

Introduction:

Soft Interfacial Materials: From Fundamentals to Formulation

The science of soft interfaces (lipid membranes, emulsions, particle-stabilised droplets etc.) is rapidly moving into an era of predictive capability that allows the design and development of advanced materials to be based on secure scientific knowledge. This Theme Issue reports papers presented at a Discussion Meeting intended not only to address the fundamental science, focussing on generic design principles for self-organisation and interfacial structure, but also to explore the resulting prospects for “informed formulation” of new and improved industrial products.

At the end of this introductory essay we briefly summarize some of the scientific progress reported in the individual research and review papers included in this volume. Before doing so, we take the opportunity to describe some of the background thinking that shaped the content and aims of the Meeting as conceived by the organizers.

This essay is intended to be thought provoking, not definitive; much of it is based on a wrap-up discussion that two of us (Alex Lips and Wilson Poon) contributed at the end of the Meeting itself. In it, we focus on the relationship between science (“fundamentals”) and technology (“formulation”). At least in the soft materials area, this represents a subtler and more interesting form of symbiosis than is often assumed.

From fundamentals to formulation?

‘Soft interfacial materials’ are ubiquitously encountered across a wide range of chemical, fast consumer goods, pharmaceutical, agri-business and petroleum technologies. Not surprisingly these, and other, industries are crucially dependent on ‘formulation’ expertise. While scientific understanding has advanced impressively in recent years, formidable challenges remain for understanding and controlling structure, dynamics and functional performance in generally complex ‘formulated’ products. Moreover, escalating competitive and environmental pressures set a rich agenda of change for industrial R&D and for academia. Demand by industry for ‘high tech’ formulation solutions has intensified: the goal is not only to realise transformative product opportunities, but also to sustain and enhance the competitive position of companies in established product technology areas.

The UK Government, like many others, is well aware of these needs and pressures, and it has implemented a number of initiatives to raise the profile

of formulation science and its connections with industrial R&D. First, the organisers of this Discussion Meeting belong to a scientific community funded by two multi-million-pound Programme Grants awarded by the UK's Engineering and Physical Sciences Research Council (EPSRC) for 'Design Principles for New Soft Materials' (centred on Edinburgh) and 'Sculpting Dynamic Amphiphilic Structures' (centred on Imperial College). More recently, after prolonged lobbying by industry, 'formulation' achieved prominent status in the UK's science agenda with Government announcing funding for a £28M National Formulation Centre in late 2014, and with the EPSRC soon afterwards investing some £40M in a 'Future Formulations' call. Of course, formulation science has always been used and practised across numerous industrial sectors. Communities such as the Formulation Group of the Royal Society of Chemistry have been in existence for some time and have greatly contributed to the sharing of knowledge and expertise.

We may ask what lies within the scope of the word 'formulation'. Industry may refer to R&D staff as 'formulation chemists' or 'formulation engineers' but neither label does justice to the hugely multi-disciplinary mind-set and endeavour demanded of technologists under the 'formulation' umbrella. Soft matter science, and especially its sub-discipline of interfacial soft matter, provides an important link here from bioscience, physics and chemistry all the way to manufacturing. Not surprisingly, 'formulation' is increasingly used in UK academia as a catch-all term for conveying industrial impact in a general sense. Indeed, soft interfacial materials are ubiquitous not only as industrial products (household and personal care, agrochemicals, paint, drilling mud, foods, drug delivery, etc.), but also as process intermediates such as ceramic 'green bodies', which are pastes injected into moulds and then sintered to form a hard ceramic material. Of course, industrial formulation issues are not confined to soft matter: the design and processes associated with low consistency fluids such as beverages, can be highly, if differently, challenging. We should also bear in mind that many industrial soft formulations are designed not only for stability as products, but for controlled failure in use, e.g. on shear or dilution, to create or potentiate end use functionalities. In product design, it is therefore often at least as important to understand and control the processes of use, as it is the processes of manufacture.

Against that background, this Discussion Meeting had a number of aims.

