Essays

Israel Journal of Chemistry

DOI: 10.1002/ijch.201800128

A Brief Manifesto for Chemical Ingenuity and Insight in the Heart of Biology: A Time is Right for Sophistication not Simplification?

Benjamin G. Davis[a]

1. Introduction

1.1 What has Chemical Biology Done and What is it Doing?

There has perhaps been a perception that the field of chemical biology, as for chemistry, has a future as a 'service technology' rather than an independent science. In addressing this then one must perhaps think about the role of chemistry in biology, as well as Chemistry in Biology. Without wishing to seem arrogant, chemistry is a longstanding and hence, in part through historical accrual, a sophisticated science. It certainly creates uniquely powerful molecular technologies that can be transformative but perhaps more importantly sets up its own aesthetic, philosophy and approach. Its power in society is undeniable and, aside from arguments about what is chemistry and what is not, the list of fundamental discoveries that have merited the Nobel prize (as a gauge of "the most important chemical discovery or improvement")[13] reads as a list of societal evolution. It is therefore not only an intellectual imperative that this power is as accessible as possible, it is an ethical one too. This raises the prospect of 'service'.

Full exploitation of the depth and subtlety of knowledge necessarily requires expertise, sometimes at a level that may frustrate those who wish to gain access. Yet, maintaining rigour is also a prime ethical imperative (see below). We must therefore find moral solutions and philosophies in a space where the ethical tension arises between rigour and accessibility. There is no doubt, for example, that attachment of fluorophores (proteinaceous or otherwise) to biomolecules has been transformative, yet it is the hypothesis-testing that they enable that is the scientific joy – it is easy therefore to see why some might say, as a now ex-collaborator of mine once said several years ago, "Bolt me on a fluor and I can take it from there.". It might be said that we have more than enough ways of 'bolting on fluors' or similar – instead, it is the molecular precision in the chemical understanding of biology that is the rich seam that I think modern chemical biology is now tapping.

What then is chemistry's distinction or position (for example in the chemical understanding of biological questions)? Phrases such as 'the central science' give comfort but sometimes deepen a sense of service. One core centrality, as I would see it, is one of access to and control of *informational content* in biology. The molecular level is the cutoff at which the units of information (genes in their original sense)[9] become discernible and usable. Those units may be found in all parts of biology (not simply nucleic acids)[4] and, without wishing to open a debate that is not strictly relevant to this essay, one might argue that information transfer is an imperative thread in what we consider to be life.[5,6] Analysing such informational constructs is at least one centrality that we should take on board. This should be done in a suitably clear manner, lest we create issues that faced even Kant: 'I am often accused of obscurity, perhaps even deliberate vagueness in my philosophical discourse, to give it the air of deep insight'[10] – some current analyses draw on notions of 'systems' as similarly intractable, 'vague' blackboxes; these too will become accessible in time to precise chemical thought in the areas of, for example, the origin of life, epigenetics, and even the molecular basis of thought or memory – all of which remain very much open questions. These perhaps seem hard to understand using current modes of nucleic acid-derived linearity but may be more readily understood in beautiful, thermodynamically-precarious systems maintained at far-from-equilibrium hotspots with great functional value: in biology'the instructions are ready made but their fulfilment is epigenetic'.[11]

These ideas are perhaps, to the chemically-minded, no more than simply notions of kinetic control of informational content. Therefore the initial programming of information, largely covalently, has been a central goal. An example that I often return to, is that of what is loosely described as mutagenesis. Transformative manipulations in nucleic acids[15] lead directly from a connection between structure and 'gene', yet the more complex question of information closer to functional output (e.g. in proteins) has barely been touched on, despite profound insights set down over 50 years ago.[17,21]

This brief essay will explore a few illustrative areas with the goal of capturing the distinctive nature of chemical analysis of biology, which to me lies in great part in the precision that it might bring to bear.

[a] B. G. Davis
Department of Chemistry, University of Oxford, Oxford, OX1 3TA

1.2 A Plea Against Over-simplification – A Possible Direction for the Field

As science steps from model-to-model, hypothesis-to-hypothesis, the method by which we collectively analyse and describe what we observe can play a critical role. We accept a moral responsibility, as experts, to set out our stall in a manner that maintains intellectual momentum. Clarity is vital; distillation of a conceptual essence (finding the 'heart of the matter') can play a powerfully useful role in enabling cognitive analysis. But, taken to extreme, this becomes caricature that loses all benefit of the ideas being described.

