*J.Natn.Sci.Foundation Sri Lanka 2022 50 (Special): 195 - 211*
DOI: http://dx.doi.org/10.4038/jnsfsr.v50i0.11241

**REVIEW**

# Molecular logic-based computation and fluorescent sensors: The story so far

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**Summary:** The path to molecular logic-based computation began in Colombo, Sri Lanka and proceeded to Belfast, Northern Ireland. From there it spread to many cities around the world when over 1260 laboratories contributed examples and ideas to advance the field (Figure 1A-C). The formative experiments and some future directions are mapped out in this perspective. Principles discovered here should have a bearing on the computing performed continuously by molecule-based living things to survive and prosper. The more mature field of fluorescent sensors served as the springboard for molecular logic, and still serves a continuing need in society for monitoring atomic and molecular species in various situations for improving health, environment and economy.

**Keywords:** Blood electrolyte analyzer, fluorescent PET sensing/switching, molecular logic-based computation, photoinduced electron transfer.

## INTRODUCTION

A powerful approach for relaying atomic and molecular information to us humans relies on 'off-on' fluorescence signalling of molecular sensors (Bryan *et al*., 1989; de Silva *et al*., 1997; Lackowicz, 2006; Demchenko, 2009; de Silva, 2011a; Valeur & Berberan-Santos, 2012). These designed molecules can infiltrate living cells which are also molecule-based. Then the private world of atoms in living cells (Tsien, 1992; de Silva *et al*., 1999) and tissues (de Silva *et al*., 1999) becomes no longer private. Such gathering of information illuminates physiology and enables diagnostics for medical purposes. Extension of this idea leads to fluorescent signalling systems, which respond to different sets of atomic/molecular species. Input-output patterns of this type fit the logic gates described by George Boole's students in the 19th century (Boole, 1958; Malvino & Brown, 1993; Gregg, 1998) and which are exploited in modern semiconductor-based information technology. The first experimental approach to molecular computation arose in this way (de Silva *et al*., 1993) and serves to connect chemistry to biological sciences and to computer science.

## COMMUNICATING BETWEEN WORLDS

Light signalling from the molecular world to ours requires careful design of the signaller according to engineering principles. The design arose as follows. One of the authors was fortunate to be exposed to the principle of photoinduced electron transfer (PET) (Weller, 1968) during his PhD student days under the supervision of Jim Grimshaw at Queen's University Belfast (Grimshaw & de Silva, 1980; 1983). Ajita Abeysekera had pioneered the Colombo-Belfast nexus during his PhD work with Ron Grigg (Abeysekera *et al*., 1976a; 1976b; 1977a; 1977b; 1979; 1980; 1985). After returning to Colombo, one of the authors found that PET could be arranged within a 'fluorophore-spacer-receptor' system so that the fluorescence was switched 'off'. This turned out to have substantial precedent, but the recovery of fluorescence to an 'on' condition was rare (Wang & Morawetz, 1976; Selinger, 1977; Shizuka *et al*., 1979; Konopelski *et al*., 1985). Although not previously recognized as such, 'fluorophore-spacer-receptor' systems were hiding in plain sight within anti-malaria drugs (Bissell *et al*., 1992a). Our first reported case **1** was modelled on these (de Silva & Rupasinghe, 1985). Here, an amine group served as a receptor for $H^+$. Thus, we had a new class of fluorescent

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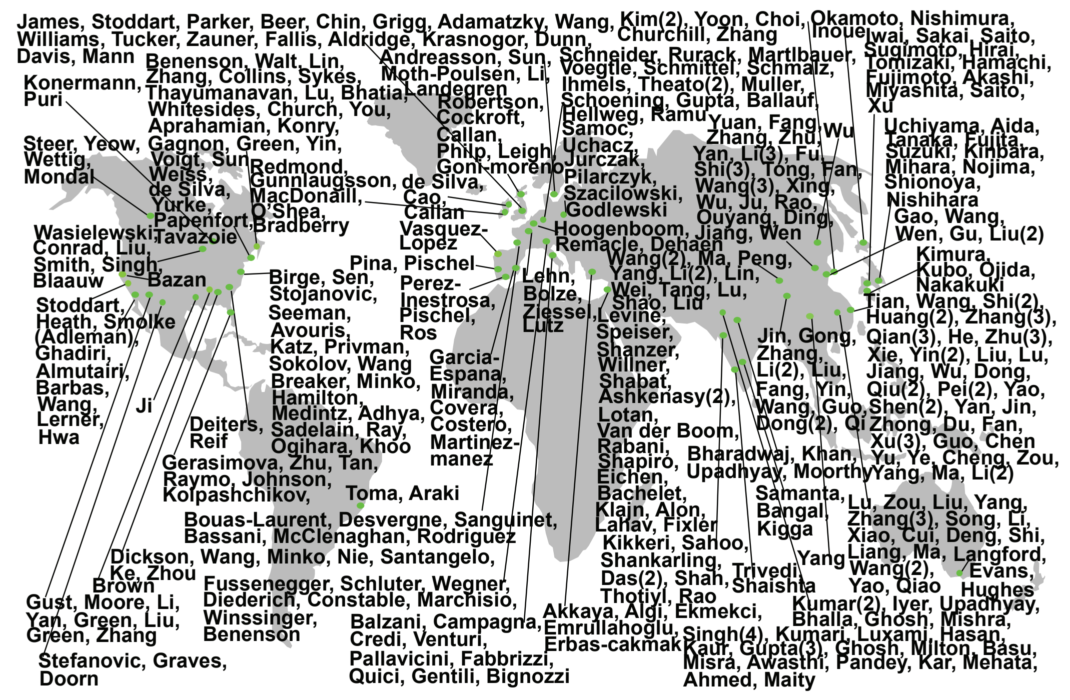


**Figure 1A:** Approximate world maps of some sources of molecular logic devices and cases which are understandable as such. In all cases, only the names of corresponding authors from the literature are given. The simplest cases of single-input, single-output binary logic devices are not included.

