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Introduction to organic bioelectronics

Organic bioelectronics is an interdisciplinary research field at the intersection of electronics and biology, which aims to investigate and transduce biological signals and functions using devices and systems based on organic electronics. The properties of organic materials such as mixed ionic-electronic conduction, low temperature fabrication and mechanical, physical, and chemical flexibility and tunability make them an ideal candidate for biotechnological applications, providing vast opportunities. With a long history dating back to the 1780s, from Luigi Galvani and Alessandro Volta's experiments with "animal electricity",¹ the field of bioelectronics has made significant developments in electrophysiology, neural electrodes, biosensors and implants, organ on chip technologies, and many more.^{2,3} Since the 1990s, organic electronic materials have been proposed as potential replacements for traditional electrode materials, particularly where the application requires close contact of the biological component (e.g. cell or protein) with an electrode. The most obvious reason is because of the chemical similarities between organic electronic materials and biological molecules, which became the primary motivation behind pursuing this area of interdisciplinary research. The combination of suitable material properties and application-oriented research has led to different research specialities coming together, but the greater challenge remains to combine traditional research identities to generate a result which is greater than the sum of its parts.

As one of several up-and-coming interdisciplinary fields of research, (organic) bioelectronics faces the challenge of bringing together varied areas of research. When broken down into the fundamentals, it requires the coming together of scientists

with expertise in organic chemistry, semiconductor physics, electrical engineering, material science as well as cellular and molecular biology and a whole host of biological application scientists, be they immunologists, infection biologists, cancer biologists, neuroscientists *etc.* With the current structure of academia and education, the most common "recipe for success" still remains for a scientist to establish themselves within an area of expertise, master the skills within that field, and address key challenges therein. Interdisciplinary research becomes uniquely challenging in this context because it requires finding solutions to previously unimaginable problems by combining research methodologies, and research questions across the divide. As an example, animal-based studies and extensive human clinical trials have been the standard for drug and toxicology testing, with techniques of optical microscopy and molecular biology to gain as much information as possible. It is only with the introduction of microfluidics and electronic transduction that it became possible to even envisage alternative and disruptive technologies such as organ on chip and *in vitro* organ models. Bioelectronics represents one of the interdisciplinary fields of research which combines not only diverse areas of expertise, but also diverse ideas and approaches coming together to drive cross-disciplinary research. To quote rat-chef Remy from the popular Disney-Pixar film *Ratatouille*, when he describes experiencing cheese and fruit together: "Each flavour was totally unique. But combine one flavour with another, something new was created". The field of bioelectronics definitely possesses the potential to create that "something new" and provide solutions for the most pressing human challenges of our times. The real question remains, how do we accommodate rat-chefs into the kitchen? How do we create a fertile, welcoming and accommodating environment for area experts in their own right to enter a new territory and provide their unique perspective to it, in a way that will not only benefit the research prospects of this

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interdisciplinary field of science, but also their individual research interests and careers? This piece aims to address these continuing challenges in terms of research interests and collaborative methods, as well as the way forward.

We, Róisín Owens and Rachana Acharya, represent the two, distinct areas brought together in bioelectronics. Róisín is a biochemist, while Rachana is a Materials Scientist.

Roisin's background – a biochemist's journey to organic electronics

I studied Natural Sciences at University – at Trinity College in Dublin. I recommend this as a degree choice because it gave me a foundational grounding in mathematics, chemistry, and biology. This grounding served me well when I entered the field of organic bioelectronics. I later specialised as a biochemist, studying protein structure and function in the context of infectious disease. After my PhD, I travelled to the US, to work as a postdoctoral researcher at Cornell University, working on *Mycobacterium tuberculosis*, the causative agent of tuberculosis. While there, I became interested in new technologies for doing biological assays – going beyond the commercially available microscopes and fluorescence plate readers. While doing so, I came across the world of organic electronics and was excited by the potential of interfacing these materials with biological organisms or biomolecules. However, to truly use these materials well and take advantage of all of their properties, I had to immerse myself in a new field.⁴ Organic electronic materials, at first glance, in terms of their chemical structure, look quite like biomolecules. They are almost exclusively composed of carbon, hydrogen, oxygen, and nitrogen, with some occasional sulphurs thrown in. Although ordinarily not able to transport electrons, like a traditional electronic material (e.g. a metal like gold), in certain chemical environments or contexts they could be induced to become conducting. These materials are typically classified into conducting or semiconducting polymers or small molecule semiconductors. At the time, I encountered them, around 2003, organic electronic materials were mostly used for applications like OLEDs (organic light emitting diodes) that you can find nowadays in your curved flat screen TV, or OPVs (organic photovoltaics) that could be made to fit on backpacks or adhering to buildings as power sources. In contrast to the traditional materials used for these applications, organic electronic materials, I could be formulated as liquid chemicals that could be processed or fabricated using techniques like screen or inkjet printing or even spraying.

