programme promises a selection of the best and most exciting current physiological research, including inspirational plenary and keynote lectures. There will be three days of the latest exciting physiology including Special Interest Group meetings, symposia, oral communications, and posters. Abstract submission is open from 1 March until 31 March 2024.

The venue, Northumbria University, in in the heart of the city, and a 20-minute walk from Newcastle station. Newcastle upon Tyne is easily accessible from most parts of the UK, and also mainland Europe, either by train or air.

Dr Stuart Goodall

Society Rep, Northumbria University, UK

"As the Society Rep at Northumbria University, I am looking forward to welcoming colleagues to the university. We were named the Times Higher University of the Year in 2022 and many of my colleagues are members of The Society. We are looking forward to building stronger connections with our Scandinavian colleagues and also showcasing the breadth of research we undertake here. It will be a great privilege to welcome you all here in July."

Places are limited and registration will open to The Physiological Society and Scandinavian Society members on 1 February, with non-member registration opening later, if there is capacity.

https://www.physoc.org/physiology-in-focus-2024/

The Physiological Society Prize Lectures

The Annual Review Prize Lecture
Professor Jens Juul Holst, University of Copenhagen, Denmark

The Bayliss-Starling Prize Lecture
Professor Colin Nichols, Washington University St. Louis, U.S.

The Joan Mott Prize Lecture
Professor Janna Morrison, University of South Australia, Australia

The Michael de Burgh Prize Lecture
Professor Alexander Gourine, University College London, UK

Otto Hutter Teaching Prize Lecture
Professor Frankie MacMillan, University of Bristol, UK

The Paton Prize Lecture
Dr Sean Roe, Queen's University Belfast, UK

Key dates

Member registration opens: **1 February 2024** • Abstract submission opens: **1 March 2024**

Abstract submission closes: **31 March 2024** • Member early bird registration closes: **31 May 2024**

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The impact of artificial intelligence on teaching writing skills to life science students

Dr Matthew Hardy
University of Bradford, UK

On 28 November 2022, writing for The Guardian, Rob Reich published an article with the headline "Now AI can write students' essays for them, will everyone become a cheat?" (Reich, 2022). I cannot know whether this was written with prior knowledge, or if Rob Reich simply demonstrated remarkable insight; this was just two days before the company OpenAI released a version of ChatGPT for free access to anyone with an online device. Since then, the use of ChatGPT, as well as other large-language models (LLMs), has become a topic of intense scrutiny within the higher education sector. One of the reasons for this, as indicated in Rob Reich's article, is because of the potential of LLMs to "write" responses to academic questions.

An LLM can be defined as an artificial intelligence (AI) algorithm that has been trained with a large dataset to summarise and predict content. A closely related term is that of generative AI – AI that has been designed to create text-based content; ChatGPT algorithms are examples of this. Since the release of that early version of ChatGPT, there are now a number of LLM/generative AI algorithms available for use, either with subscription or for free. The most well-known include not only the differing versions of ChatGPT, but also Google's chatbot Bard (powered by the LLM LaMDA) and Microsoft 365 Copilot.

For me, the sudden widespread awareness of LLMs, and their potential for (mis)use in writing, is perhaps of more interest than for most academics. I don't just teach my students about the intricacies of physiology and pharmacology. I am also responsible for delivering academic writing skills to students across programmes within the Faculty of Life Sciences at the University of Bradford. Even if only a minority of students are likely to use AI to cheat in their assessments, this is something I have to address.

I am of the belief that, when it comes to using AI for writing academic content, "the cat is out the bag", so to speak. In the US, a recent survey of 1,000 students demonstrated that more than a fifth had used an AI application to help complete academic assignments or exams (Welding, 2023) . There is no reason to think that the numbers would be much different within the UK. Therefore, if students are using these tools anyway, perhaps we should be showing them how to use them in an ethical and effective manner. In this regard, I am not alone, as can be seen by the following principles outlined by the Russell Group universities last July (Russell Group, 2023):

- Universities will support students and staff to become AI-literate.
- Staff should be equipped to support students to use generative AI tools effectively and appropriately in their learning experience.
- Universities will adapt teaching and assessment to incorporate the ethical use of generative AI and support equal access.
- Universities will ensure academic rigour and integrity is upheld.
- Universities will work collaboratively to share best practice as the technology and its application in education evolves.