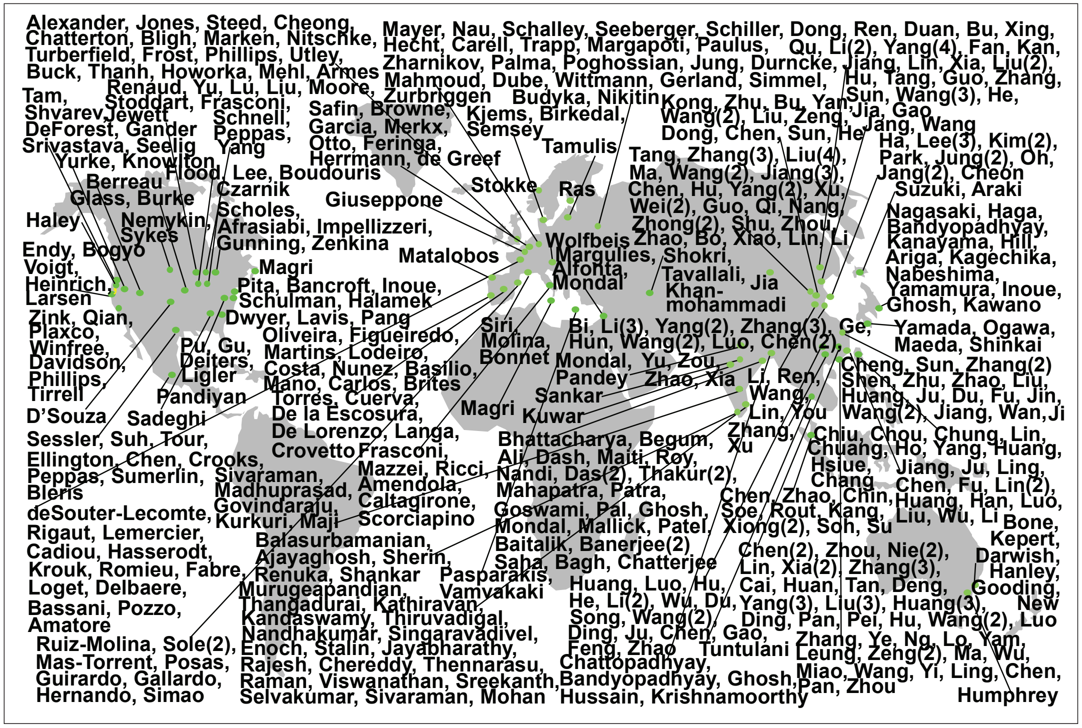


**Figure 1B:** Approximate world maps of more sources of molecular logic devices and cases which are understandable as such.

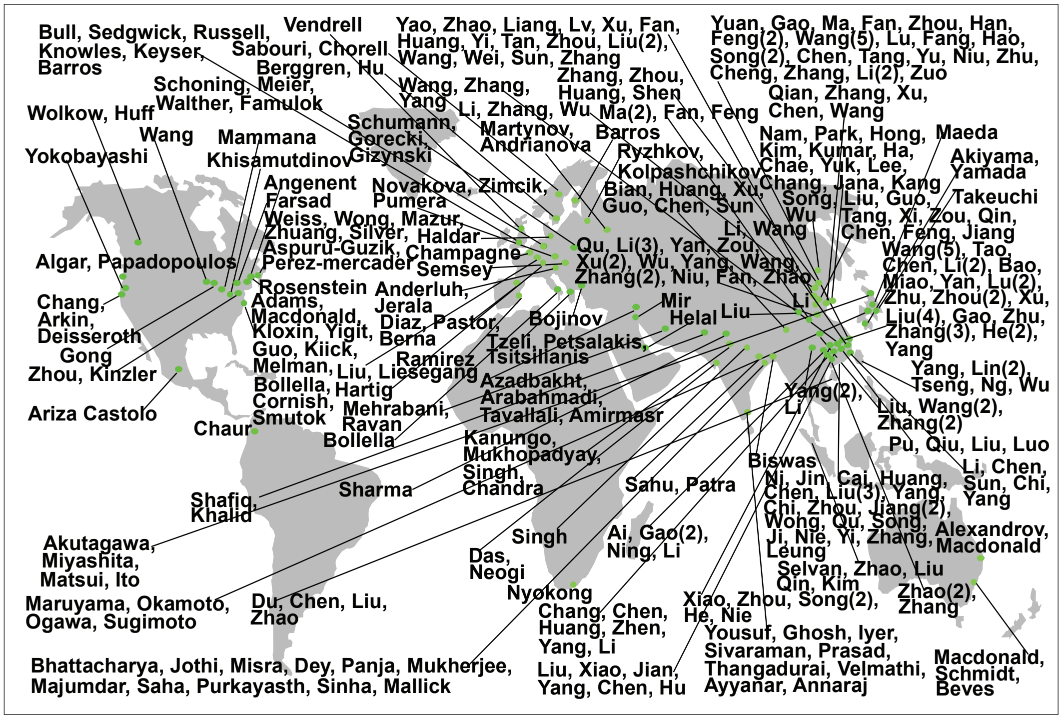


**Figure 1C:** Approximate world maps of further sources of molecular logic devices and cases which are understandable as such.

pH indicators on our hands. Perhaps pH indicators themselves did not need additions, since innovative uses continue to emerge (Wang & Anslyn, 2011) for these venerable compounds (Bishop, 1972). However, the 'off-on' switching of fluorescence, the modular engineering design and the resulting predictability of several electronic spectroscopic parameters (de Silva *et al*., 1989) promised that fluorescent PET sensors had launched with protons and that more would follow. Indeed, it was quickly demonstrated that $Na^+$ could be sensed in a similar way simply by replacing the amine with an azacrown ether (Konopelski *et al*., 1985; de Silva & de Silva, 1986). Other exploitations of modularity were also made for sensing applications (de Silva *et al*., 2007). As far as we can discern, over 950 laboratories around the world have contributed to fluorescent PET sensors thus far (Figure 2).

The fluorescent 'off-on' signalling mechanism deserves elaboration. When the amine receptor of **1** becomes protonated, its oxidation potential rises. So the PET process becomes energetically expensive. The previously allowed electron transfer becomes disallowed, so that the excited state de-excites via fluorescence emission (de Silva *et al*., 1997; Daly *et al*. 2015a; Magri, 2015). Such an increase of a redox potential in the presence of a cationic input species, e.g. $Na^+$, was later found to be rather general (Beer *et al*., 1989; Kenmoku *et al*., 2004).

The engineering design suggested that more modules could be added to 'fluorophore-spacer-receptor' systems to endow them with new properties. However, this had to wait until one of the authors had returned to Belfast. Nevertheless, University of Colombo put its stamp on this process in two ways. Satish Namasivayam gave instruction on logic gate hardware. Gihan Wickremanayake and Kevin Seneviratne passed on computer programming knowledge. These valuable inputs prepared us to link the worlds of computing and of chemistry/biology in a new way. Computational chemistry and computational biology employ conventional semiconductor computers to solve problems in these fields (Kohn, 1999; Pople, 1999). However, now we have chemical computation and biological computation, where chemical and biomolecular systems perform the computation itself. This should not be too surprising since living things have always processed information from their environment in order to survive and prosper. Here lies the original information technology.

