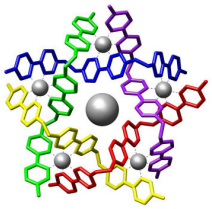

Beyond the Molecule

A Roadmap to Innovation

The EPSRC Directed Assembly Network

Initial Draft

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EPSRC

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Beyond the Molecule: A Roadmap to Innovation

Introduction: The Importance of Understanding Assembly Processes and the Role of the Directed Assembly Network

The importance of the chemical sciences in developing solutions to the world's grand challenges cannot be underestimated. From security in food production to personalised healthcare, from optimised manufacturing to clean energy sources, this vital field of knowledge underpins all the developments needed for a safe, sustainable future. We in the UK can rightly be proud that our leading academic research and industrial output makes such a significant contribution to the chemical sciences sector.

- In academic research, the UK's contribution to chemistry-related fields is ranked 4th in the world behind the USA, Japan and Germany and, in terms of citation impact, is second only to the USA. The Research Assessment Exercise of 2008 identified many areas where UK strength in this research space is world-class or world-leading, including materials chemistry, supramolecular chemistry, computational chemistry & modelling, and structural chemistry.

- In industrial production, the Chemical Industries Association[a] points out that chemical and pharmaceutical industries contribute £60 billion - around 3% - to the UK GDP and that 600,000 people are directly employed by or have jobs that depend on this sector. Historically, the chemicals sector has also shown better growth than traditional manufacturing.

Yet we cannot afford to be complacent; there is a shift of bulk chemicals manufacturing from the UK to overseas and we have recently seen major pharmaceutical companies reduce the size of or close down research establishments in the UK. In its analysis of academic strengths and weaknesses, RAE 2008 also noted there were poor links between the disciplines of chemistry and chemical engineering which needed to be corrected, a need for better connectivity with downstream businesses and insufficient public engagement. EPSRC's 2009 international review of UK chemistry[b] noted that transformative, multidisciplinary research needed to be better supported along with better provision for early-career researchers – the scientists and engineers who will be driving innovation for the future.

Thus, if we are to maintain the health of chemical sciences research and industrial activity in the UK we must then strengthen the research connections between chemistry and chemical engineering, as well as those fields where new advances are likely to occur – the interfaces with solid-state physics and biology in particular. To rebuild and retain our industrial strength we must not only enhance the efficiencies of existing industrial processes but drive the creation of transformative new industries by adopting breakthroughs in fundamental academic research, enabling the UK to compete globally on knowledge rather than bulk production. Recognising that it is people that transfer technology, we must build a better cultural understanding between academia and industry, guide the public to a greater appreciation of the field and speed the path to success for our best researchers.

This is why significant investment into fundamental research and training in the field of directed assembly is so important. Understanding and controlling molecular and supramolecular bonding will enable both new routes to synthesis of existing materials and the synthesis of entirely new materials with optimally-designed properties and function. Developing this understanding allows not just the creation of new materials but, by revolutionising production processes, can bring about the creation of whole new industries.

Sharing skills and knowledge between disciplines and institutions will help produce the UK's new leaders who can develop this manufacturing for the future.

These new and enhanced production routes will have immense impact in products and applications over the next 50 years – from sustainable manufacturing to personalised healthcare. Table 1 lists some of the products that can be envisaged as resulting from breakthroughs in this area.

Such important breakthroughs can only be achieved by building cross-disciplinary research communities, leveraging the strengths of our acknowledged world-class research areas to lift-up those subjects identified as needing development in the UK and combining knowledge across diverse fields. The research communities and their end-users must be given opportunities to come together to develop adventurous joint research programmes, encouraged to produce and share a grand vision of these new technologies and to strengthen the expertise of all participants, particularly those at an early stage of their careers. This is the role undertaken by the Directed Assembly Network.

Formation and Structure of the Directed Assembly Network

Recognising the importance of this research area, EPSRC provided funding for the Directed Assembly Grand Challenge Network in 2010 to bring together a new research community, to determine the current state of the field and draw up a roadmap to drive progress towards these goals.

The Network's Grand Challenge vision is:
To be able to predict and control the assembly of matter with sufficient certainty and precision to allow preparation of materials and molecular assemblies with far more sophisticated and tuneable properties and functions than are accessible in materials synthesised using current methods.