First was the distinctive focus on "Soft Interfacial Materials". This delineates a sub-field of soft matter cutting across the usual classifications based on the types of material (polymers, colloids, lipids, proteins) and usefully instead focussing on structural similarities between different material types. These structures have strong applications potential, which will only increase

further with the advent of personalised medicine and the continuing search for new energy capture and storage materials. Here the required pace of technological change demands radically new approaches to materials design, with science-based rather than empirical control of micro- and nano-structure, and also of temporal behaviour, on widely separated scales.

A second goal was to attract international leaders of academic research, alongside substantial participation by industrially affiliated scientists from around the globe. In particular, the presentations combined leading-edge science with some of the highly imaginative, but more applied, research currently ongoing in an industry context. This was aimed to help academics better understand how industry internalises new science, and allow both parties to explore new opportunities and priorities.

Thirdly, by focussing on the cross-cutting “interfacial” theme we hoped to reconnect areas that have become rather fragmented during a period of rapid growth in the soft matter field generally. Because of this growth, academic research on lipids and model membranes is increasingly carried out within Biophysics / Biochemistry Departments; that on surfactants and emulsions within Chemistry or Chemical Engineering Departments; and work on complex fluids and colloids within Physics Departments. Of course it has never been forgotten that these areas share many common features, but now each is moving forward at such a speed that it is very easy for workers in one of these areas to lose touch with the others. The Discussion Meeting was intended to provide a structured opportunity to “compare notes” among those now addressing similar scientific questions on different classes of material.

Finally, the organizers wanted to raise awareness of two EPSRC Programme Grants that we hold. Of the two grants, one (EP/J007414, Design Principles for New Soft Materials) targets novel energy materials, biomaterials, and food colloids, while the other (EP/J017566, Sculpting Dynamic Amphiphilic Structures) targets new delivery structures and fundamental understanding of membranes. The meeting also allowed the postdoctoral staff and students on these grants to showcase their results through posters and to learn about ground-breaking work in related areas.

Against these four goals, the organisers can claim a rather successful meeting. There was strong attendance and a rich level of discussion. The combination of high calibre deep science talks from academics with industry-facing presentations from industrial researchers worked well, as did the poster sessions. Academics from all specializations enjoyed the meeting. The only real concern was that the overall attendance of industrially affiliated scientists remained below target despite our best efforts, and despite the obvious excellence of the industrial speakers, who amply demonstrated the

value of fundamental science to technology and how industry is alert to new opportunities.

The declining attendance by industrial researchers at open scientific meetings has become a familiar phenomenon in recent years; perhaps industry prefers to engage in managed relationships with specific partners rather than engage with an open community of academics. Whatever its cause, we believe this to be to the detriment of both the industrial and academic research communities.

Raising this point at the meeting itself led to a discussion of the relationship between industry and academic science in general, and in the domain of ‘formulation’ in particular. The subtitle of the Meeting, ‘From Fundamentals to Formulation’ itself invites us to reflect on how science in this area informs technology. While as organisers we did not intend this subtitle to be rigid, it subtly encodes a presumption of one-way movement: *from* fundamentals *to* formulation. This unidirectional narrative, that fundamental science (here, the science of soft interfacial materials) is the fount of technology (here, the technology of formulation), is commonplace. Researchers rely on it to justify their grant proposals; Funding Agencies rely on it to justify their budgets to Governments; and Governments rely on it to justify science spending to tax payers. But familiarity by repetition does not make a truth – that much is enshrined in the motto of the Royal Society itself (*Nullius in verba* – “on nobody’s word”).

History may lend a helping hand. The goal of technology (from the Greek *technē*, art in the sense of ‘the art of (say) metal working’) is to get something done, *irrespective of whether we understand why it works*. The goal of science is to understand. The ‘Eureka!’ moment for a technologist is ‘It works!’, the ‘Eureka!’ moment for a scientist is ‘I see!’. The two, of course, can feed off each other. But this virtuous circle was not discovered until well after the rise of modern science. One of the key characteristics that makes modern science ‘modern’ was memorably summarised by Richard Feynman when he said, ‘what I cannot create, I do not understand.’ In a less memorable but nonetheless erudite analysis, the historian and philosopher Amos Funkenstein argued that the transition from a ‘contemplative’ to an ‘ergetic’ (from the Greek *ergein*, to do) mode of knowledge lies at the heart of the transition from medieval to modern science.¹ The feedback loop made possible by the marriage of ‘knowing’ with ‘doing’ is what gives us today’s *high* technology, with its breath-taking speed of change. But all this does not alter the fact that technology is, first and foremost, about getting things done without having to first understand everything.