Thus, my response to the widespread use of AI has been to adapt and rewrite the lectures and workshops that I use to deliver writing skills to my students; I now not only include more traditional approaches to developing written content, but also discussion of alternative means: namely the use of AI. This is not only limited to the use of generative AI for creating content; I have also developed lessons for using AI to: develop assignment plans; search and map literature (using tools such as Elicit), transcribe/write from spoken word (using tools such as Audiopen); and to refine language using either generative AI or alternative AI tools (e.g. Grammarly). There are also ethical and legal considerations – for example when submitting papers to applications that "summarise" articles (e.g. ChatPDF), there are risks of breaching copywrite (Chatpdf.com, 2023), as well as of inaccurate reporting and cognitive dissonance. These are concerns that students need to be aware of.

At the time of writing, I have already delivered the first of these workshops to a group of Year 1 students. Students were not told when they could and couldn't use AI. Instead, we looked at a variety of approaches together and they could make up their own minds whether they were beneficial. The content included examples of an essay prepared using generative AI. Whilst on the surface the subject matter seemed quite impressive, the class identified how it demonstrated a number of flaws. These included LLMs' tendency to "hallucinate" facts and in some instances, references. Even when the references were real, they were often not the most appropriate for the topic and were frequently outdated. Additionally, we looked at different types of writing, including a reflective essay. Initially, students were surprised that the reflection was written by an algorithm as it presented as a very personal piece of writing. However, students soon realised that this was immaterial as, when studied using a rubric, the essay was not of passable quality. It was also acknowledged that the AI checker in Turnitin identified the writing being discussed as being AI-generated – were these real assignments, the work would have been cited for academic misconduct.

We didn't just look at the negatives; whilst it was acknowledged that everything would need to be fact-checked, asking a generative AI about a topic one was unfamiliar with wasn't necessarily a bad place to start. Similarly, repeated adjustment of the prompts (or inclusion of specific parameters) used to elicit a response could generate sequential improvements for a plan or outline of an assignment (by this stage, it was accepted that simply using generative AI to write an assignment was not good academic practice, but that other approaches may be used to help in the generation of content without compromising the final piece of work).

My closing remarks are as follows: I am not teaching writers; I am teaching scientists. The rapid uptake and evolution of accessible AI means that it is likely at least some of my students will use the same or similar technology in their future careers. On this basis, it can be argued that we have a responsibility to teach students to use AI tools in a responsible and ethical manner. However, the following is worth noting: the last exercise in the workshop was to prepare a plan for a drug monograph using whatever means students felt appropriate. Despite having identified some useful approaches to using AI, not a single student opted to use them.

This article was prepared without the use of AI.

The content included examples of an essay prepared using generative AI. Whilst on the surface the subject matter seemed quite impressive, the class identified how it demonstrated a number of flaws.

In the US, a recent survey of 1,000 students demonstrated that more than a fifth had used an AI application to help complete academic assignments or exams.

If students are using these tools anyway, perhaps we should be showing them how to use them in an ethical and effective manner.

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Congratulations to the 2023 Honorary Fellows

The Physiological Society's Board of Trustees is delighted to announce the appointment of our new Honorary Fellows and Fellow Members.

Honorary Fellowship is the highest honour that The Physiological Society presents to an individual and it recognises persons of distinction in science who have contributed to the advancement of physiology.

Professor Rose Anne Kenny

MD FRCP FRCPI FRCPEdin FESC FTCD FFPHMI (Hon) MRIA D.Sc. h.c

Rose Anne Kenny is Regius Professor of Physic (Medicine) and holds the Chair of Medical Gerontology at Trinity College Dublin. She is the founding Principal Investigator of The Irish LongituDinal study on Ageing (TILDA) and Director of the Mercer's Institute for Successful Ageing (MISA) at St James's Hospital, where she is also director of a large national falls and syncope and autonomic function laboratory.

She has received a number of international awards and has published widely, authoring over 600 publications including her recently published book "Age Proof – The New Science of Living a Longer and Healthier Life", which was shortlisted for the Royal Society Science Book Prize 2022.

Professor Philip Nolan

MB BCh BAO BSc PhD MRIA

Philip Nolan was appointed Director General of Science Foundation Ireland (SFI), Ireland's primary funder of science and engineering research, in January 2022, and in May 2023, the Minister for Further and Higher Education, Research, Innovation and Science, Simon Harris TD, appointed Philip the CEO-designate of Research Ireland, the new research funding agency to be formed by the amalgamation of SFI and the Irish Research Council. He is a strong advocate for the importance and value of fundamental curiosity-driven research across all disciplines as the foundation of a thriving research and innovation ecosystem. He is a Member of the Royal Irish Academy, an Honorary Fellow of the Faculty of Public Health Medicine of the Royal College of Physicians of Ireland, and an Honorary Fellow of the Physiological Society.