This vision requires a multidisciplinary approach involving not only chemists and chemical engineers, but also physicists, material scientists, biologists, mathematicians, and computer scientists and so incorporates all the engineering, physical and life sciences. Delivery of the Grand Challenge vision also depends critically on full and appropriate engagement with end-users, including industry, health professionals and others.

This is a 50 year goal as it requires fundamental science to be developed to allow controlled assembly of molecular building-blocks in ways that are not currently possible, and to be able to develop the properties of materials across length-scales from the molecular to the bulk. It must necessarily involve a multifaceted approach as there are many targets to be set and met and many challenges to be overcome on the way to the absolute goal of being able to prepare and fabricate any material with *predesigned properties*, whether they are physical, chemical or biological.

In consultation with the research community, the Network management team focussed its discussion and roadmapping activities into five theme areas:

1. Controlling the assembly of designed molecular frameworks and hybrid materials with targeted properties.
2. Controlling nucleation and crystallization processes.
3. Controlling molecular self-assembly in biological and biomimetic systems.
4. Controlling surface-based molecular self-assembly for applications in interface science.

5. Developing self-optimised chemical systems through self-evolution.

These themes should not be seen as stand-alone, as the categories were chosen for the purposes of Network administration; in many cases the research in a theme 'cross-fertilises' with that of others.

Over the past 18 months, the Network has run consultative meetings on these topics and on cross-theme issues, and fostered debate through newsletters, the Network website, social media and direct emails, drawing input from researchers and end-users. Reports on each theme area, based on that community input, appear in the following sections.

Impact of the Directed Assembly Grand Challenge

As Table 1 shows, developing an understanding of and learning to control molecular assembly to engineer functional materials will have a huge impact in many areas. A few examples are outlined below and further cases are detailed within the thematic area of particular relevance. The activities of the Directed Assembly Network are geared to focus and speed the delivery of these outcomes.

Societal Impact

The research field of directed assembly has great relevance in many areas affecting the society of the future, including healthcare and transport.

With an aging population, improved healthcare becomes more important – understanding directed assembly allows improvements in drug delivery and opens up the use of new therapeutic molecules as well as the development of bio-compatible, implantable materials, devices and organs.

With current concerns around long-term fuel supplies and polluting end-products, the applications of controlled molecular assembly are highly relevant. Transport systems can be made more environmentally-friendly and energy efficient through the use of improved fuel cells, better catalysts and, in the longer term, the possibility of using high-temperature superconductors.

Our work and leisure activities will be enhanced by new consumer electronics based around improved batteries, printable and organic electronics and new display devices.

Industrial Impact

Whilst the most obvious uses of a better understanding of molecular assembly are around creating faster, more efficient chemical synthesis methods and reclamation techniques, a whole range of new technologies are opened up through its application.

For example: smart, functionalised, structural materials which can incorporate energy-generation will transform the construction industry; anti-corrosion and anti-fouling treatments for surfaces will improve pipeline flows and the lifetimes of exposed metal; foodstuffs and drug production and delivery will be enhanced by better insight into nucleation, dissolution and the formation of gel structures.

By linking together academic expertise and industrial requirements and helping develop an understanding of each other's operating cultures, the Directed Assembly Network assists in speeding the uptake of new technologies into production processes, thereby maintaining the UK's industrial competitiveness.

Academic Impact

The Directed Assembly Grand Challenge Network was set up, in the first instance, to benefit academic research into molecular assembly. In the following sections we describe a wide research landscape containing scientific goals which might be achieved in the coming decades. There is no single, monotonic route-map to achieving these goals, no "man on the moon" project; instead we view progression as a "many-pointed crown" where breakthroughs can be achieved on many fronts and many valuable outcomes achieved along the way, with developments in fundamental science underpinning each of these successful outcomes.

The benefits of defining and working towards these goals are already percolating into the academic community: building and sharing an inspired vision; recognising where fundamental problems are shared between different topic areas, for example the need for multiscale modelling and measurement appears across themes, and assisting the development of collaborations to tackle these; breaking down traditional subject-based barriers, for example between chemistry and chemical engineering; identifying areas of weakness which need development and areas of strength which can be built upon. Encouragingly, in this process, the disparate communities are beginning to "speak the same language" when communicating ideas that they have in common.

Early Career Researchers, identified as needing particular help in earlier reviews, are already receiving targeted help, through their interactions with senior academics at theme meetings, through their own DREAMS meetings focussed particularly on their needs and where their importance in the wider field can be explored. In future the Directed Assembly Network expects to target additional funding to these researchers to enable them to develop and enhance their skills through sharing best practice between institutions.