¹ A. Funkenstein, *Theology and the Scientific Imagination from the Middle Ages to the Seventeenth Century*, Princeton University Press (New Jersey:1986), Chapter V *passim*.

Thus, for example, the appearance of Dolly the sheep in 1996 was generally hailed as a ‘scientific’ breakthrough, but strictly speaking it wasn’t one. Few, if any, of the hundred or so steps involved in bringing Dolly to birth were understood at the time; many are still not understood today. So Dolly was primarily a breakthrough in doing, not in understanding. Crucially, like numerous other such breakthroughs in history, it left a trail of scientific opportunities in its wake. The know-how (i.e., doing, or technology) involved in making Dolly the sheep enabled a string of advances in understanding (that is, science). In today’s world of *high* technology, the mechanisms are in place to feed such understanding back into technology almost ‘in real time’; so the virtuous circle is set, and the thing snowballs. Nevertheless, the first breakthrough in Dolly’s case was a *technological* one.

A more historical example, but intellectually closer to home, comes from Irving Langmuir when, three years after his German Ph.D. with Nernst, he started working for General Electric in their (and the world’s first) corporate research laboratory in Schenectady, New York. Seemingly, Langmuir’s first job was to work on light bulbs. The wisdom of the time was that sucking out more gas was the way to make incandescent bulbs last longer. Langmuir realised that to go that way would involve him, a physical chemist by training, in becoming a vacuum engineer – pumps had reached the then current limit. Instead, he introduced various gases back into bulbs to see what would happen. When he got to argon, he (and General Electric) hit the proverbial jackpot – introducing the right amount of this gas made the bulbs last longer! The rest is history – this *technological* breakthrough initiated the whole field of surface *science*.² The ethos at General Electric was such that the virtuous circle of Langmuir’s nascent surface science rapidly fed back into corporate technology. Indeed GE, where Langmuir remained for the rest of his career, was one of the first *high tech* companies.

We now return to the area of the Discussion Meeting itself: soft interfacial materials. Here, as often as not, basic scientific progress has been stimulated by the discovery that some empirical technological know-how *works* for the formulator: a case of ‘from formulation to fundamentals’ and not vice versa. For now, at least, a ‘green fingered approach’ to formulation can still compete favourably with machine based (high throughput) and with rational design approaches based on fundamental science. Perhaps the most interesting question is whether the time is at last right for soft-matter formulation to enter the era of *high* technology, so that the loop can close on a regular basis: ‘from formulation to fundamentals ... and back’. If this is true, and we hope it is, the recent burst of enthusiasm for formulation-related basic science is fully justified.

² A. Rosenfeld, *Irving Langmuir*, Pergamon Press, Oxford (1966)

Of course, any 'black and white' distinction between science and technology is overdone. These represent two ends of a continuous spectrum in which most graduate and doctoral scientists find careers as technologists. Moreover, the most prestigious and important 'science' in the public's mind, medicine, remains largely a technology: fortunately, our doctors can often cure ailments without fully understanding their causes. Finally, good scientists have often shown a determined 'technological bent' in persuading recalcitrant experiments (or code, or even calculations) to deliver scientific understanding. But the existence of a continuous science-technology spectrum does not obviate the distinction between its two ends; nor does this tell us the direction of information flow along it.

We are not aware of a published scholarly enquiry into the evolution of current political narratives on the relation between science and technology. Nonetheless it seems clear that the 21st century rhetoric, whether it be from scientists, technologists, civil servants, or politicians, is overwhelmingly couched in the terms implicit in this Meeting's subtitle: knowledge flows *from* science *to* technology. This rhetoric could be potentially harmful if it means that an equally powerful traffic in the opposite direction gets ignored.