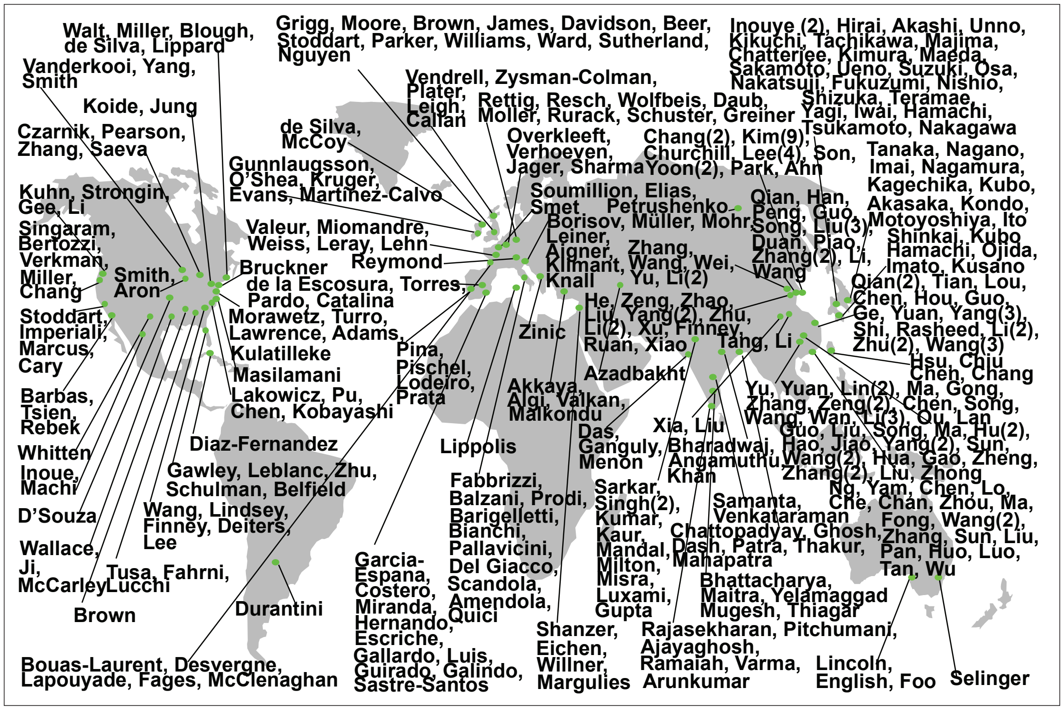


**Figure 2A:** Approximate world maps of some sources of fluorescent PET sensors and switches and cases which are understandable as such.

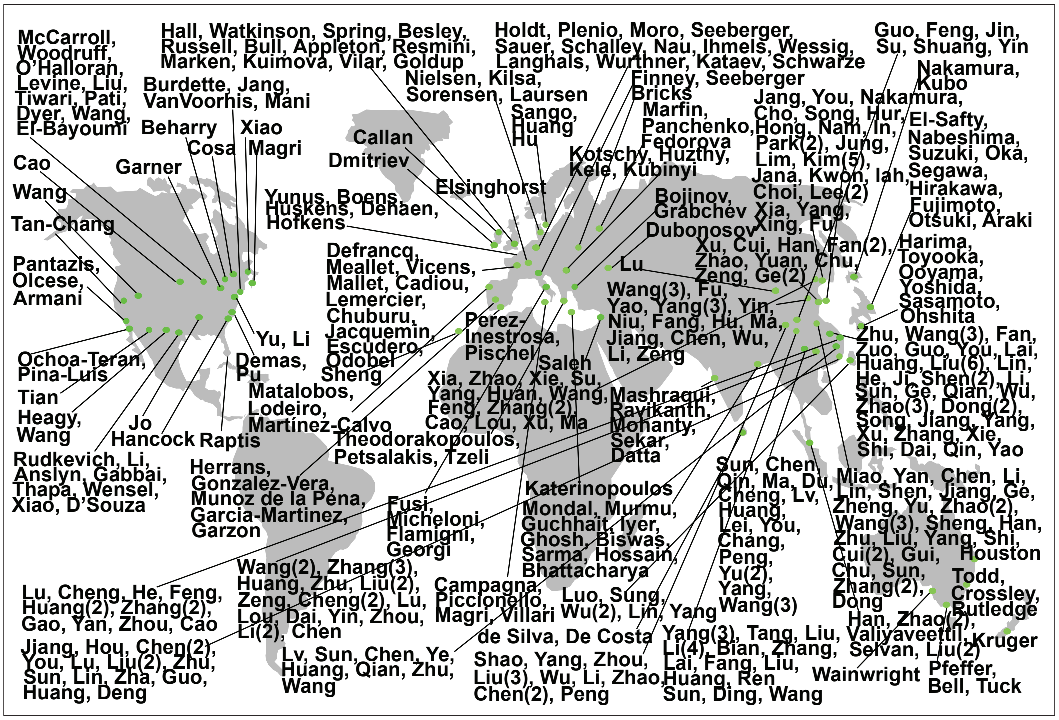


**Figure 2B:** Approximate world maps of more sources of fluorescent PET sensors and switches and cases which are understandable as such.