The World Picture

Whilst the development of the Network has always been outward looking, involving input from international experts and interactions at international meetings, the focus has been on developing the capability of UK plc. For the UK to maintain and improve its international rating we need to compete and collaborate with the best in the world. In the area of Directed Assembly there are very strong research programmes in the USA, Japan and mainland Europe and these governments are earmarking funding to break down many of the barriers to progress we identify in this document. For example, the recently announced US Materials Genome Initiative[c] is targeting $100 million to enhance multiscale modelling, create a data transfer and sharing system and develop the next-generation workforce through a multi-disciplinary approach.

The UK is identified as world-leading in some aspects of Directed Assembly such as computational chemistry and modelling, and would benefit from international collaborations in others, such as surface templating. The flexible connectivity of the Network enables these existing world-leading areas of knowledge to be broadened across the UK and, by using its absorptive capacity, it can leverage and benefit from the knowledge of external experts. International links have already been established through the Network membership and these will be strengthened in the future.

While the next stage of the Network will be to focus on the 5-50 year targets identified by the UK community, input from abroad will also be encouraged so that the best of British can work with the best in the rest of the world to achieve our overall goal.

Table 1: Products resulting from potential breakthroughs over the next 5-50 years.

	5-10 years	10-30 years	30-50 years
Theme 1	Improved photovoltaics, fuel cells, heterogeneous catalysts and batteries. Better catalysts for greenhouse gases, pollutants & enhanced industrial processes. Enhanced sensors. Smart structural materials.	Higher-temperature superconductors. Self-healing materials for construction. Industries based on efficient recovery of scarce resource materials & remediation of pollutants through advances in catalysis and waste-to-fuel processes.	New industries based on atom-efficient material production. New transport systems, energy distribution networks and consumer electronics based on high-temperature superconductivity.
Theme 2	Improved drugs from control of small molecule crystallisation and amorphous materials. Enhanced dyes, pigments and fluorophores for applications from display devices to solar cells.	Advanced drugs based on large molecules and biological components. New industrial-scale production systems based on continuous flow technology. Improved food production from enhanced agricultural chemicals.	Locally-produced, custom-personalised drugs on demand. New drugs based on in-body molecular assembly of biological and/or artificial components in concert.
Theme 3	Prototypical biological computing and self-assembled molecular machines. Sensors for non-invasive diagnostics. Self-assembled structural materials from biological components, e.g. DNA & proteins, combined with electroactive components. Enhanced enzyme catalysis and artificial enzymes for catalysis applications. Support and contact materials for single-cell sensing and single-cell computing. . Suite of chemical and biochemical (single enzymes) as well as biological (whole cell / organism) processes for the production and processing of biopolymers.	Self-assembled active support materials for tissue engineering for regenerative medicine. Biomimetic conversion of small molecules (especially CO_2) to chemical feedstocks. Artificial photosynthesis. Control of diseases caused by protein misfolding, e.g. CJD. Bio-compatible implantable devices for continuous sensing. Biocompatible and bio-derived self-assembled molecular machines using biological energy sources (e.g. sucrose, ATP). Harvesting bioenergy through wiring up cells. Integrated processing relying on biologically compatible chemistry (aqueous, ambient temperature) and chemically resistant biochemical/biological processes (adapted/optimised enzymes/cells/organisms).	Growing artificial organs from stem cells in responsive self-assembled support materials. Bio-compatible implantable devices for continuous sensing and treatment. Full bio-mimetic and enhanced-biological manufacturing processes. Access to balanced portfolio of fit-for-purpose designer crops and robust chemical and processes and engineering for the generation of sufficient food, renewable feedstocks for green materials and biofuels for a world population of > 9 billion.
Theme 4	New synthesis techniques for monolayers, bi-layers, thin films, mesophases and other soft materials, fibrous and functionalised surfaces. Anti-corrosion & anti-fouling technology. Smart, functional packaging. Better food & drug formulation. Printable electronics. Surface properties by design: modelling/design methodologies and computer controlled fabrication technology	Membranes for water purification & desalination. Biocompatible and bio-mimetic membranes. Improved fuel cells. Surface-functionalised construction materials. 3D materials with layered functionality. Optimised organic photovoltaics; recyclable plastic electronics	Surfaces and membranes with dynamically-controllable functionality. Artificial skin.
Theme 5	New engineering and production control systems for industrial scale self-assembly. Molecular 3D printing. Auto-optimised functional materials. Optimised bio-product synthesis through DNA coding.	Consistent production systems based on variable feedstock inputs to revolutionise industry in developed and developing countries. In system reaction control through DNA & other information-coding molecules.	Self-adaptive production systems, with optimised custom outputs from multiple feedstocks, including the ability to create elements of the production system itself when process changes are required.