Professor David Paterson

DPhil DSc

David Paterson is Professor of Physiology and a Fellow of Merton College, Oxford. Since 2016 he has been Head of the Department of Physiology, Anatomy & Genetics at Oxford (QS Ranked 1st) and is immediate Past President of The Physiological Society of the United Kingdom and the Republic of Ireland. He is a graduate of the University of Otago (NZ), University of Western Australia and New College, University of Oxford, where he completed his DPhil on chemoreception. Rising through the ranks at Oxford from a Junior Research Fellowship at Christ Church then Tutorial Fellowship at Merton College, he became Professor of Physiology over 20 years ago. As a cardiac neurobiologist, he is best known for his work linking the nervous system to heart rhythm, which was featured in the 2012 BBC Four documentary Heart v Mind: What Makes Us Human?

Professor David Attwell, President of The Society said:

This year's Honorary Fellows and Fellows represent the true breadth and diversity of the discipline. It is a pleasure to recognise their unique achievements and contributions to the physiological sciences.

Presenting our 2023 Fellows

The Society is also delighted to recognise the experience, commitment and contributions of distinguished members by appointing our 2023 Fellow Members.

Professor Omar Mahroo *MA MB BChir PhD FRCOphth FHEA FRSB*

Omar Mahroo is a clinician scientist investigating retinal physiology and pathophysiology. He is a consultant ophthalmologist and retinal specialist at Moorfields Eye Hospital and St Thomas' Hospital in London. He is also Professor of Retinal Neuroscience at University College London. In 2011, he was appointed Academic Clinical Lecturer at King's College London, where he set up an ERG research laboratory at St Thomas' Hospital to investigate retinal responses in the TwinsUK cohort and retinal mechanisms driving myopia. He has received awards for teaching excellence and for patient and public engagement from the UCL Institute of Ophthalmology and the Moorfields Biomedical Research Centre. He has co-authored over 130 publications (including in the *Journal of Physiology, New England Journal of Medicine, Nature Genetics, Ophthalmology, Brain* and *Proceedings of the National Academy of Sciences*).

Professor Bamidele Victor Owoyele *PhD FNSN FNISEB*

Bamidele Owoyele obtained his BSc and PhD in Physiology at the University of Ilorin, while his Master's was from the University of Ibadan, Nigeria. He is a tenured professor at the Department of Physiology, University of Ilorin, where he has been teaching and doing research since 1999. He has been a member of The Physiological Society since January 2010 and is a Society Representative at the University of Ilorin. He is a Board member of many scientific journals and is an external examiner to many universities within and outside Nigeria. His research focus is on pain and neuroinflammatory diseases. He has supervised many PhD theses, Master's dissertations, and undergraduate projects. He is currently the Dean of the Postgraduate School at the University of Ilorin, Nigeria.

Professor Holly Alice Shiels *PhD*

Holly Alice Shiels is a Professor of Integrative Physiology at the University of Manchester, UK. Her research explores cardiac function in response to environmental change and how this impacts organismal metabolism, locomotion, and behaviour to determine the intersection of the cardiovascular system and the environment on fitness. Her lab works across species, across life stages and biological models, embracing comparative approaches to provide deeper understanding of the mechanisms that adjust or collapse at environmental extremes. Holly has been a member of The Physiological Society since arriving in the UK as an NSERC-Canada Fellow in 2002. She has taught Animal Physiology at the University of Manchester since 2005 and is currently working with colleagues on the next edition of the Oxford University Press textbook "Animal Physiology".

Professor Changhao Wu *MB MD PhD*

Changhao Wu is a Professor in Cell Physiology at the University of Surrey. He studied medicine as his first degree followed by a Master's degree in medicine and a PhD in physiology/pharmacology. He has worked in Sun Yat-sen University of Medical Sciences (China), Guy's and St Thomas' Medical School, University College London, and University of Surrey. As a principal Investigator, he has carried out innovative research and made significant original contributions with a particular focus on the bladder tissues, smooth muscle, epithelial and interstitial cells. He has published over 100 peer-reviewed publications in a physiology or life science journals including *The Journal of Physiology, Journal of Clinical Investigation, European Journal of Epidemiology, European Journal of Urology,* and *Frontiers in Immunology.*

The Fellowship appointments will be celebrated at the 2023 Member Forum, which will be held at The Royal Society on 1 December 2023.

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https://doi.org/10.36866/pn.132.40

Developing trusted healthcare tools: How physiology can unlock the potential of artificial intelligence for health

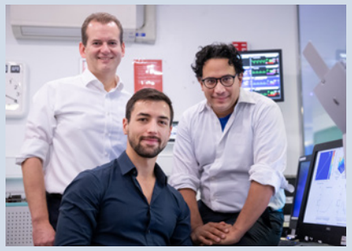
In June 2023, The Physiological Society launched its policy report, "From 'Black Box' to Trusted Healthcare Tools" in the Houses of Parliament. This report places a spotlight on the role of artificial intelligence (AI) in healthcare and the necessity of integrating physiological evidence into its application to prevent health inequalities.