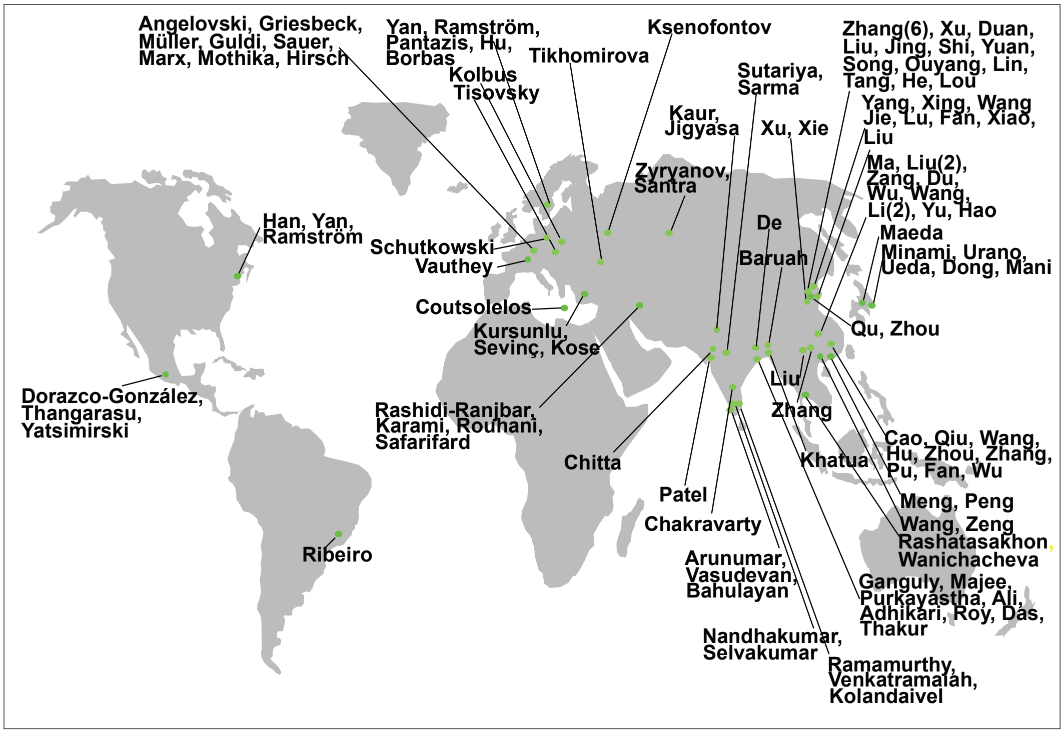
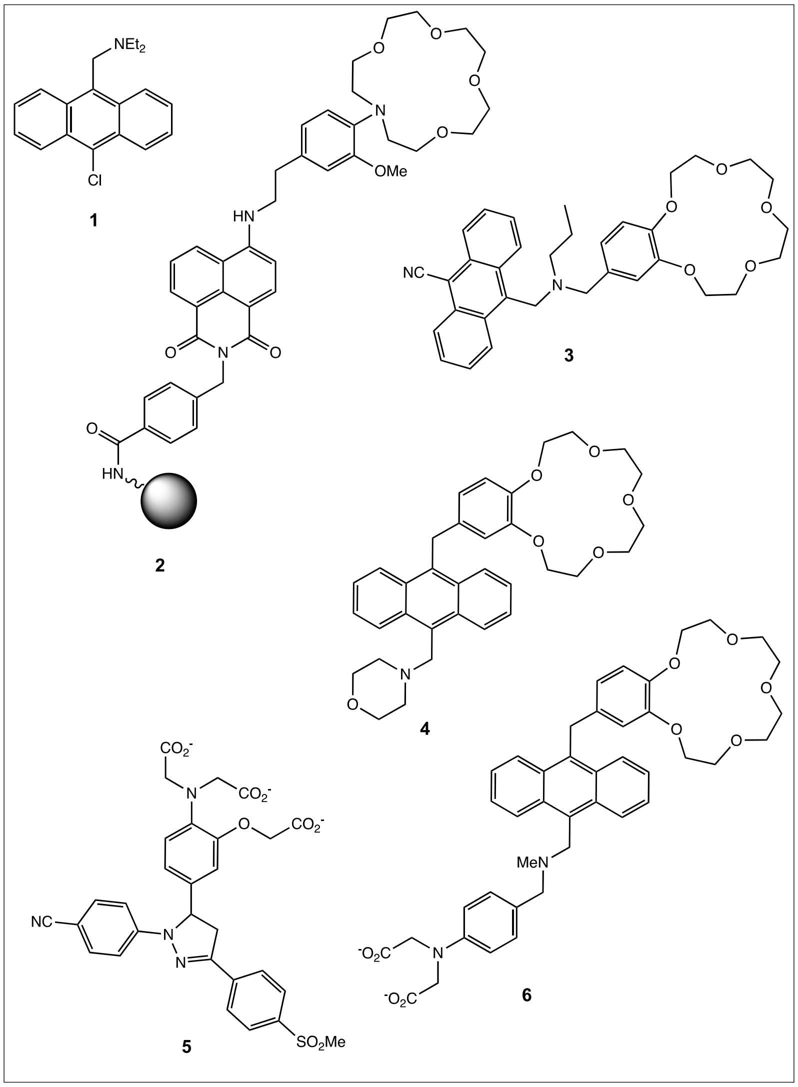


**Figure 2C:** Approximate world maps of further sources of fluorescent PET sensors and switches and cases which are understandable as such.

## Sensing for lifesaving

Molecular computing (Carter *et al*., 1988; Brown *et al*., 2002; de Silva *et al*., 2006; 2007; Magri *et al*., 2007; 2021; de Silva & Uchiyama, 2007; Balzani *et al*., 2008; Feringa & Browne, 2011; de Silva, 2011a; 2011b; 2013; Szacilowski, 2012; Katz, 2012a; 2012b; 2019; Daly *et al*., 2015b; Andréasson & Pischel, 2018; Erbas-Cakmak *et al*., 2018; Yao *et al*., 2020) at its simplest level concerns single input-single output devices. In Boolean language, this amounts to YES or NOT logic (Malvino & Brown, 1993; Gregg, 1998). The former has the output following the input whereas the latter has the output opposing the input instead. Compounds like **1** satisfy YES logic because 'high' levels of $H^+$ cause 'high' levels of fluorescence intensity. Thus, YES logic gates serve as sensors. We were challenged by the giant multinational Roche to develop a similar compound for tracking $Na^+$ in whole blood (He *et al*., 2003; Tusa & He, 2005). An important practical obstacle was removed by passing the blood through a micron filter so that the serum could be interrogated with a blue light-emitting diode. Polymer-bound compound **2** satisfied the challenge since its aminonaphthalimide fluorophore (Qian *et al*., 1989; Alexiou *et al*., 1990; de Silva *et al*., 1995; Zheng *et al*., 2012) absorbed blue light effectively and emitted green-yellow light in the presence of 'high' $Na^+$. Its N-aryl-azacrown ether receptor captured $Na^+$ while rejecting $H^+$ at neutral pH. Importantly, this receptor also carried a OMe sidechain which improved the size-match with $Na^+$ while rejecting the larger cation, $K^+$, at its usual concentration in blood (Schultz *et al*., 1985). Also, the binding constant for $Na^+$ in water (ca. 10 $M^{-1}$) for this receptor is ideal for sensing $Na^+$ concentrations around the normal value in blood (0.1 M). The OPTI blood electrolyte analyzer, built around fluorescent PET sensors like **2**, has been deployed around the world in hospitals, ambulances, general practice surgeries, as well as veterinary situations, for over 20 years now (*www.optimedical.com*; *www.idexx.com*). A particular instance of lifesaving is where ambulance crews can inform the hospital of a patient's blood $Na^+$ level so that a blood bag can be suitably prepared in order to avoid salt shock after transfusion.