Where are we now?

Before looking at routes to future goals, it is useful to consider the current state-of-the-art, both in terms of research issues and aspirations, and in terms of the human capability in the area.

Research State-of-the-Art

The chemistry of "the molecule" produced by manipulating covalent bonds is relatively well understood and we can control molecular properties and reactivity to an extent. The theories for interactions between molecules are well developed. To achieve the targets outlined in Table 1 we need to be able to design and control the preparation of and to engineer the fabrication of any material with a targeted property. Currently, we can barely control the formation of supramolecular assemblies in solution or the solid state, let alone plan their assembly in a rational way so that they have a specific property. We need to be able to control the "chemistry beyond the molecule".

In Table 2 we give an outline breakdown of the main issues facing this research area generally and the aspirations of the research programme outlined in this roadmap.

Table 2: Research Issues and Aspirations

Issues	Aspirations and Targets
General	
We do not yet understand the nature and balance of intermolecular interactions, nor how structures of assembled materials relate to their observed properties. We have little or no quantitative control over the directed assembly process. At present it is not straightforward to scale up reactions, in terms of physical size or speed, when developing a chemical process. It is not possible to control chemical or biological processes over a range of length scales or time frames.	To develop rational and evolving designs for any material with a targeted property and to build an understanding of structure/property correlations. To develop methods for building large arrays selectively through a self-assembly process and to be able to control the end point of a reaction. To control the kinetics and dynamics of the self-assembly process. To build a coherent research programme and obtain sustained funding for research and development in the area of Directed Assembly.
Theme 1	
We do not fully understand how the assembly processes work for molecular frameworks and hybrid materials in terms of kinetic and thermodynamic processes involved and have only occasional empirical control over these processes. We do not understand how a structure can be modified to alter a physical property in a controlled manner.	To be able to retro design a material with a targeted property or a supramolecular assembly with a specific function. To be able to carry out a cyclic design process so that the structure and desired property of a material or assembly can be optimised
Theme 2	
We do not understand how to control the growth of crystals or amorphous forms of molecules. We do not know how to reliably produce a material with specific physical properties	To define the range of solid forms accessible to a given (e.g. pharmaceutical) molecule, and their physical properties. To produce a particular polymorph of a material that has optimal properties.

	To design methods of producing the desired solid form, both for initial discovery and for controlled manufacture. To elucidate the atomic level mechanisms for the nucleation and growth of specific polymorphs and the resulting physical properties, to determine the assumptions required for predictive modelling.
Theme 3	
We are, for the most part, unable to mimic self-assembly processes that occur so effectively in nature. Our control of interactions in aqueous solutions is lacking, specifically there is a lack in predictable specificity. The network of interactions between bio(macro)molecules is poorly understood, both in terms of equilibrium thermodynamics and kinetics. Exploration of the interactions of advanced materials and biomacromolecules, cells and tissue is in its infancy. Renewable bio-derived materials and fuels have been developed but these impact negatively on food production.	To develop biomimetic methods to achieve a similar selectivity, both in interactions and in catalysing processes, to those that enzymes display. To develop a better understanding of this selectivity and apply it to a range of biologically important systems. To link biology and materials in the pursuit of hybrid multifunctional and responsive systems with applications in health (biosensors and active support materials for whole cells and tissue engineering) and energy (interfacing materials with green biological energy). To develop a balanced portfolio of fit-for-purpose crops to address the demand both for bio-derived renewable materials, for biofuel and for food production.
Theme 4	
There is an increasing importance in developing heterogeneous systems, both solid-liquid and solid-gas interfaces. The interface/surface is not well understood at the molecular or supramolecular level.	To be able to control the growth of materials at the interface, taking into account the evolution of the structure and function as the length-scales increase. The development of the understanding of the kinetics and thermodynamics of the growth process on a surface or other interface is vital.
Theme 5	
We cannot control the pre-organised arrangements of chemical building blocks so that they spontaneously form nanostructures or large arrays with a particular functionality.	To selectively pair up the right molecules, and to develop controlled choice so that structures with wrong pairings can be eliminated. To build in the design whereby systems vary their structures to optimise a desired property.