The report was based on consultations with over 30 leading experts in the field. The evidence gathered and case studies developed highlight how physiological measurements and knowledge are being used to develop AI tools, as well as examine how to ensure the safe and effective implementation of AI to support clinical decision-making and transform healthcare.

On these pages we share with you a few of the case studies published in the report to showcase the human-centred technologies being developed to improve the quality of healthcare, from assessment to monitoring conditions and providing new treatments for patients.

Professor Aldo Faisal, Dr Matthieu Komorowski, Professor Anthony Gordon

Imperial College London, UK



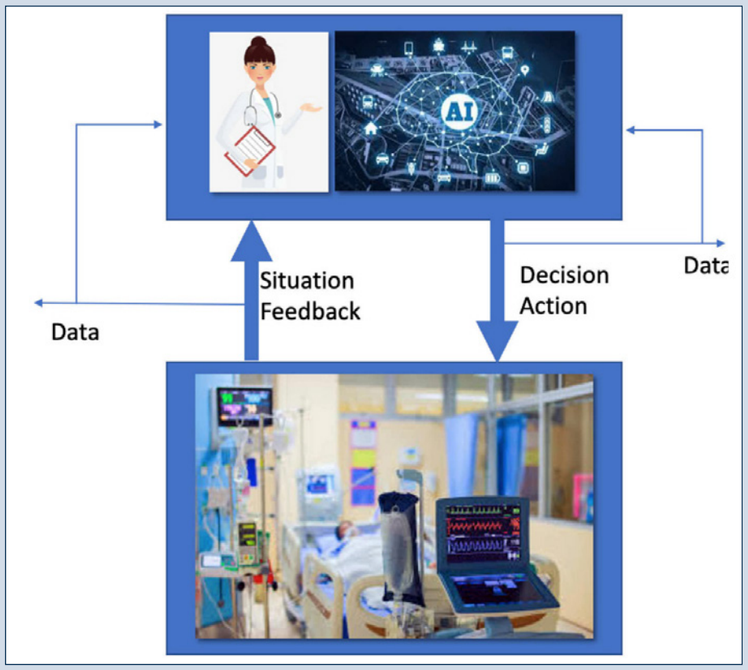
AI as an everyday tool: optimising intravenous fluid and vasopressor doses in patients with sepsis in intensive care

Sepsis is a life-threatening condition, when the body's response to severe infection causes vital organs to stop working normally and is a major worldwide healthcare challenge and the primary cause of death in hospitals. A key part of the treatment of sepsis is the administration of intravenous fluids and vasopressors to keep the cardiovascular system working while the antibiotics do their work. However, there is huge uncertainty and vast interpatient differences around the individual dosing of these two drugs in an individual patient. An AI tool to personalise these medications and their dosages could improve patient survival.

We have developed a new method to automatically and continuously review and recommend the best doses of these medications to clinicians. To this end we developed AI techniques applied to large medical databases, including large amounts of physiological data, that learn from patient data and doctors' treatment decisions the best strategy for treatment. As previous work had shown potential to improve patient survival rates, our team at Imperial College London has been developing a tool capable of processing patient data within the electronic patient record of NHS hospitals in real time, to recommend a course of action. This tool is being evaluated and refined in simulation studies being deployed across four London hospitals.

The AI Clinician extracted implicit knowledge from an amount of patient data that exceeds by many-fold the life-time experience of human clinicians and learned optimal treatment by analysing myriad (often suboptimal) treatment decisions. Its use is now being systematically tested to see how it performs with NHS clinicians in both simulated and real clinical scenarios.

It has previously been demonstrated that the value of the AI Clinician's selected treatment is on average reliably higher than that of human clinicians. It is currently being tested in four NHS hospitals, first in a "shadow mode" when the AI recommendation is not provided to the clinicians to allow comparison and understanding of actual decisions vs recommended AI decisions. In the second stage, that started this summer, the clinical evaluation is displayed at the bedside to the treating clinicians to allow researchers to assess the clinical acceptability of the tool and also confirm the technical feasibility for future large-scale clinical trials.