One of us has explored elsewhere why this asymmetric rhetoric can promote risk-aversion among the public.³ Scientists themselves are increasingly good at quantifying and handling ignorance (including that generated by technology), but the increasing power of science, coupled with a one-sided rhetoric of '*from* science *to* technology', creates a false idea that technology should not really begin until the underlying science is perfected. Yet, from the earliest times of human history, technologists have always innovated in the face of ignorance, with the risk not only of failure but also of damage. A misunderstanding of this may mean that not enough socio-political effort is devoted to discussing and managing technological risks as a community.

The UK was for decades a self-confessed underperformer in turning science into technological innovation. This has driven a dominant 'impact agenda' in academia; only time will tell how well this improves matters. Nonetheless, if the new generation of budding scientists and engineers only hear a one-sided narrative (*from* science *to* technology), there will inevitably be a presumption of prestige in favour of science. This adds to the acknowledged prestige deficit for technological education in Britain as compared, e.g., to Germany.

Imagine instead a scenario in which the dominant narrative was replaced with the following one. Science is about systematically dealing with ignorance;

³ W. C. K. Poon, Growing Scientific Citizens in a High-Tech World, in 'Growing Citizens', ed. Alison Elliot and Heidi Poon, St. Andrew Press (Edinburgh, 2009), pp. 99-112.

technology is a vast and dependable source of interesting ignorance. Thus technology is the main fountain of science rather than vice versa. (It often exposes problems that do not have to be solved for the technology itself to move forward, so this is somewhat different from the oft-made distinction between technology ‘pull’ and science ‘push’.) Perhaps some of the perceived bottlenecks of the ‘science to innovation’ pathway would find it harder to establish themselves in a culture informed by this alternative worldview.

Within the soft matter domain, our own experience is that some of our best science has arisen by first looking at technological know-how, and wanting to puzzle out why things are done as they are (which also means finding out why they are *not* done in other plausible-looking ways). To sustain the traffic of knowledge from fundamentals to formulation, we also need to promote the corresponding flow from formulation to fundamentals. With more attention paid to the latter, the former might increasingly take care of itself; and co-creation of new technology between entrepreneurs and academic scientists might become more seamless.

As stated previously, the opinions expressed above are intended to invite reflection and scrutiny, rather than offering a definitive view or way forward. Meanwhile we can be certain of three things: that soft interfacial matter is increasingly yielding to ‘informed’ design; that this needs to happen at an ever faster pace to address the challenges ahead; and that genuinely two-way knowledge transfer between industrial research and academia is crucial to making this happen. These thoughts inspired the planning of the Discussion Meeting; they permeated the event itself; and they are reinforced by the papers in this volume.

These were solicited, and presented at the meeting, under four themes: Functional amphiphiles and lipids; membranes and delivery; particles and proteins at interfaces; and uncoventional emulsions and multiphase gels. This running order is maintained in the current volume, exposing connectivities within these groupings. In what follows we briefly discuss the papers in a different sequence that emphasises instead some of the cross-grouping themes that emerged.

Particles at interfaces give an exquisite level of control of interfacial properties either by harnessing the direct interactions between the particles or by making use of effective interactions due to the host medium. For a system of particles confined to a fluid interface and interacting via soft electrostatic repulsions Kralchevsky et al. find that the surface pressure reflects the state of aggregation of the particles – with the degree of aggregation being self-limiting [Kralchevsky]. By contrast, Liu et al. envision a route to organizing particles at an interface via effective interactions

[Stebe]. They achieve control by combining the distortion of the interface induced by the particle with a curvature that is already imposed on the interface. They compare this situation with the case where a liquid crystalline director field takes the place of the curvature; again distortions that are intrinsic to the interface need to be combined with those imposed by the presence of the particle.