Until now the accomplishments of chemical biology have been predictable in part, more enabling but now finally tending towards uniquely revealing – it is key that the future will not be solely in 'tool delivery'. Without chemical mechanism, Biology and Medicine will stumble increasingly into an intellectual bankruptcy based on reductionism. We must therefore lead more, follow less until balance is resumed. As Medawar pointed out beautifully more than 50 years ago, the problem is that 'propositions are sometimes taken to import that biology is, or soon will be, nothing more than a kind of super physics-and-chemistry. In reality they do nothing of the kind….. We are mistaking the direction of flow of thought when we speak of 'analysing' or 'reducing' a biological phenomenon to physics and chemistry. What we [should] endeavour to do is the very opposite: to assemble, integrate, or piece together our conception of the phenomenon from our particular knowledge of its constituent parts.'

It has never been a better time to be a chemist. The subject's unparalleled sophistication may, however, be stimulating an intellectual crisis that could necessitate new analytical frameworks that serve to stimulate new knowledge. So how do we address the dilemma of a greater need to describe well our science, on one hand, and even greater detail in *that* science, on the other? This is therefore a tension in breadth and depth. I present here, using some strategic examples, an opinion that such frameworks should also embrace sophistication rather than merely simplification if they are to succeed.

1.3 Lego-like Chemistry

Philosophies of efficiency are important and have been ever present (Chiron,[8] Atom Economy[18] and perhaps now Click)[16] – few would disagree with key aspects of their message. There is value in the distinction between Science and Technology/Engineering (poorly distilled to discovery and exploitation, respectively). But, there is also a false opposition as noted above. For chemical biology, Click has been a powerful driver for biology using chemistry as a tool technology (largely as a conjugation tool) but it is perhaps no more than a reiteration of sensible approaches intended to open up possibilities in future work (a manifesto rather than a method *per se*). Adoption of single examples of e.g. reaction types, however then becomes dogma that stifles Science (whilst potentially allowing 'engineering-only' development – i.e. everything becomes built from the same lego).

No doubt, technologies are enhanced and made useful by a modularity that comes from reductionism that allows ready engineering 'off the peg' – this drives accessibility. Science on the other hand benefits from 'bespoke' solutions. If all molecules are linked by heterocyclic motifs from hereon in then there is no doubt that Chemistry will plough a strategically fatal track. Neither, *in extremis*, is correct. I would argue that there is perhaps a need to sometimes stop and analyze goals with better clarity. 'Forced Click' may generate little knowledge; it may simply be bad design. Diversity of method is a strength of chemistry's depth that should be embraced by and for Science, but that diversity may, of course, not be necessary for Technology.

It is a trite observation, but one can more readily spot something built from *Lego* – we understand what the facsimile is supposed to be but we also respond differently. The same is true of biology. Science perhaps then does not need more *Lego*-like methods, but to remember the need to 'play well' (*leg godt*). Nonetheless, such modular, standardised methods may powerfully allow and drive engineering approaches (i.e. engineering might ultimately need them in the implementation of useful outcomes or interventions).

1.4 Synthetic or Synthesis of Biology?

Another example of potentially useful modularisation (where the pressure of engineering upon biology is now also leading) lies in notions of bio-bricks, chassis, biosynthetic pathways as pipes, and refactored genes that has become a prevalent mode of what is now termed Synthetic Biology. This construction with potential for recapitulation through effective mimicry presents a golden opportunity for science yet there remains a risk that this may become solely (or too much) a process methodology. The application of such engineering-only production principles to biology has undoubted merit in enabling fresh viewpoints and some more immediate societal exploitation but, again, extreme approaches that strip back and so ignore the inherent 'fuzziness' (iterative feedback at condition edges) may 'throw the baby out with the bathwater'.

The desire in this sub-field also to simplify and modularise has been wonderfully embraced by a much wider engineering community and, indeed, has created an accessibility through e.g. iGEM competitions that generates a powerful, raw enthusiasm for predictable biology akin to old-fashioned/home-made chemistry sets or *Raspberry Pi* coding sets. We should perhaps recognise too that this may be in part reflecting an inability of our sciences to bridge gaps in conceptual understanding. It may therefore say something about how little of Engineering biologists understand and *vice versa* – maybe that should be addressed through sophistication as well as reductionism. Without it, there remains the possibility not only of missed opportunities (a descent into a form of Process

Microbiology) but also the danger of an abdication of ethical responsibilities based on professed ignorance.[12] For me, the potential to justify and test (on soils foreign to the agencies funding the work)[20] extreme implementations of engineered biology, such as mammalian variants of so-called 'gene drives', is a step too far, too soon. Whilst I am an advocate of courage in science, there seems to me to be a moral imperative to confine the consequences of failure to those taking the risk ('on your own head be it') – appropriate analyses of such risks seem to be either lacking or weakly reasoned in some current publicized examples in the field.