My initial work on organic bioelectronics was as a “friendly biologist”. I helped the people in the Materials Science labs to work with proteins where I had significant expertise. The early work was in the development of glucose sensors, by immobilising the enzyme glucose oxidase on an organic electrochemical transistor.⁵ I quickly realised however, that there were many other applications for these materials, and that I could bring my wealth of experience in biological sciences, across molecular biology, microbiology and cell biology to bear in designing exciting new applications.

Rachana's background – a material scientist's journey to cell biology

I started with a very traditional engineering background in India as a metallurgical and materials engineer and continued with materials science as my core field of research. My doctoral research revolved around organic electronics, particularly organic thin-film transistors (TFTs), and involved their fabrication, characterization, and analysis. The traditional target applications for organic TFTs are large-area flexible displays which demand electrical performance metrics such as a low operating voltage, low power consumption, a low contact resistance, along with other functional requirements such as mechanical and chemical stability. My research focussed on investigating different organic semiconductors and other materials for the fabrication of organic TFTs, understanding device physics at the interface between materials, and improving the electrical performance towards target applications. It was during this period that I came across other domains of organic electronics and even more challenging applications such as organic electrochemical transistors and their development towards biosensing. The prospect of developing organic electronic devices towards bioelectronic applications was extremely intriguing and prompted me to pursue inroads into the new, challenging yet exciting domain.

For my postdoctoral research, I started working with Róisín at the University of Cambridge where I have continued my work with organic electrochemical transistors, except now these are integrated with 3D tissue-engineered conducting polymers and *in vitro* cell culture.

Challenge for materials scientist vs. challenge for biologist

Challenge for a material scientist

R. A.: “As a material scientist, I had only ever worked in chemical and physical laboratories, cleanrooms, and microfabrication labs where I gained experience with thin-film deposition equipment, microscopy techniques, and chemical synthesis. Upon introduction to a bioelectronics experimental setup, I was exposed to a traditional biological laboratory as well and learned about cell culture, microbiology techniques and different optical procedures employed in cell biology. There were several challenges that accompanied this change, akin to an entirely new academic beginning for me. I was familiar with working in a cleanroom environment which requires one to limit skin exposure with protective covering, but biological work required me to learn working in a sterile environment, and to prevent any contamination of biological samples. I found myself developing an entirely new state of mind while performing biological work and was grateful for the many tips and tricks from my colleagues who had years of experience with it. Much like a new chef in training, I was taught the best way to place my hands and elbows, to keep my workstation organized, and work swiftly and efficiently to shorten the time the cells are outside the incubator. One of



the major take-aways for me as a scientist during this time was the importance of on-the-job skills and the wisdom of hands-on experience, and even more so, the benefit of having accomplished colleagues sharing those with me, something I couldn't have absorbed from a textbook or in a classroom. As a physical scientist, we are not trained for the set of safety precautions that biological work requires, and it was a considerable shift adjusting to a new pattern where there is a two-way hazard risk between you and the experimental samples. After all, the most harm one can cause in a cleanroom is getting dust on the microfabricated chip, unlike biological work where one might contract an illness! I also experienced a paradigm shift in the scientific design and methodology with the need for experimental replicates to validate the results of your experiment. The physical sciences require the demonstration of a statistically significant conclusion but operate on an assumption of reproducible and repetitive physical phenomena. If I ever, as a young, naïve high school student thought of biology as an "easy science" as compared to physics or engineering, this transition has made me realise the error of my ways. The learning curve in biological research has reinforced the necessity to account for unknown biological variation. Working with live tissue meant dealing with a certain level of uncertainty which was a completely new experience for me and has tested my scientific perseverance like never before.

The most drastic change I have noticed is the need for consistency and uniformity in experimental protocols and the inherent long-term results of biological work. During physical or electrical measurements, it is quite common to perform minor tweaks in the equipment or in the operating parameters and observe its effect immediately. In fact, one might need to tweak the laser position, adjust the electrical current, or change the position of the sample to get the experiment going. In the course of biological work, I have realised it's vital to stick to the same experimental protocol throughout the course of the experiment, observe the effects at the very end and implement any changes only in the next experiment. The absence of immediate validation of results is frustrating at times but has taught me the importance of consistent and robust protocols.