Professor Rohan Lewis

University of Southampton, UK

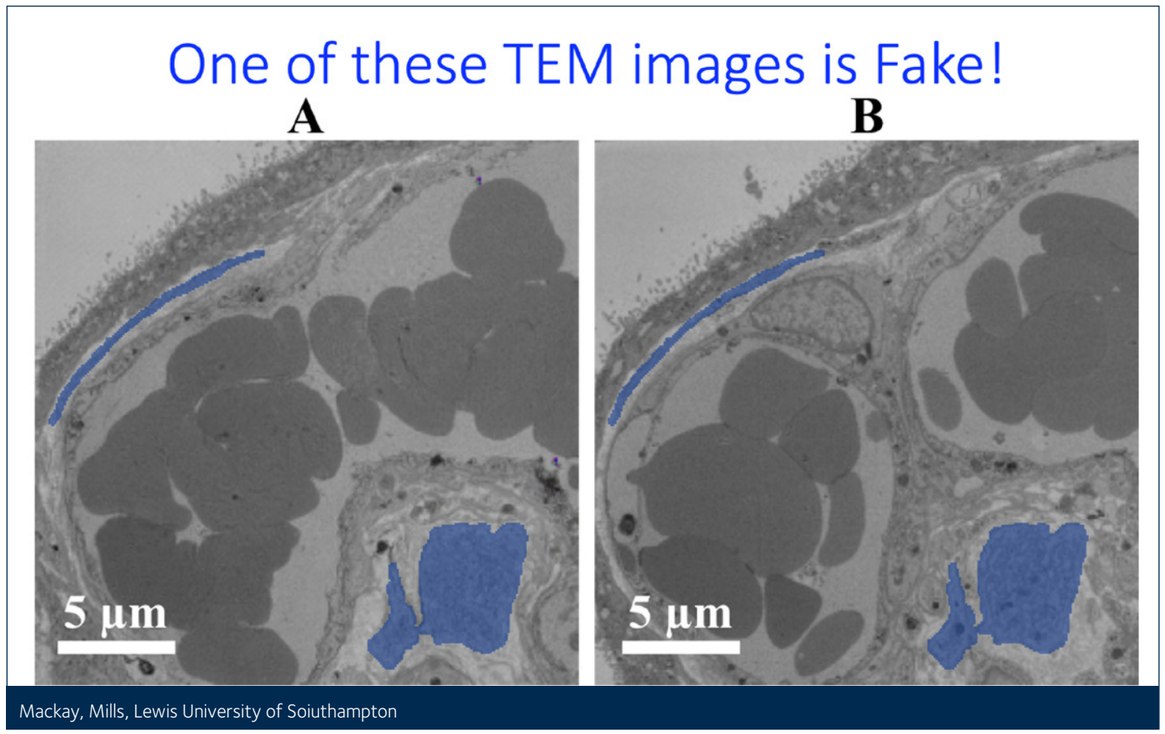
Understanding the basis of reproductive health through machine learning

By enabling babies to grow well in the womb, the health of both mother and the child can be improved. We are exploring structure and function relationships in the placenta and endometrium. Advances in imaging techniques are helping to achieve this, but they generate complex datasets, which are time-consuming to analyse. Using machine learning, our research seeks to analyse these images more quickly and to gain additional insights from this technology.

Machine-learning algorithms can effectively recognise cell types and features in placental and endometrial tissue, allowing these data to be analysed much more quickly. We trained machine-learning algorithms to make fake photorealistic electron microscope images of placental tissue. These fake images demonstrate that the trained algorithm "understands" all the spatial relationships between anatomical structures within the tissue, including intracellular components. The aim is to use the knowledge within the algorithm to explore how cells change in different physiological and pathological states.

Our research has demonstrated the potential of machine learning to speed up image analysis and provide new ways of extracting biologically exciting and clinically relevant data. In doing so, machine learning can help enhance the health of mothers and babies during pregnancy and across the life course.

Machine-learning algorithms can effectively recognise cell types and features in placental and endometrial tissue, allowing these data to be analysed much more quickly.



Mackay, Mills, Lewis University of Soiuthampton

https://doi.org/10.36866/pn.132.42

https://doi.org/10.36866/pn.132.42

Dr Oliver Todd
University of Leeds

Can ambulatory blood pressure measures inform shared treatment decisions in hypertension for older adults who are at risk of falls?

Two out of three people over 65 take treatment to lower blood pressure to prevent heart attacks and strokes. Blood pressure treatment also increases the chance of having a fall if blood pressure is lowered too much. As people get older, their blood pressure tends to rise and fall more dramatically. All this makes it hard to know how to accurately prescribe blood pressure treatment in later life.