Simpler fluorescent YES logic gates based on PET, like **1**, also serve to monitor the after-effects of radiotherapy (Paglin *et al*., 2001) and to track acidic lysosome compartments inside living cells (*www.thermofisher.com*). The results of such experiments with fluorescence microscopes also feed back into healthcare applications of the near future.



## From one input to two

One of the strengths of modular systems is the ease with which extra modules can be added (Bissell *et al*., 1992b; de Silva *et al*., 2008). For instance, a 'fluorophore-spacer$_1$-receptor$_1$-spacer$_2$-receptor$_2$' system carrying orthogonal receptors could enable a PET process to be launched from either receptor to quench emission from the fluorophore. Then, both receptors need to be occupied by their respective target species before PET processes are fully disabled. Fluorescence switching 'on' becomes possible only at that stage. According to Boolean ideas, this would be AND logic behaviour, since output becomes 'high' only when both inputs are separately 'high' (Gregg, 1998; de Silva, 2013). Compound **3** extends the structure of YES logic gate **1** with an extra methylene spacer and a benzocrown ether. The latter is reminiscent of compound **2**, so that the fusion of two YES gates driven by $H^+$ and $Na^+$ respectively produces a $H^+$,$Na^+$-driven AND gate (de Silva *et al*., 1993). A 'receptor$_1$-spacer$_1$-fluorophore-spacer$_2$-receptor$_2$' system is another permutation of these modules where the distances involved in the PET processes are minimized (de Silva *et al*., 1997). With these faster PET rates, the ratios of fluorescence intensity output between the 'on' and 'off' states become larger. This makes for more distinct AND gate performance in compound **4**.

AND is only one of 16 logic types which deal with two inputs and one output (Gregg, 1998; de Silva, 2013). For instance, OR logic produces a 'high' output signal whether one or other input is 'high'. A molecular illustration of this is presented in 'fluorophore-spacer-receptor' system **5**, where the amino acid receptor binds $Ca^{2+}$ strongly or $Mg^{2+}$ moderately to suppress PET and switch 'on' fluorescence in either case if sufficiently high concentrations of either cation are applied. Examples of each of the 16 types are now available from various laboratories to demonstrate how all possible combinations of two species of 'high' or 'low' concentrations can be sensed (de Silva, 2013; Yao *et al*., 2020).

## From two inputs to three…

Continuing the modular theme (Bissell *et al*., 1992b; de Silva *et al*., 2008), the system 'fluorophore-spacer$_1$-receptor$_1$-spacer$_2$-receptor$_2$' can be extended to a 'receptor$_3$-spacer$_3$-fluorophore-spacer$_1$-receptor$_1$-spacer$_2$-receptor$_2$' version while ensuring orthogonality among the three receptors. As before, these modules can be chosen so that a PET process originates from each receptor to quench emission from the fluorophore. Then, all three receptors need to be blocked by their respective target species before PET processes cease and intense fluorescence emerges. This is three-input AND logic action (Gregg, 1998; de Silva, 2013). Although this extension might seem trivial in a mathematical sense at first sight, it is worth remembering that a change from two to three is not at all trivial in several other contexts. Even in decimal mathematics, a two-number password can be guessed in a maximum of 100 attempts whereas a three-number password would require a much larger number of tries (1000). In the natural sciences, a change from two dimensions to three gives the occupant freedom to fly and jump instead of crawling or walking along a surface. In medicine, detecting the presence of three chemical targets simultaneously instead of two can sharpen the detection of a disease, e.g. cholesterol, low density lipoprotein and C-reactive protein indicate heart problems.

Compound **6** is a forerunner of 'lab-on-a-molecule' systems (Magri *et al*., 2006) where simultaneously 'high' levels of $Na^+$, $H^+$ and $Zn^{2+}$ are signalled by a switching 'on' of fluorescence. 'High' levels are defined as being significantly larger than the reciprocal of the corresponding binding constant of the input ion with **6**. Orthogonality among the benzo-15-crown-5, aliphatic amine and N-aryl amino acid receptors are enhanced by limiting the pH range to around neutrality. As suitably selective receptors continue to be discovered, they can be co-opted into these 'lab-on-a-molecule' systems to deliver a single 'yes' or 'no' answer for diagnosis of certain illnesses. The alternative of performing three separate tests and then considering the three results would take longer besides requiring an intervention by a professional. 'Lab-on-a-molecule' systems (Magri *et al*., 2006; 2014; Chen *et al*., 2015; Scerri *et al*., 2019) should be suitable for rapid diagnosis of disease, especially in a post-pandemic world where the public remembers overstretched health systems only too well.

## Putting memory into molecular logic-based computation

Everyday computers have stored programs or applications which perform a specific set of functions, such as those needed to compose a document, to produce a spreadsheet or to order a meal from a restaurant. A memory is an essential requirement in such situations. On the other hand, many information-processing tasks, such as those discussed in previous sections, require no memory. Computer scientists and electronic engineers distinguish between combinational and sequential logic (Malvino & Brown, 1993). The former has no memory whereas the latter does. Importantly, memories can be built from the same gates which are employed in combinational logic operations, if feedback loops are provided. For instance, the RS flip-flop is a common memory unit which is constructed from two NOR gates which are cross-wired for feedback purposes (Figure 3) (Malvino & Brown, 1993). A given output state, which is set-up by a specific input signal, can be maintained until such time that it is deliberately switched over to the other state by provision of another specific input signal.

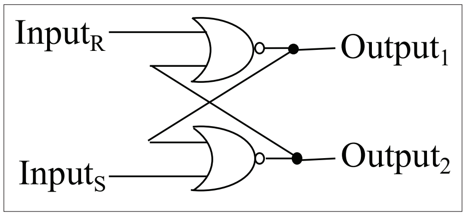
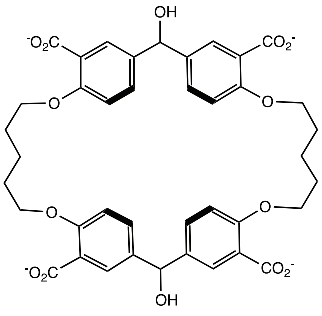


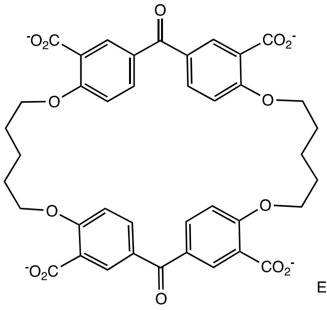
**Figure 3:** Physical electronic representation of the common memory unit, the RS flip–flop. The system is set by making Input$_S$ 'high' and Input$_R$ 'low', Output$_1$ becomes 'high' and Output$_2$ becomes 'low'. This output situation is maintained until the system is reset by making Input$_S$ 'low' and Input$_R$ 'high'. Then Output$_1$ becomes 'low' and Output$_2$ becomes 'high'. This output situation is maintained until the system is set again.