Apart from the challenges faced in experimental work, I felt the need for a significant increase in my knowledge of basics, particularly at the intersection of electrochemistry and electric circuit theory. I knew how a resistor and a capacitor interacted with electronic charges, the new challenge was to imagine mammalian cells as different circuit elements, and model different biological processes as charge-transport processes."

Challenge for a biologist

R. O.: "I often resent the implication that biology is a "soft" science compared to physics or chemistry or engineering, all considered "hard" sciences. Although it is possible that what's meant is the literal softness of tissues, I suspect that the implication is that biology is easier to learn. Now, in teaching cell biology to chemical engineers, the constant refrain is that

there is too much content to learn in biology, and unfortunately there are no principles to be derived and formulae to routinely apply. I suspect those engineers would quite like to avoid studying biology as they find it very difficult to grasp which parts are important. Crucial for biology, however, is understanding. Initially it seems hard to figure out which bits to concentrate on, but gradually as the jigsaw pieces come together, a broad understanding of biology and an appreciation of the inherent complexity can be obtained. In fact, there is a branch of biology where electronics knowledge is essential, and that is in electrophysiology, particularly applied in neuroscience. This may partially explain why many of the initial applications of organic bioelectronics have focussed on interfacing with neurons or cardiac cells.

In contrast, the barrier for a biologist wanting to enter the field of organic electronics, is the implied applied mathematical/physics knowledge, where formulae are routinely used, and physical laws invoked. This implies a thorough grounding in physics or applied maths. Specifically for organic bioelectronics, concepts such as resistors and capacitors (Ohm's law), diffusion at interfaces, electronic properties of materials, seemed insurmountably difficult at the beginning. As a young assistant professor my solution was to hire bright postdocs and offer an exchange of knowledge – electrical impedance spectroscopy tutorials (thank you Dr Jimison) in exchange for a crash course in mammalian cell culture. I later came to realise that that was a truly equal exchange of knowledge without any real evidence that one was easier or harder than the other. I particularly remember one conference presentation where a PhD student (Credit to the now Prof. Khodagholy) had taken the time to explain time constants in preparation for my talk. Imagine my delighted surprise when, after the talk, an audience member asked me where I had studied physics.

One could argue that my later specialisation in biochemistry was one of the more quantitative of the biological subjects which gave me somewhat of an edge in understanding electronics. However, I think it was actually my chemistry knowledge which was particularly useful in understanding the biotic/abiotic interface which is the key hurdle in any bioelectronic device – the molecular interface where electrode meets biology. In many cases, devices relied on biofunctionalization where biological components would be assembled (e.g. cell membranes), electrostatically adsorbed (e.g. antibodies) or covalently bonded (e.g. enzymes)."

Importance of communication

Effective communication is at the foundation of any well-functioning organisation and research group, but perhaps even more so in interdisciplinary fields such as bioelectronics, involving colleagues of diverse working backgrounds. In the academic structure, research projects often function with a bottom-up approach, designed, and led by graduate students and postdocs with valuable inputs and guidance from research supervisors. However, projects in bioelectronics often involve



the juggling of several simultaneous moving parts. For example, the development of a biosensor has parallel goals for improving device performance, achieving device uniformity, creating biomimetic environments, and ensuring selectivity and specificity. The mechanical aspects of device design and fabrication along with the electrical operating parameters need to align with the requirements of the cell and tissue systems, ensuring compatibility and accurate transduction along the way. This extends beyond the basic requirement of biocompatible systems to accommodate and simplify the various experimental procedures involved. It's often the case that the requirements of cell systems are not entirely intuitive to a device engineer, and communication with a biologist colleague can bridge the gap between "the best performing device" and "the best cell-hosting device". The seemingly vast gap between materials scientists and clinicians could also be bridged by continuous and bilateral communication towards the use and translation of biomedical materials. When the materials scientist or the engineer can observe the clinician operating with state-of-the-art tools, they may immediately realise how new materials can bring additional functionalities. This could be making medical devices smaller, thinner, more robust, biodegradable *etc.* To ensure uptake however, the advances must be significant, for anything else, the pain involved in implementation – altered ethics, clinical trials, approval for new materials *etc.* is too high. In the same way a clinician can express their seemingly unattainable wish list of futuristic technologies, which triggers the material scientist to realise a path towards building that technology, even if the time scale may span many years. This may involve a completely new modality (for the clinician), such as wirelessly powered and controlled devices or magnetically piloted implants. The balance between push and pull is important – the pull comes from the end user; the clinician has a current need which can be answered potentially swiftly. For example, this could mean miniaturisation using new capabilities for materials processing. The push may come from the material scientist, realising that there is technology which can create a step change in terms of functionality. A typical example would be combining optical and electrical monitoring to create multiple modalities in a single system. Areas of interdisciplinary research pose excellent opportunities for scientists to hone and develop a wide range of skills and techniques through collaborative projects. A materials scientist would want to develop biological research skills to better understand the need for efficient and biocompatible electronic device design. A biologist, on the other hand, would benefit from a more fundamental understanding of electrical signalling and processes to transduce cellular behaviour from device outputs. This kind of research is an excellent opportunity for area-experts to expand their research horizons to encompass a more holistic approach to science. It is then a natural requirement for such a work environment to have constant two-way communication channels for fostering open and inquisitive learning. The ultimate goal is to develop improved solutions to problems. However, we do recognise that the pressure of not just publishing but also the time-sensitive nature of projects which deters researchers