Ambulatory blood pressure measurement (ABPM) works by equipping patients with wearable monitors that take readings two to three times an hour over the course of a day and night. Currently the output of this device is provided as a graph to the clinician but without prognostic information to aid its interpretation. We will use routinely collected ABPMs undertaken in the NHS over the past 25 years in three UK city regions. This more reflective measurement of a patient's blood pressure will be analysed with machine-learning techniques. We will look at the 24-hour patterns of blood pressure, allowing novel pattern recognition to predict risk of heart attack and stroke, as well as falls, with potential for proactive intervention and tailoring of medicines to prevent harm.

Our research will improve the safety of blood pressure treatment in older adults at risk of falls and make it easier for patients to be involved in decisions about their treatment. The databases built will be the largest and most detailed of their kind worldwide and help us understand hypertension in older age. From this, we plan to develop future research questions that use real-world patient data, in combination with other physiological measurements, to improve patient care for older people in the UK and internationally.

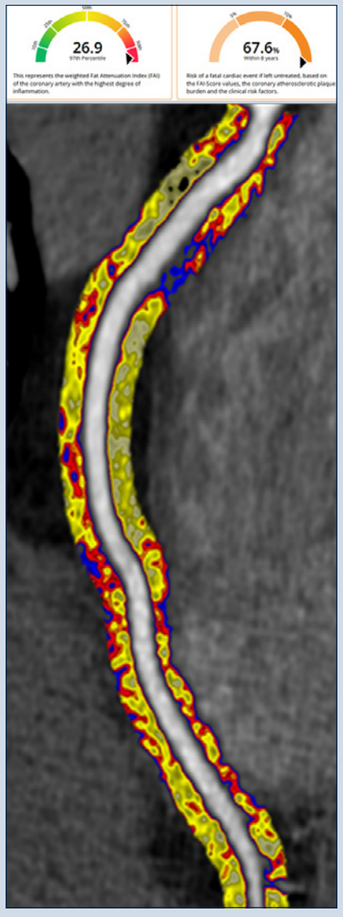
Professor Charalambos Antoniades
University of Oxford

AI technology can be used to predict heart attacks from routine coronary computed tomography angiograms

Cardiovascular disease is the number one cause of death in the UK. Heart attacks happen when inflamed atherosclerotic plaques in our heart arteries break up, blocking blood flow to the heart. Finding these inflamed plaques would allow aggressive treatment of the right patients with low-cost drugs like statins, preventing heart attacks and saving lives.

Our research team at the University of Oxford revealed that the inflamed arteries trigger changes in the texture and composition of the fat surrounding them. We then developed an artificial intelligence method that measures these changes in the fat tissue around heart arteries by analysing images obtained from coronary computed tomography angiograms (CCTAs), a test happening routinely in the NHS for the investigation of chest pain. The technology was able to predict fatal heart attacks at least eight years in advance. This would allow doctors to direct timely deployment of treatments to the right patients, preventing heart attacks and saving lives.

The technology led to the Oxford Spinout company Caristo Diagnostics, to develop a CE-marked medical device called CaRi-Heart®. This cloud-based medical device is now deployed in the first NHS Trusts, allowing doctors to predict heart attacks and focus their attention to the right patients. CaRi-Heart® currently changes medical management in about 40% of the patients undergoing the test, transforming patient care.



The technology was able to predict fatal heart attacks at least eight years in advance. This would allow doctors to direct timely deployment of treatments to the right patients, preventing heart attacks and saving lives.

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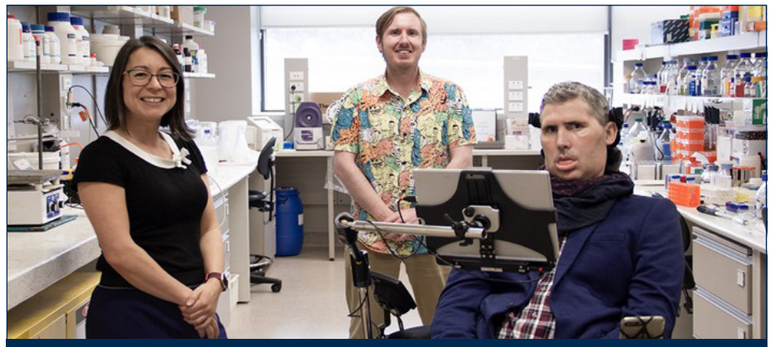
A tribute to Professor Justin Yerbury: an advocate and beacon of hope for motor neurone disease

Professor Justin Yerbury AM died on 28 July 2023, aged 49. Justin was a molecular biologist researching motor neurone disease (MND), whilst also living with the disease. He was a multi award-winning scientist, known for his work on protein homeostasis (proteostasis) and was an advocate for people with disabilities (Yerbury and Yerbury, 2021).