Human Capability

We recognise that progress in the area of the Directed Assembly Grand Challenge depends just as much on developing human capability as it does on scientific breakthroughs. Feedback on these human issues, gathered from the research community at network meetings and in written comments, is described in more detail throughout the themed chapters and a simple summary of that feedback is presented here in Table 3.

Table 3: Developing People – Sharing Expertise and Promoting Leadership

Where we are now	Aspirations and Targets
Physical scientists trained to a high level in small focussed areas. There is a tendency towards a 'silo mentality'.	Develop multidisciplinary expertise to facilitate the development of boundary crossing science in order to meet the Directed Assembly Grand Challenge.
Experimentalists and theoreticians usually work independently and often fail to communicate effectively.	Foster collaborations between experimentalists and theoreticians, to exchange knowledge, and to work on the same problems, providing iterative feedback in both directions.
The majority of chemists and engineers currently work in separate environments, looking at systems with different length scales.	Facilitate the closer interaction between chemists and engineers to bridge the length scale divide and together study systems on the nanoscale. This new knowledge exchange will feed into future manufacturing initiative as materials with evolving properties across the length scales are developed.
Little interaction between biologists and inorganic chemists.	Facilitate interactions between biologists and inorganic chemists to develop biologically important multicomponent assemblies containing metals as sensors and for use in clinical applications.
Academia and industry work independently to a large extent and there is a lack of understanding of the needs of each group.	Facilitate greater interaction between academia and industry through short and longer term exchanges. Embed academics in industrial laboratories for one to three months and, similarly provide opportunities for industrialists to spend short periods in academic research laboratories. This would supplement the small number of Fellowships that currently support these exchanges. It should be remembered that it is people that transfer technology. Personal contacts, with a specific target, would be very effective in enhancing this transfer.
Early career researchers may be isolated with a greater need for supportive community.	Develop early career researchers through exchanges, workshops and networking events. These early career researchers will be the future leaders as the push towards the Grand Challenge targets gathers pace. It is essential that they are embraced and supported within a multidisciplinary approach. Within this community there is huge enthusiasm for taking part in short exchange visits to other laboratories to learn new skills and exchange ideas, to be involved in workshops to tackle specific problems, and to network with their peers across disciplines.
The community perceives that the ability of young researchers to advance fundamental research is not recognised by funders. There is a fear that limitations of training reinforce discipline silos rather than breaking down barriers between subjects.	It is essential to develop modes of cross-disciplinary training, focussed on solving real research problems, through workshops, schools and networks, to build the multi-skilled workforce of the future.

Introduction to the Individual Theme Overviews

The following thematic sections pull together community views gathered through networking meetings and ongoing discussions. Some theme areas have been established for some time and are well-defined, although the barriers to progress are still significant research challenges. Other areas are newly-emerging and the definition of the research space and its challenges are still being shaped by the community.

For each theme we describe why the area is important, the scientific challenges faced, where breakthroughs are needed to be made and what we can do to increase the capability of the community in the area. Table 4 gives highlights of key research areas for each theme – progress in these areas is described in more detail in each of the following chapters.

Whilst the scientific goals of each theme are, in general, complementary, it will be seen that similar structural issues around training, infrastructure provision, requirements for experimental data and new techniques for its measurement, limitations of existing modelling techniques, etc, are raised by the communities involved in each theme. As investment in tackling these issues will provide synergistic development across all themes we make recommendations for tackling these, as well as the science challenges, in our summary at the end of this document.

Table 4: Areas in which it is important to implement progress, listed by theme

Theme 1	Theme 2	Theme 3	Theme 4	Theme 5
Multi-component self-assembly	Discovery of solid forms	Control of interactions in any solution	Solid-liquid surfaces – solubility and dissolution	Computer directed assembly by control of multiple physical properties
Functions of supramolecular assemblies	Determination of atomic structure and properties	Modelling methodologies for biomolecular interactions	Fluid surfaces and structured liquid formulations	Enable self-evolution in non-biological systems
Solid state bonding to predict the outcome of multi phase synthesis	Phase diagrams	Kinetics & time-dependence in biomimetic systems	Polymeric functional materials and surface coatings	Methods for measuring multiple properties simultaneously
Kinetic control of self-assembly	Particle properties	Multi-component systems at the biology/materials interface	Surface-templated self-assembly	DNA-based evolvable matter
Optical and electronic materials	Modelling capabilities	DNA structures & DNA-hybrid materials production		
	Design principles	Food, biofuel and bio-renewables production.		