from pursuing new skills. Particularly when it involves learning a completely new research methodology and the challenges which encompass it. For the overall benefit of interdisciplinary research, it justifies letting researchers exercise their own field of expertise and collaborating together on projects demanding of these diverse skills. Nevertheless, it becomes increasingly important for area-experts to familiarize themselves with at least the basic principles of adjacent fields, the goal being to aspire to be a "jack of all trades, master of one". It is only then, that we can go from being a multi-disciplinary field of research, akin to having a large buffet with a variety of dishes from different cuisines, each prepared separately by expert chefs, to having a truly interdisciplinary approach, a fusion dish where ingredients from different cuisines are blended together to create something entirely new. Scientific language and vocabulary play a huge role in establishing good communication pathways, similar to any diverse environment of individuals with a multitude of identities and backgrounds. These become even more relevant when different disciplines of science might employ the use of similar or even identical terms for completely different purposes. As an example, for a material scientist the word "substrate" would signify a physical surface for device fabrication, while for a biochemist it would mean a molecule for enzyme function. Other examples include electrode/membrane "potential" and at the very basic level, a possible conflation between an electrochemical and a biological "cell". Apart from similar vocabulary, a significant other challenge is the introduction of completely new terminology altogether. It is of vital importance to establish proper channels of communication for productive idea exchange and knowledge transfer in such an environment.

Importance for safe space

One of the primary requirements for good communication in a seemingly unfamiliar scientific territory is the establishment of a safe space where different scientific expertise is respected, resulting in healthy co-operation.

This is particularly important for early career scientists. R. A.: "My own experience upon joining the bioelectronics field included being overwhelmed and frankly intimidated by the sheer number of unknown terms, tools, and techniques. I had limited pipetting experience and needed to familiarise myself with the vocabulary and working of well-plates, stripettes, flasks and falcon tubes. It was only through a consistent period of working together with my colleagues that I realised the mutual requirement for joint learning and idea exchange. While I was absorbing new concepts in biochemistry and cell biology, my colleagues were learning about electronic devices and polymer chemistry. Through conversations hunched over the lab bench or hovering behind the microbiological safety cabinets, we discovered that there really are no stupid questions. It led to several interesting conversations which included questions from my biologist colleagues such as "What do you mean the circuit is imaginary?", when talking about electrical impedance, or "How can the material conduct holes, when they don't even



exist!" when talking about p-type semiconductors. Of course, I wasn't far behind with my own questions of "Why can't I make the cells grow faster with more media?" and most frequently, "Are the cells still alive or do I have a contamination?". No doubt these made for interesting workplace anecdotes but continue to be massive learning experiences as well. Along with positive research culture, good laboratory practice also demands physical safety of the individuals, and even more prominent in interdisciplinary research fields. For scientists transitioning from multiple years of experience in a particular field to a new lab environment, it poses a dual responsibility to establish new safety and hazard protocols. Improved training protocols might need to be developed to initiate and introduce very field-specific precautions, for example, safeguarding against electrical equipment for a biologist or preventing biological cross-contamination for a physical scientist.

As healthy research culture is thankfully now being increasingly encouraged and rewarded, we need to recognise the important role that a group leader plays in establishing safe spaces for researchers. Especially for interdisciplinary work, the contributions of all parties must be recognised as having value.