1.5 Towards Mechanistic Biology

So where might some future of a 'chemical biology' lie? One area that I find truly appealing (and perhaps lacking) is the construction of a series of mechanistic schema that like, for example, the detail of 'curly arrows' backed by Physical Organic methods in Organic Chemistry or quantitative enzymology in Biochemistry, integrate function with precision. A consequence of lack of depth in some parts of 'modern' chemical biology may mean that we might miss such immediate opportunities to go deeper in understanding Biology. Exploitation of common, longstanding chemical principles is still not widespread in Biology and perhaps in some areas has even regressed in frequency of use in recent decades (e.g. detailed kinetics, kinetic vs thermodynamic control, Curtin-Hammett principle). Analysis of dynamics, for example, whilst now increasingly viewed as sometimes important still draws on misplaced notions of the dominance of certain equilibrium points (the misplaced idea that if you can see a lot of it, it *must* be important). Chemical principles and approaches will therefore be of value in this form of Mechanistic Biology.

That said, it is vital that Chemistry expands its often dogmatic horizons to embrace and understand that the complexity and sometimes emergent nature of certain systems is itself the very point of biology, if it delivers desired function. This necessitates an open-mindedness in judging the endpoint of that function, which may jar with some modes of typical A-goes-to-B thinking. This will therefore necessitate a fine balance between inductive and deterministic strategy (see above).

Once realised there are several experiments that might fit the bill and these excite me. For example, using rapid, high-throughput, 'deep' proteomics to obtain quantitative endpoint measurements on complex, endogenous substrates might enable a form of personalised, non-invasive medicine in individuals that would directly track the multiple effects of pathology and corresponding treatments. When coupled, with direct 'in vivo chemistry' and/or functional mimicry[2,19] to modulate and perturb such pathways then the resulting detailed chemical understanding of the biology of health and disease (if you will, a *Chemical Medicine* based on precision) is tantalising. This approach based on a greater sense of causation seems, to me at least, a more realistic and useful vision of 'personalised' or 'precision' medicine then many current views based on often quite loosely correlated genomic traits or 'markers'.

2. Summary

2.1 Some Final Words on Open Science, Chauvinism, Rigour and Utility

Mechanisms of science transmission must be considered with care. The protectionism of restricted access is clearly unacceptable. That said, the democratization of science coupled with an increasing reduction in the reverence for expertise, breeds shallowness in not only appreciation but also approach. This may, in part, be a symptom of an emphasis on disseminative units as a currency of scientific progress that can push towards lowest common denominator papers. A curious argument emerges under such circumstances that all papers deserve to be published. In such a climate, scientific bubbles can emerge that may say less about scientific progress than they do about societal approaches to science and a rebalancing of Chemistry from new knowledge to more application.

No doubt, some (but not all) elements of Open Science ('Garage Science') will necessitate such democratization and perhaps the modularization and standardisation discussed above. Sometimes such modes of discovery are criticised as being merely superficially impressive but I feel this is unfair – its distributive model is egalitarian in principle, and hence exciting, and so has recruited many new scientists. That said it would be a great loss to our field if a generation of very able scientists were effectively to emerge as *idiots savant*, wrongly treating DNA sequences or modularly-conjugated molecules as contextless, programmable units and so potentially ill-equipped to elicit further knowledge (as opposed to exploit existing). It may also be possible that certain chemical skills will become lost in those accepted as scientists.

Is this necessarily wrong? The basic simplicity of a Tracey Emin or a Cy Twombly piece similarly often irritates some of the art-viewing public but these pieces also convey a unique and valuable creativity – is therefore such resistance more than ill-directed snobbery? This community (those who consider the molecular depths of biological function) should at least I feel be concerned about this potentially becoming a dominant mode for the molecular study of Biology. I know that I am. I worry that Chemical Biology may become as two-dimensional as parts of Synthetic Biology have become; more algorithmic solution (molecular crosswords or *sudoku* puzzles) rather than free-ranging works of art. We cannot have only Engineers or only Scientists.

We must therefore lead by example and embrace the best of both approaches. One area in which there is the increasing danger of selling ourselves short is in the rigour of chemical method. One striking example is in the discipline of molecular

characterization. Sometimes seen by the uninitiated as 'stamp-collecting', the panel of complementary, coherent data that routinely supports compound identity for small molecules has helped Chemistry avoid some of the pitfalls of low reproducibility encountered by the antibody-reagent-driven era of biological science.[1] This rigour must translate into Chemical Biology. Although there may possibly be rare occasions when a gel (just as a tlc once did) might apparently suffice, more often than not it creates ambiguities of outcome that should instead be supplemented by the full range of spectroscopic and spectrometric methods now available for complex biomolecules and routinely used in omics, biophysics and structural biology. The first source of this rigour should be in the hands therefore of those interested in furthering the science; Chemical Biology is about biology first-and-foremost and those who see biological application as merely 'tinsel' to a chemical method miss opportunities in both chemistry and biology.