In the molecular sphere, such memories are available in the form of photochromic compounds (Irie, 2000). These can be set in a coloured state by uv irradiation, and returned to the colourless state by visible irradiation (Pischel & Andréasson, 2010). We chose a different route to molecular memories by using an alcohol state which is set by reduction, and returned to a ketone state by oxidation (Daly *et al*., 2019). By outfitting this system with a macrocycle, it was possible to arrange a large cavity in the alcohol state (**7**) whereas the cavity was constricted in the ketone state (**8**) by exploiting the pi-delocalization capability which is only present in the ketone. So we have the ability to capture a guest (**9**) in the alcohol state **7** and to release the guest from the ketone state **8**. Molecular-scale delivery can thus be accommodated in logic designs.

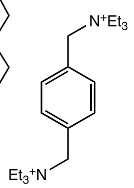
Additional logic functions can be integrated with the RS flip-flop because the guest occupancy within host **7** results in the loss of its fluorescence ability. This is due to PET occurring from the electron-rich phenylene walls of host **7** to the electron-poor aromatic unit within guest **9**. From a general viewpoint, here we have a fluorophore within the receptor which interacts with the bound guest in a pseudo-intramolecular fashion. An everyday analogy would be a taxi which indicates occupancy with a light signal on its roof.



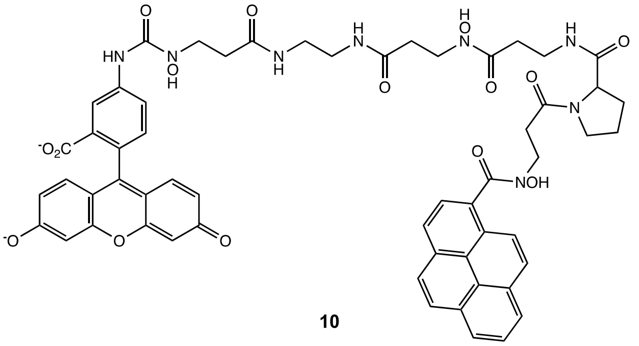
**7**



**8**



**9**

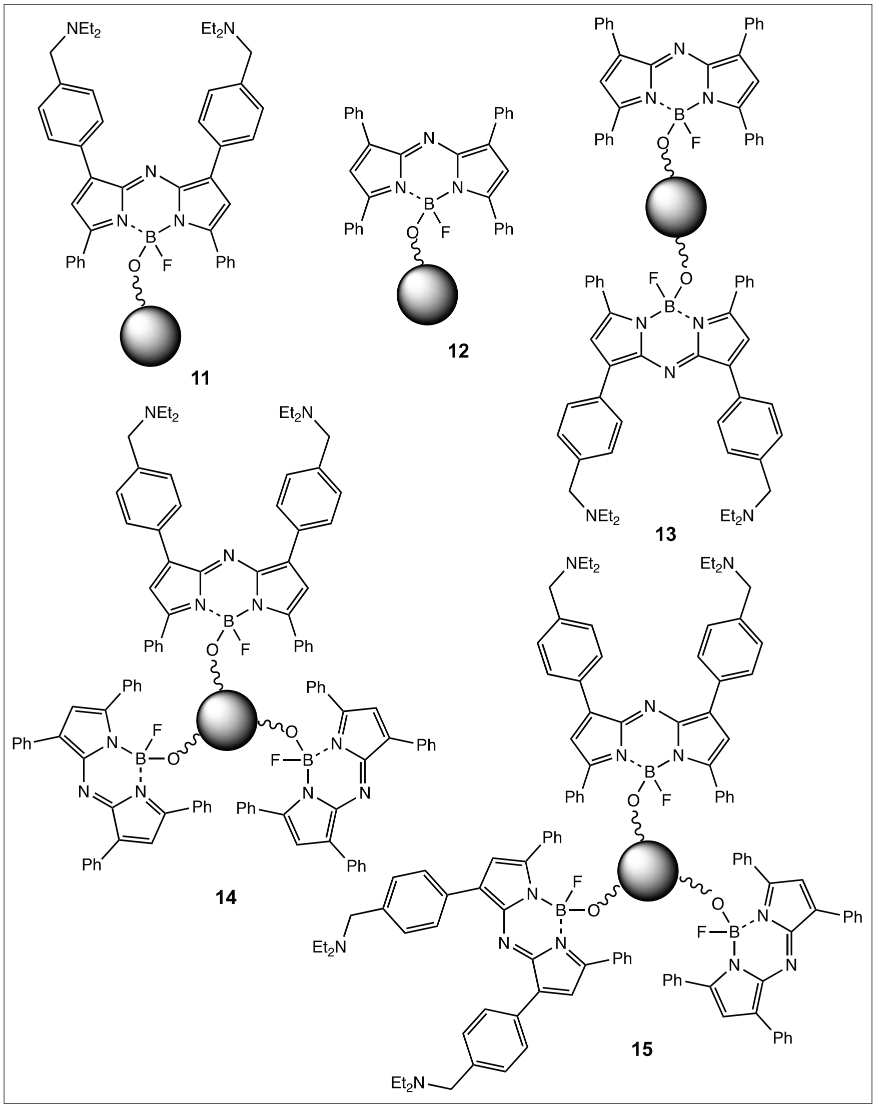


**10**

An important avenue of modern research in molecular logic - security (Andréasson & Pischel, 2018) was energized with compound **10** (Margulies *et al*., 2007). Generally, memory is essential for security applications since it needs to be remembered against whom the security is required and under what circumstances. A molecular keypad lock is a device where inputs need to be applied in the correct temporal sequence before a 'high' output signal is produced which can actuate a lock-opening. From an electronics viewpoint, such devices are essentially AND gates where one input is prioritized for being applied earlier than another. When complexed with $Fe^{3+}$, **10** is non-fluorescent owing to the open-shell nature of the metal ion creating PET and electronic energy transfer pathways for de-excitation. A 'high' green fluorescence signal emerges only if an acidic EDTA (ethylenediaminetetraacetic acid) $input_1$ is added first to extract the $Fe^{3+}$ away from **10**, followed by the supply of an acetate $input_2$ to create the well-delocalized fluorescein fluorophore under the basic conditions and concluded by provision of near-ultraviolet light (which is counted as input$_3$) to excite this fluorophore. Other permutations of the input string fail to produce the 'high' fluorescence output under the strictly defined conditions. **10**, or versions thereof, has been exploited previously to build combinational logic systems (Margulies *et al*., 2004) and subsequently to develop hack-proof communication protocols (Sarkar *et al*., 2016; Lustgarten *et al*., 2019) as well as combinatorial sensors (Rout *et al*., 2014).