From left to right: Professor Lezanne Ooi, Dr Luke McAlary and Professor Justin Yerbury. Credit: Paul Jones (University of Wollongong, Australia) Credit: Paul Jones (University of Wollongong, Australia).

Many scientists are driven by the pursuit of knowledge and dreams of contributing to society or finding a treatment to a disease. Sometimes the journey is personal, forged through a connection that shapes a career choice, an undercurrent that establishes a specific direction. So it was for Justin, whose close family members succumbed to a familial form of motor neurone disease (MND).

Justin had a brief career as a professional basketballer and studied a degree in commerce but chose to pursue a scientific career after losing several close family members to MND. He completed a Bachelor of Science Honours degree, followed by a PhD at the University of Wollongong, Australia.

I had the privilege of meeting Justin when I first started my lab at the University of Wollongong in 2012 and we began working together on projects shortly afterwards. Justin had a unique ability to bring other researchers along with him and he quickly established himself as a fantastic collaborator with many labs across Australia and internationally. This is how he built a cohesive research team and network of collaborators, all intent on the same goal of fighting MND. One of his most potent qualities was in giving life to new ideas and he was always supportive, no matter how naïve, or possibly absurd, the ideas may have sounded. Concepts were bounced around with energy and enthusiasm, and most of all I will remember Justin for his sense of humour and generally being fun to be around.

Justin's research focused on understanding molecular mechanisms of MND and later focused more heavily on drug development for MND, work that continues to this day through the dedication of his research team. Justin was an expert in protein homeostasis (proteostasis) (Yerbury, 2016), the balance of protein expression and function that is necessary for all cell systems. The entire proteome exists in a delicate equilibrium that requires the coordination of a symphony of pathways to maintain functionality. Many neurodegenerative diseases, including MND, Alzheimer's disease, Parkinson's disease, and Huntington's disease, exhibit a proteostasis imbalance, resulting in protein aggregation and neuronal death – characteristic hallmarks of these diseases. The proteome appears to be particularly vulnerable to stress in motor neurons and Justin's work focused on unravelling the mechanisms underlying these vulnerabilities. These research areas included the roles of protein misfolding, aggregation and ubiquitin homeostasis disruption in amyotrophic lateral sclerosis (ALS), with his later work testing new drugs and treatment approaches, including gene therapy.

Justin had shared the battles of his family with our colleagues privately, but also with the public by participating in news articles and TV documentaries (ABC News, 2018). It was his own passion and commitment and seemingly endless ideas for new research directions that inspired many of us to work on MND. Justin's family members carried an MND mutation in the *SOD1* gene, which encodes superoxide dismutase 1. The SOD1 protein is expressed in mitochondria, and detoxifies the free radical superoxide, protecting against oxidative stress.

In 2016, Justin told us the devastating news of his MND diagnosis. His physical decline was rapid and painful to watch. As time went on, he lost the use of his arms then his legs. Nevertheless, he continued to work and came into the lab aided by his wheelchair to maintain the momentum of the research of his lab and collaborators. Within a year, Justin was given only months to live and made the difficult decision to have surgery to prolong his life. Through a tracheostomy, a machine controlled his breathing and as he was no longer able to speak, he used eye-gaze technology to communicate with his family, friends and colleagues. "I'm towing a jumbo jet" is how Justin described the enormous wheelchair and breathing apparatus and since he needed round-the-clock care, his care team joined every meeting. Yet still, the research continued. Such is the drive of a man on a mission. MND is a disease that takes away the physical aspects of a person piece by piece, but it is heartening to know that Justin lived his life to the fullest. He persevered through significant challenges, in order to continue contributing to fundamental knowledge of MND and therapeutic studies, as well as supporting the development of junior researchers and colleagues.

When we lose the best and brightest, we can be left with an enduring need to be more like them, to emulate their best qualities and continue their battles. Yes, Justin's story is one of sadness, but it is also one of hope, motivation and courage. It is a reminder that as scientists our legacy is not only our direct research outcomes but also the network of people we inspire to continue our mission.

Written by Professor Lezanne Ooi, University of Wollongong, Australia

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Obituary: John Nicholls (1929–2013)

John Nicholls at an IBRO VLTP course in Arba Minch, Ethiopia in 2010

John lectured to standing-room only halls of medical students, and resulted in a collaboration with his life-long friend Denis Baylor that opened up the study of neurobiology in the leech

John Graham Nicholls cast a spell over us all. Whether for the hilarious tales of his life, recounted in *Pioneers of Neurobiology: my brilliant eccentric heroes* (Nicholls, 2015), or for his many formative research contributions to neurobiology, or for the influence of his lectures, or – and this may be the most familiar to readers of *Physiology News* – by writing the first modern neuroscience text book with Stephen Kuffler, *From Neuron to Brain*.