Theme 1: A Roadmap for Controlling the Assembly of Designed Molecular Frameworks and Hybrid Materials with Targeted Properties

The Grand Challenge Vision of Theme 1

We are challenged by a world where resources, such as petrochemicals and rare metals needed for microelectronics, are depleting and where the requirement to deal with environmental problems, such as increasing CO_2 levels and water shortages, becomes ever more important.

Directed assembly delivers the capability to deal with these societal problems in a transformative way, by changing the manufacturing paradigm from one of handling bulk materials to one where we control manufacturing on length scales from the molecular level upwards.

Supramolecular self-assembly is therefore an enabler for an entirely new industrial base, where understanding the synthesis of functional materials is an essential precursor to developing a new, high-value manufacturing industry - reducing waste, harvesting recyclable materials and using abundant feedstocks in novel ways.

We can envisage some of the new materials and technologies created through directed assembly, such as high-temperature superconductors, advanced catalysts and molecular electronics, which will revolutionise the coming decades. Others, required to deal with future societal problems, are not yet known but, through fundamental research now, we can build knowledge and understanding to give the UK's science and engineering base a world-leading suite of capabilities to draw upon and the resilience to deal with the challenges of the future.

The Scientific Challenges

We can divide the scientific challenges into two categories:

1) Self-assembly of molecular systems, where the functionality of the assembled material comes from the combination of properties of individual molecular components;
2) Assembly of functional materials, where the individual components have no function themselves but, through co-operative properties, function arises in the bulk material.

Combining components by control of self-assembly

For the first class of challenge, even when the functions of individual molecules or motifs are known, the routes to combining them into a material with a designed set of properties are not well understood. It is as if we have all the components of a car, but are trying to assemble it by putting them in a bag and shaking – we need to develop a deeper understanding of how the ways in which components combine can be controlled to build in all the desired properties of a material. It is entirely possible that the same components, combined in a different way, could result in an entirely different function; so control of multi-component assembly is the key here which will unlock a huge range of potential functions.

At present we are generally able to control self-assembly to a limited extent using strong, directional bonds such as metal-ligand bonds or multi-point hydrogen bonds – although even this is challenging. But we can exert little control over weaker interactions, such as single hydrogen bonds, π-π stacking interactions or van der Waals' forces, particularly as

they are, in some cases, non-directional and easily disrupted in the ambient conditions under which we wish our new manufacturing techniques to take place. Our most elaborate examples of self-assembled artificial systems combine only two or three types of different component, which severely limits the range of potential functions. In contrast, the function of the photosynthetic reaction centre arises from the specific combination of the functions of light-absorbing porphyrins, quinones, proteins and redox carriers all with precise spatial relationships between them.

Thus the most important challenge in this field is to be able to control the assembly of a large number of different types of components – possibly 10 or more – in the correct sequence. This may require use of 'orthogonal' interactions to direct specific pairwise recognition processes and prevent undesired combinations from forming. It may also require kinetic control (*i.e.* assembly under non-equilibrium conditions, using templates, low temperatures or surfaces to control the assembly path) before we can start to replicate some of the functionality of the 'manufacturing' processes which occur in nature.

Thus a **fundamental target** on the roadmap to solve the first challenge is to develop the understanding of how assembly works, through a combined programme of modelling and measurement, exploring methods of controlling the assembly process through techniques such as templating, temperature regulation and the use of templates and surfaces. Developing this capability will enable us to build our metaphorical car, combining many valuable molecular properties into transformational materials. This assumes that the properties of the components are retained in the assembly, such that the function of the assembly can be predicted based on an understanding of the component properties, which may often be the case. If we have components such as wires, light bulbs, switches and resistors we can be sure of what the function of a circuit will be based on how the components are connected. *In this case, control of function arises from control of assembly.*

The molecular factory – better than nature

Nature produces many materials within cellular factories, capturing molecules from cell solution into enzyme proteins and carrying them around the cell to combine with other molecules in turn. Understanding how to engineer functional materials would allow us to create, for example, designer catalysts with a gradient of properties spanning a rigid assembly line of molecular components in sequence. The gradient would turn these individual molecular components with their specific (e.g. catalytic) properties into a designed assembly line, where molecules could be captured into the pores of the material, held so they could be combined with others, then released to pass through to the next stage. Such materials would have almost unlimited use in manufacture, remediation & recycling.