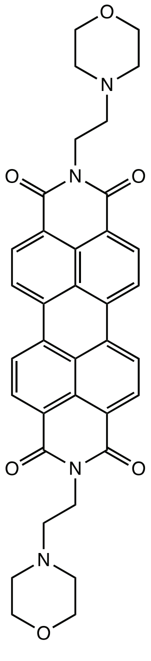
## Useful molecular logic-based computations

An early challenge to the field of molecular logic-based computation was to provide possible solutions to currently unsolved problems. The fact that molecules are small and biocompatible cannot be matched by semiconductor devices, even though current transistor sizes are well in the molecular size range. This is because operational transistors always require wires or antennas to interface with the human world, besides semiconductors being different in nature to living systems. Such peripherals always add to the size of the working device system, as in radiofrequency identification for instance (Shepard, 2005). As pointed out above on several occasions, molecules can interface with the outside world by using light. The recent growth in intracellular computation by designed molecules (Bronson *et al*., 2008; Win & Smolke, 2008; Murale *et al*., 2013; Finkler *et al*., 2016; Grimm *et al*., 2016; Green *et al*., 2017; Matsuura *et al*., 2018; Eordogh *et al*., 2020; Zhang *et al*., 2021) has provided a powerful response that is bound to grow into the future. However, the first useful computation was demonstrated with inanimate objects.

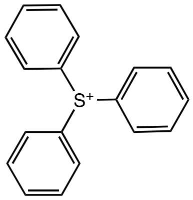


**11** **12** **13** **14** **15**

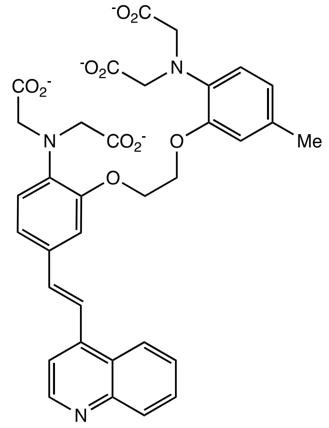
Polymer beads of micrometric size are employed in so many applications that they are even considered a pollution hazard nowadays (Chen, 2020). One of these applications concerns their use as vehicles for compound libraries built-up by combinatorial chemistry (Wilson & Czarnik, 1997). Each bead requires a tag for its identification during tests for the efficacy of its compound in drug discovery for example. Fluorescent dyes can serve in this capacity but the broadness of molecular excitation/emission bands and the limited bandwidth in the visible spectrum combine to constrain the number of distinguishable tags to around a hundred (Smith Kline Beecham Corporation, 2001). Enhancing fluorescent dyes with logic capabilities significantly increases the number of distinct tags since various input species can be employed to trigger the fluorescence signal in various patterns satisfying different logic functions of bead-bound cases like YES (**11**) and PASS 1 (**12**) (de Silva *et al*., 2006; Brown *et al*., 2008; McKinney *et al*., 2017; Refalo *et al*., 2018; 2019; Yao *et al*., 2019). Attaching two logic tags to a bead multiplies the logic diversity even further. For instance, a YES gate and a PASS 1 gate can be attached to separate samples of beads in different ratios in order to produce distinguishable logic types, e.g. YES + PASS 1 (**13**), YES + 2PASS 1 (**14**), 2YES + PASS 1 (**15**), etc. Each of these can be identified within a population by fluorescence microscopy (Yao *et al*., 2019).



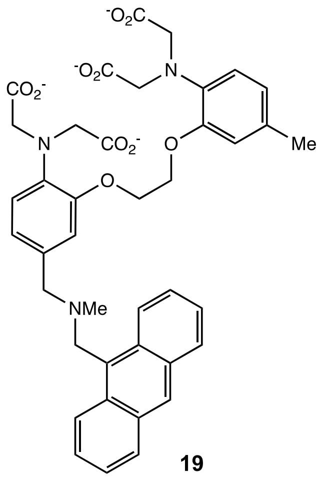
**16**



**17**



**18**



**19**

## Computations that we do unconsciously

Although we might like to believe that we are continuously applying high intelligence, everyday living requires many decisions to be taken in the background. For instance, our eyes help to evaluate the threat potential of approaching objects (Bruce *et al*., 2003; Lazareva *et al*., 2012; Hock & Nichols, 2013). Within milliseconds, an image of the object is recorded and the image is processed into a set of lines which correspond to the detected edges. A significant reduction of the dataset is achieved in this way, so that it can be easily sent for comparison with a series of edges stored in the brain under the class of dangerous objects. If a match is found, our legs are actuated to flee the scene. Such suitable evasive action can ensure survival. All these computations are carried out by molecule-based systems within ourselves, and have been emulated by information technologists in recent years (Shapiro & Stockman, 2001).

Remarkably, such security operations can be conducted by carefully chosen mixtures of molecules **16** and **17** (Ling *et al*., 2015a). Compound **16** is a 'fluorophore-spacer-receptor' system whose fluorescence output responds to $H^+$ in a YES logical manner (Daffy *et al*., 1998). Compound **17** supplies the required $H^+$ when it is photoexcited (Dektar & Hacker, 1990). This allows a fluorescence to be switched 'on' anywhere which is illuminated by 254 nm writing light. However, the situation alters as the writing times are extended, since an electron-rich photoproduct accumulates. This quenches the fluorescence via intermolecular PET between the photoproduct and the fluorophore within **16**. In other words, the fluorescence in the illuminated regions undergoes an 'off-on-off' process as a function of writing time. Our focus is on the edges between illuminated and dark regions because a bright fluorescent border becomes visible here alone. This occurs because $H^+$ diffuses from the illuminated areas into the unilluminated areas to switch 'on' the fluorescence of **16** which are localized here. Fluorescence is not quenched because the quenching photoproduct is too slow to diffuse across from the illuminated regions during the timescale of the experiment. The sharpness of the visualized edge depends on slowing the $H^+$ diffusion rate by controlled drying of the paper matrix. Overall, the paper serves as a graphic user interface where large numbers of molecules work together to solve the edge visualization problem.