John Nicholls was born in London to parents who had left Germany in the 1920s. It was a cultured background. He went to school first at The King Alfred School in Hampstead, a progressive school, which must have encouraged his mischievous and very obvious sense of humour. It was a school that one of us also attended who, when asked whether we wanted to learn woodwork or reading, the choice was so clear that it made a laboratory career inevitable. After attending Berkhamsted, which he hated, for the scholarly training that King Alfred had trouble providing, John studied a BSc in Physiology from King's College London before graduating MBBS from Charing Cross Medical School. He joined the Biophysics Department at University College London (UCL) in 1951. There he was supervised by Bernard Katz for whom he retained a profound admiration. This was the formative influence both in terms of his interest in cellular physiology and for the great spread of contacts he developed through that department.

After completing both his PhD and his medical training, John became a research fellow at UCL and at the University of Oxford. He then gained positions in neuropharmacology at Harvard University and in physiology at Yale University before returning to Harvard to join Kuffler's new neurobiology department. Started in 1966, this was the very first neurobiology department and set the style for all that subsequently became neuroscience. John's early work with Kuffler laid the foundations for understanding ion movements around glia (Nicholls and Kuffler, 1964). This was followed by a period at Yale, where John lectured to standing-room only halls of medical students, and resulted in a collaboration with his life-long friend Denis Baylor that opened up the study of neurobiology in the leech (Baylor and Nicholls, 1969).

While at Yale a perfect example of John's humour appeared in a letter to *Science* (Nicholls *et al.*, 1967). At the time, reports had been published about worms, claiming that if worms that were trained to crawl in a maze for food were then ground up and fed to other worms, those worms seemed to perform better in the maze than controls! Inspired by this, John's *Science* letter described an experiment to test whether a Tektronix 502 oscilloscope, unable to store images, could be converted to "indefinite persistence" by pounding up and grinding to dust the components of a "donor" Tektronix RM564 Storage Oscilloscope. After the dust was carefully washed and dried, it was then sprinkled over a "recipient" oscilloscope. John reported that in 18 out of 33 experiments an increase in image persistence was observed in the recipient oscilloscope!

In 1968 he became a professor in David Hubel's Physiology Department at Harvard but only for a brief period. In 1973, he moved to Stanford University as a full professor to help found a neurobiology department there, Stanford may have felt it was missing out in this exciting new field. The main research focus of John's laboratory at Stanford remained the leech. It was during his time at Stanford and three summers at the Salk Institute that he and Kuffler wrote the first edition of *From Neuron to Brain* (from Chile to China now known simply as "FN2B"). Four editions followed, all with John as coauthor. The book has been translated into many languages and it is now in its sixth edition.

Stanford was also where his collaborations with neuroscientists around the world subsequently led to the start of the International Brain Research Organization (IBRO)-funded Visiting Lecturer Team Programme (VLTP) bringing contemporary neuroscience ideas to students in developing countries. John thought that the most critical aspect of this programme was to give students the confidence to be able to give well-structured and concise scientific talks so that they could participate in scientific exchange anywhere. A considerable effort during these visits was devoted to students practising presentations about their own project work. The model was of course the original communication style for The Physiological Society. The IBRO VLTP, subsequently organised together with his Stanford colleague Jack McMahan, visited over 40 countries over three decades, sometimes working in primitive conditions, but each time John and his co-opted lecturers found themselves talking to packed eager groups of students and faculty. A number of internationally distinguished neuroscientists owe their career beginnings to this programme.

John's subsequent moves to the Biozentrum in Basel, Switzerland in 1983 as Professor of Pharmacology and finally as an emeritus professor to The International School for Advanced Studies (SISSA) in Trieste, Italy in 1998, are each characterised by a restless and inquisitive advance into a new area. His group in Basel worked on the developing spinal cord and the brainstem breathing rhythm using the short-tailed opossum, *Monodelphis domestica*, to find how the development of the cord takes place after birth.

John engaged all who met him. He remained an indefatigable traveller until his very last few years and hundreds of neuroscientists all over the world will have their own Nicholls stories. He believed a passion for science, music and cooking was an essential bond, while his lectures and teaching were masterclasses of presentation that captivated students everywhere. But maybe it is his powder blue jumper, so characteristically rolled up at the sleeves, the same colour as the FN2B cover, by which we shall also remember him.

Written by Jonathan Ashmore and Alasdair Gibb
University College London, UK

He believed a passion for science, music and cooking was an essential bond, while his lectures and teaching were masterclasses of presentation that captivated students everywhere.

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