Emotionally, the description of science as a journey or excursion into unknown territory[11] where one observes new sights and so reaches some understanding has always appealed. This balance of choosing a direction to journey in but an open-minded approach to what one sees has, as others have noted,[11] already been beautifully set down in several places as 'hypothesis plus deduction'.[14] It helps avoid the arrogance that can sometimes grip those who carry a (essentially correct) sense that they can, in principle, make anything and replies to that sense by saying 'So what? – what are you going to make? What is worth making? Where will you journey?'.

One answer to that is to explore utility. As you will see from my comments above, I do not advocate blind, 'top-down' applied research (a pre-determined journey/a 'package tour') but that does not mean we are better for rejecting those challenges of application either. Medawar argued that our notions of 'pure' vs 'applied' science date back to the Romantics' perceptions of poetic endeavour, and has led to a bizarre notion that 'pure' is better (and hence as he points out the equation *Useless* = *Good*).[11] As, Coleridge himself highlighted, 'in the country … where Davy has delivered lectures on agriculture, it would be folly to say that the most philosophic views of Chemistry were not conducive to making our valleys laugh with corn.'[3] Such a societal imperative can provide, in my experience,[7] a deeply fascinating intellectual 'journey'.

Acknowledgements

I'd like to thank many people but particularly Hagan Bayley F.R.S., Gideon Davies F.R.S., Steve Withers F.R.S. for numerous enjoyable discussions over many years that have usefully tempered some of the ideas set down here.

References

[1] M. Baker, *Nature*, **2015**, *521*, 274–276.
[2] M. Bilyard, H. Bailey, L. Raich, M. Gafitescu, T. Machida, J. Iglesias-Fernández, S. Seo Lee, C. Spicer, C. Rovira, W. Yue, B. G. Davis, *Nature* **2018**, *563*, 235–240.
[3] S. T. Coleridge, *Treatise on Method* **1818**.
[4] F. Crick, *Nature* **1970**, *227*, 561–563.
[5] T. Gánti, *The Principles of Life* **2003**.
[6] Approaches to Building Chemical Cells/Chells: Examples of Relevant Mechanistic 'Couples', P. M. Gardner, B. G. Davis in *The Minimal Cell, The Biophysics of Cell Compartment and the Origin of Cell Functionality*, **2011**, pp 153-170.
[7] C. A. Griffiths, R. Sagar, Y. Geng, L. F. Primavesi, M. K. Patel, M. K. Passarelli, I. S. Gilmore, R. T. Steven, J. Bunch, M. J. Paul, B. G. Davis, *Nature* **2016**, *540*, 574–578.
[8] S. Hanessian, *Total Synthesis of Natural Products: The 'Chiron' Approach,* Pergamon, **1983**.
[9] W. Johannsen, *Elemente der exakten Erblichkeitslehre*, **1909**.
[10] I. Kant, *The Metaphysics of Morals*, **1797**.
[11] P. W. Medawar, *The Art of the Soluble*, **1967**.
[12] R. Mullin, *Chem. Eng. News* **2018**, *96*, 34.
[13] The will of Alfred Nobel, 27 November, 1895.
[14] K. Popper, *The Logic of Scientific Discovery*, **1934**.
[15] C. A. Hutchison, S. Phillips, M. H. Edgell, S. Gillam, P. Jahnke, M. Smith, *J. Biol. Chem.* **1978**, *253*, 6551–6560.
[16] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021.
[17] C. Zioudrou, M. Wilchek, A. Patchornik, *Biochemistry* **1965**, *4*, 1811–1822.
[18] B. M. Trost, *Science* **1991**, *254*, 1471–1477.
[19] S. I. van Kasteren, H. B. Kramer, H. H. Jensen, S. J. Campbell, J. Kirkpatrick, N. J. Oldham, D. C. Anthony, B. G. Davis, *Nature* **2007** *446*, 1105–1109.
[20] *Could WA be the genetic testing ground for 'synthetic mice' to end mice?*, Sydney Morning Herald, 24 February 2018.
[21] T. H. Wright, M. R. J. Vallée, B. G. Davis, *Angew. Chem. Int. Ed.* **2016**, *55*, 5896–5903.

Manuscript received: September 14, 2018
Version of record online: November 27, 2018