R. O.: Through years of observing the many students and postdocs that have been in my group, experts in biology or materials science (or other fields), I can unequivocally state that all scientific fields have their experimental challenges. In bioelectronics, while a mastery of both biology and materials science may require many years of training, at least an acquaintance with both is essential. After one particularly difficult discussion with a postdoc who dismissed biology as "just pipetting", I resolved to make sure that all future materials scientists in the lab would learn cell biology with a task of maintaining cells in culture for a couple of weeks. After enduring contaminations, and unexplained cell deaths and numerous other calamities, there was newfound respect for biological colleagues. Likewise, biology researchers who treated the electronic devices as black boxes or couldn't be made to understand the difference between the black and red cables, were asked to independently carry out impedance experiments. In practice, many of our researchers now work in collaboration with each other or with scientists from other groups. Given the current publishing paradigm where the contributions of the sole, first author can be make or break for a researcher's CV, multiple contributors pose problems and recognising all parties equitably can be highly challenging. A move to recognise individual contributions in multidisciplinary research is therefore essential for healthy research culture and to promote ECRs.

Recognition that materials community is potentially more welcoming

R. O.: My experience has been that the Materials Science community has been incredibly welcoming to me as a biologist. The technological and applied focus of the materials science community has meant that they embrace and value expertise in different areas. Indeed, Materials Science as a discipline, first emerged as a fusion of Chemistry and Physics, where Scientists

of both disciplines had to learn to get along, much as described above. This may explain why this community is welcoming of new mergers, *e.g.* with biology. Conferences such as the Materials Research Society Annual meetings have been pivotal in my career. When I started to go to this conference back in 2009 there were initially only a few bio-related symposia, but now the biomaterials/biological applications are one of the major themes with upwards of 10–15 parallel symposia. This is also true when it comes to publication – there is genuine interest and excitement around the development of new materials and devices for biological applications within the Materials Science community and there has been a steady upward trend in numbers of publications and also the sophistication of the applications. Interestingly, while clinicians are avid seekers of upgraded technology and devices, the acceptance by biological scientists has been somewhat harder. This is in part related to the effort and time required to validate new materials and ensure biocompatibility, potentially exacerbated by bad experiences with batch-to-batch variation and a misunderstanding by the physical sciences/materials community around the exigencies related to maintaining sterility, for example. As the field of bioelectronics matures, there is a lot more expertise and knowledge out there, as well as a new breed of early career researcher who understand the requirements from both biology and materials sides. This is likely to drive progress and ensure that ultimately, materials and devices are designed with biology in mind, are fit for purpose, and most importantly bring new functionalities to the table that were hitherto impossible.

Future – what needs to happen

With a global shift to more multidisciplinary research, the number of papers with the word "interdisciplinary" in their title is at an all time high in the 21st century.⁶ When broken down subject-wise, a study found general biology, material science, biomedical research in the natural sciences and social studies of medicine and health to have the largest number of papers cited outside their own respective fields.⁷ The current state of research in bioelectronics has already outlined the path forward for scientists. The true magic of interdisciplinarity lies not only in different area experts coming together, but also a synthesis of different approaches to tackle unique challenges.

Huge problems to society include climate change, food security, and healthcare. Bioelectronics could potentially be a pivotal technology in all of these areas, whether in developing biophotovoltaics,⁸ stimulating plant growth⁹ or treating Parkinson's disease.¹⁰ Scalable new technologies and nature-based solutions offer great promise in mitigating greenhouse gas emissions and achieving a low-to-zero carbon bioeconomy.¹¹ Improved agricultural yields, bioengineered plant-breeding techniques and selective nutrient enhancement through biotechnological tools offer solutions for sustainable agriculture and meeting global food demands. With translational research, the field of bioelectronics could potentially bridge the gap between fundamental materials/biological studies and clinical



applications in drug and toxicology testing, remote health monitoring and cure of infectious disease.

Successful research solutions will only be realised with a strong foundation and adequate institutional support along the way. Starting right from education at the undergraduate level, a mixed coursework across disciplines and general seminars should be encouraged. Interdisciplinary PhD cohorts co-supervised by academics from different faculties are a great investment and academic programs should be designed to further support them. Funding agencies could potentially encourage more crosstalk by requesting impact on other fields in grant proposals. Reviewing panels would benefit from experts adjacent or outside the field of study. For bioengineering for example, it would be better to have panels with interdisciplinary scientists rather than a physicist and a biologist who've not actually experienced what it is to work across the divide. Individual departments with shared lab facilities or centralized equipment are an excellent way to not only reduce costs but also encourage collaborative research. With the physical and biological sciences already coming together, we should extend the collaborative spirit to the social sciences as well. The translation of lab research and technological advancement into effective social solutions can only be realised by considering the sociological impacts of our research. A fertile and constructive research environment encompassing and embracing diversity of fields is the only way forward.

Author contributions

R. A. and R. O. both wrote and reviewed the article before submission.

Data availability

This is an opinion article and no primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

The authors declare no conflicts of interest.

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