The elastic characteristics of the liquid crystalline solvent can be traced back to the underlying characteristics of the molecules. Relating the bulk characteristics to the molecular architecture in liquid crystalline media is an important challenge. Based on 10,000 observations covering different lengths of alkyl chain and different character polar regions, Bell has developed a model for selecting surfactants to yield a particular phase under the required conditions [Bell]. Interpolations are made to predict the behavior of the new molecule and / or to extend predictions to new conditions.

Frith presents his perspective on the elastic media which can be created via the hierarchical self-assembly of peptide fragments where there is a similar need for predictive power [Frith]. The molecular sub-units form fibrils through lateral association. The fibrils then combine, under appropriate solvent conditions, to form a hydrogel that can potentially be exploited. As the number of peptide subunits in the chosen fragment grows then computational insight is essential to handle the vast array of possibilities.

For some novel emulsion systems, bulk elastic effects are in competition with the interfacial energy cost. This competition can be harnessed as a route towards designing non-spherical droplet shapes as demonstrated by Dahiya et al [Spicer]. They extend a model of the partial coalescence of elastic droplets to include the effect of polydispersity of the droplets. Polydispersity of the pair should reduce the influence of the interface overall – and hence leads to arrest at lower strains. The disagreement between this conjecture and observations suggest directions for further exploration.

Saidane et al. demonstrate the control of droplet formation via control of the surface charge of cellulose nanocrystals which stabilize the interface [Capron]. Sufficiently hydrophobic particles can be used to stabilize water droplets in oil. Furthermore, combinations of particles with different charge states can be combined to create layer by layer Pickering droplets. A cross-flow membrane emulsifier with carefully controlled quantities of ingredients and flow conditions can be used to prepare relatively monodisperse emulsions, as demonstrated by Biggs et al [Biggs]. The finished objects can be droplets themselves or can be polymerized. The remaining challenge is to combine these large scale emulsification approaches with the complex interfaces and /

or complex internal rheology. To achieve this will require a high degree of control over every processing step.

A striking biological example of a soft interfacial material is the stratum corneum (SC), the outer layer of the epidermis of skin, in which a continuous lipid matrix provides the main barrier against water loss from the body. The paper by Olmsted *et al.* [Olmsted] describes atomistic molecular dynamics simulations of a lamellar phase of model SC lipids. The main lipids are a mixture of free fatty acids, cholesterol and various ceramides, forming phases with high melting points (~ 80 °C) and low hydration, giving a large barrier to water penetration: the permeability was found to be some 5 orders of magnitude lower than for bilayers of the phospholipid DPPC (dipalmitoyl phosphatidylcholine). The rate of cholesterol flip-flop was found to be surprisingly fast, of the order of a few microseconds. These studies yield useful insights into the effects of varying chainlength, chain asymmetry, and headgroup hydrogen-bonding capacity on the phase structure. From the second moment of the calculated lateral pressure profiles, the authors estimate that the Gaussian curvature modulus is large and positive (of the order of $75 - 90 k_B T$), which implies that the isolated lipid membranes would tend to adopt a saddle-curvature morphology, as found in bicontinuous cubic phases. Intriguingly, the authors cite experimental evidence for such bicontinuous morphologies in a cryo-electron microscopy study of skin.

The paper by Safinya and co-workers [Safinya] gives an important example of the interchange of knowledge between technology and basic science. They discuss how cationic lipid / nucleic acid mixtures self-assemble into liquid crystal phases, whose structure profoundly influences the ability of such lipoplexes to deliver the nucleic acid to the intracellular target. Nanoparticles of such complexes can be functionalised with targeting ligands and hydrolyzable groups to optimise uptake and endosomal escape. A complex of cationic lipid, monoolein and siRNA (small interfering RNA) forms a gyroid cubic phase (spacegroup Ia3d) which shows a high gene silencing efficiency. This appears to be related to the bicontinuous structure of the cubic phase, which induces pores in the endosomal membranes, allowing escape of the siRNA into the cytoplasm.