In order to appreciate what the molecules have achieved in this instance, it is worth considering how semiconductor computers solve the same problem. The object is raster-scanned and sharp discontinuities of light intensity occur each time an edge between illuminated and unilluminated regions is crossed. Contiguous points of these discontinuities are joined together to build lines in the two-dimensional field. A degree of spatial smoothing is also applied. All these operations require a full computer or microprocessor running such an algorithm. This represents integration of logic gates in molecular systems (de Silva *et al*., 1999) at a medium-scale. Molecular biological systems are now regularly achieving this level of integration owing to their inputs and outputs being composed of DNA oligomers which are compatible with each other (Seelig *et al*., 2006). So we see that the inanimate molecular system of **16**, **17** and specified moisture on paper emulates a considerable amount of complex computation, just like living (Tabor *et al*., 2009) or life-like (Chirieleison *et al*., 2013) molecular systems have done.

### Computations that we do consciously

The double input-single output logic, XOR, is notable because it produces a 'high' output only if one or the other input is 'high'. This is particularly important to implement at the molecular-scale (Credi *et al*, 1997; de Silva & McClenaghan, 2002) because it allows an approach to arithmetic when run in parallel with the afore-mentioned AND logic (de Silva, 2013; Gregg, 1998; Malvino & Brown, 1993) with compatible inputs. $Ca^{2+}$ and $H^+$ serve in this capacity for compounds **18** (XOR) and **19** (AND). AND gate **19** follows in the tradition of **3**, by employing an amine receptor to capture $H^+$ but with an amino acid receptor to capture $Ca^{2+}$ instead of the benzocrown ether. XOR gate **18** is based on a different design where $H^+$ binding to the pyridine receptor causes a red-shift in the absorption spectrum whereas $Ca^{2+}$ binding to the amino acid receptor causes a blue shift. Fortunately, the correct occupation of both receptors results in cancellation of the two shifts. The transmittance output pattern fits XOR logic. Then, the fluorescence output of the AND gate produces the 'carry' digit, while the transmittance output from the XOR gate gives the 'sum' digit (de Silva & McClenaghan, 2000). We are all introduced to 'sum' and 'carry' digits as children. Calculators and computers achieve manipulations of decimal numbers via the corresponding binary operations inside their semiconductor processors. The basic processor is the half-adder. So, it is important to show that molecules could do the same, at least at the proof-of-principle level. Progress is being made along this line in many laboratories (Margulies *et al*., 2005).

Another example is related to the edge detection described above. Many children perform line drawing and this activity is developed in adulthood by visual artists. Molecules can be persuaded to do the same by exploiting edge detection. Even artists start with edge detection in their eyes before representing the object as an image on their canvas. So we employed objects of arbitrarily complex shapes to produce line images of good fidelity (Ling *et al*., 2015b). The chemical basis was exactly the same as in edge detection, although more attention needs to be paid to avoid interference of diffusion fronts when different edges approach each other in space.

## CONCLUSION

Molecules have carried out computations necessary for living ever since life existed. However, these molecules need to be organized and packaged into organelles, cells, tissues and higher-level assemblies. The past three decades have yielded results which show that no particular organization is necessary for synthetic molecules to accomplish basic logic-based computations on their own. Even some human-level computations can be conducted, albeit at low efficiencies. Lessons learned in computer science and engineering have been applied to molecules to show that semiconductors are not essential to accomplish basic logic-based computations. The chemical behaviour of molecules is the bridge between modern semiconductor-based information technology and the ancient information technology called life.

Many hundreds of laboratories spread across several disciplines including chemistry, molecular biology, molecular physics, molecular materials science, physiology and genetics have published on various aspects of logic-based computation. This trend seems set to continue. In particular, intracellular applications are likely to yield answers to many interesting questions about biological complexity.

Fluorescent sensors led the way to molecular logic-based computation and still occupies a prominent place in the field. The unique ability of fluorescence to visualize processes in small spaces (Hell, 2015) will enable the intracellular applications noted above. Following the lead of cases like **2**, fluorescent sensors will probably play a bigger role in serving the analysis needs of medical and environmental science as the years go by.

### Conflict of interest

We declare there are no conflicts of interest.

### Acknowledgements

Our grateful thanks go to the University of Colombo, Queen's University Belfast, Department of Employment and Learning of Northern Ireland, Engineering and Physical Sciences Research Council UK, European Commission, InvestNI, McClay Trust, China Scholarship Council, Procter and Gamble, Japan Society for the Promotion of Science, Roche-AVL and the Leverhulme Trust (RPG-2019-314), Dayasiri Rupasinghe, Shantha Samarasinghe, Amila Norbert, Annesley Peiris, Dayal de Costa, Nalin Goonesekera, Saliya de Silva, Thilak Fernando, Lalith Silva, Sisira de Silva, V. Edwin, Sydney Ramyalal, Ranjith Jayasekera, Aruna Dissanayake, Suram Patuwathavithana, Saman Sandanayake, Richard Bissell, Nimal Gunaratne, Aiden Bryan, Mark Lynch, Alan Patty, Graham Spence, Kemuel Nesbitt, Linda Daffy, Sean O'Callaghan, Glenn Maguire, Aine Kane, Colin McCoy, Thorri Gunnlaugsson, Terry Rice, Anne Goligher, Catherine McVeigh, Emma O'Hanlon, Pamela Maxwell, Isabelle Dixon, Jude Rademacher, Juliette Roiron, Nathan McClenaghan, Allen Huxley, Joanne Ferguson, Aoife O'Brien, Marc Schroeder, David Fox, Tom Moody, Gareth McClean, Sheenagh Weir, Gareth Brown, Sara Pagliari, Manel Querol, Bernadine McKinney, Bridgeen McCaughan, Seiichi Uchiyama, David Farrell, John Callan, Gregory Coen, Robert Boyd, David Magri, Boontana Wannalerse, Catherine Dobbin, Vinny Vance, Matthew West, Gavin Melaugh, Glenn Wright, Bernard McLaughlin, Brian Daly, Esther Surender, Ben Schazmann, Jialong Liu, Shuai Zheng, Jue Ling, Gaowa Naren, Jessica Kelly, Victoria Silverson, Adam Quereshi, Zeqing Chen, Linyihong Chen, Hongyu Lin, Jialu Li and Hannah Crory. Their support allowed us to translate ideas into some degree of reality.

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