Lipid-bicontinuous cubic phases play a key role in understanding the structure of biological self-assembled systems, creating constructs that interact with biology and more widely in soft materials technology. One such application, *in-meso* crystallisation, has proved extremely valuable in the growth of membrane protein crystals for structural characterisation. Despite the enormous interest in this technique, there is little experimental evidence showing the structural changes in the lipid scaffold that accompany or facilitate the protein crystal growth. The paper by van't Hag *et al.*

[Drummond] presents microfocus small angle X-ray diffraction experiments which have allowed a bicontinuous cubic crystallisation matrix to be mapped in unprecedented structural detail. These experiments showing that the growth of protein crystals is often accompanied by a significant change in the structure of the lipid matrix, supporting previously proposed mechanisms for the process.

The biotechnical applications of lipid assemblies also include their use as structured drug carriers and controlled release agents; these offer the prospect of delivering high drug doses but minimising toxicity. The paper by D'Addio *et al.* [Prudhomme] describes an important new methodology for measuring the release kinetics from drug nanocarriers that addresses many of the limitations of traditional drug kinetic measurements when applied to these complex, structured formulations. In addition to drug containment and release, lipid assemblies have previously attracted significant attention as sustained release containers for nutrients; the work by Sagalowicz *et al.* [Sgalowicz] highlights exciting new applications of self-assembled lipid structures in food technology. Self assembled structures have been found to modulate chemical reactions that contribute to aroma, taste and colour of food. While lipids are the most commonly investigated surface active biomolecules, there are a wide range of proteins and peptides that are surface active and so can self-assemble at interfaces. An example includes BslA which can form highly elastic surface films. Morris *et al.* [MacPhee] have investigated the bulk and surface structures formed by BslA, and its ability to stabilise air bubbles with different morphologies. This work points towards important applications for this protein in stabilising novel multiphase materials.

Finally, the paper by Bassereau and co-workers [Bassereau] illustrates how concepts from soft matter physics are enormously useful in understanding the complex interplay between proteins and lipid membranes in controlling membrane morphology and remodelling. Such processes, involving membrane bending, scission (the opposite of membrane fusion), and fusion lie at the heart of trafficking and sorting of membrane lipids and proteins inside cells. As both scission and fusion involve topological changes in the membrane, the bilayer Gaussian curvature modulus will contribute to the change in elastic energy. The authors demonstrate, using BAR domain proteins as a model system, how such proteins affect the mechanical properties and the shape of membranes. Furthermore, some BAR domain proteins interact preferentially with membranes having positive curvature, whereas others bind to negatively curved membranes. The authors describe elegant experimental approaches, based upon membrane nanotubes pulled by a known applied force from lower curvature giant unilamellar vesicles, to quantify the mechanical effects of BAR domain proteins, and the degree of curvature-

induced sorting of the proteins, and to gain insight into the molecular mechanism of membrane scission.

N J. Brooks ¹, M. E. Cates ², P. S. Clegg ³, A. Lips ³, W. C. K. Poon ³, J. Seddon ¹.

1. Department of Chemistry, Imperial College of Science Technology and Medicine, London SW7 2AZ.

2. DAMTP, University of Cambridge, Wilberforce Road, Cambridge CB3 0WA.

3. School of Physics and Astronomy, University of Edinburgh, Peter Guthrie Tait Road, Edinburgh EH9 3FD.

Citations to papers in this volume (to be completed by Journal staff):

[Kralchevsky]

[Stebe]

[Bell]

[Frith]

[Spicer]

[Capron]

[Biggs]

[Olmsted]

[Safinya]

[Drummond]

[Prudhomme]

[Sagalowicz]

[MacPhee]

[Bassereau]

RUNNING ORDER TO BE USED IN VOLUME

Section 1: Functional Amphiphiles and Lipids

[Drummond]

[Bell]

[Olmsted]

[Sagalowicz]

Section 2: Membranes and Delivery

[Safinya]

[Bassereau]

[Prudhomme]

Section 3: Particles and Proteins at Interfaces

[Kralchevsky]

[Stebe]

[Spicer]

[MacPhee]

Section 4: Unconventional Emulsions and Multiphase Gels

[Frith]

[Capron]

[Biggs]