Emergent functionality in materials

For the second class of challenge we need to develop the knowledge of how functionality arises in bulk materials through cooperative combination of individual components with no function of their own as, for example, we see in superconducting or magnetic materials. In these cases – and in contrast to the previous section – the function of the assembly does not obviously follow from the properties of the component parts. We know how to create a limited range of such materials through crystal engineering methods or through layered deposition techniques such as molecular beam epitaxy (MBE), but do not fully understand how the emergent properties arise through the combination and arrangement of individual atoms, ions or molecules. This limitation is the major barrier in the way of progress towards the goal of designed materials with advanced functionality.

It could be suggested that we try combinatorial processes, experimentally combining components to see what function arises – but the parameter space is too vast for a sensible programme to be developed without some method of limiting the space studied. Full *ab initio* calculations to theoretically design these materials bottom-up are mathematically insoluble at present. The route along the roadmap must therefore include experimental processes and theoretical modelling across a range of length and timescales developing hand-in-hand – with measurement used to parameterise models, which can in turn inform the types of components to be selected for further experiment.

In the manufacture of these new materials it will be vital to develop new methods of combining molecules, not just through synthesis, but through advanced deposition methods – for example one route to the creation of new functional materials is through depositing of heterogeneous layers – the molecular equivalent of the colour inkjet printer. Thus we must combine the talents not just of theoreticians and experimentalists, but engineers too.

High temperature superconductors

Superconductors exhibit zero electrical resistance above their transition temperature Tc. Superconductivity at atmospheric pressure with Tc above 9.5K (the highest found for an element, Nb) requires the synthesis of new extended materials. The highest Tc values are found in extended copper oxides where assembly of a range of cations exercises control over the complex behaviour of the Cu-derived d electrons. These materials have complex compositions because the electronic structures are poised between competing insulating and superconducting ground states. Recently Fe-based systems (LnFeOAs Tc = 55K) have produced high Tc with a similar competition between magnetism and superconductivity. The search for extended arrays from which cooperative properties emerge is a complex task but starts with synthetic assembly. Enabling this through the measurement and computation augmented approach proposed here offers the best prospects for advancing our current understanding of high Tc superconductivity. Achieving high critical current superconductivity well above room temperature with a readily-processable material made from cheap, sustainable starting materials would have tremendous impact in reducing energy delivery costs.

The Capability Roadmap

Progress in this area of directed assembly depends on:

- building understanding through combinations of multiscale experiment and modelling, and ensuring the knowledge thus gained is openly accessible;
- developing an open database of molecular and materials measurement to facilitate the parameterisation of new computational models;
- the development of novel materials production techniques;
- understanding the balance between stable and metastable materials in the synthetic strategies to determine what new materials can be targeted under a specific set of reaction conditions; the development of computational and advanced deposition techniques will be vital to achieving these targets;
- most importantly, embedding that new knowledge in trained staff, giving the capability to respond flexibly to the changing requirements of the future.

Science & capability development to match onto product roadmap

Where are we now	Short term	Medium term	Long term	Goal
Solution-based self-assembly under thermodynamic conditions of up to four types of component using orthogonal interactions	Development of a wider range of orthogonal recognition motifs that can be incorporated into components for self-assembly	Reliable self-assembly of multicomponent (<5) systems component under equilibrium conditions	Use of bio-inspired methods, e.g. artificial proteins with numerous binding sites which will bind many different molecular components in a 3-D ordered array	Complete 3-D control of assembly of multiple different components with different functions using a combination of bio-inspired and artificial methods
Limited functions in self-assembled molecular systems mostly based on guest binding / molecular recognition / catalysis in cavities	'Designer 3D cavities' that will allow desired catalytic transformations of guests based on close control of cavity size / shape and matching it to transition state	Efficient catalysis / molecular transformations in crystalline arrays of 'molecular flasks' based on gradient diffusion of substrates across a fixed sequence of designed cavities: a 'molecular assembly line'	Development of sophisticated functions in assemblies by combining e.g. light-harvesting units, redox units, paramagnetic units, catalytically active metal complex fragments etc. in a multi-component assembly	Biological complexity: e.g. artificial photosynthesis, currently inaccessible synthetic transformations, or conversion of CO2 to methane using self-assembled functional components
Use of crystal chemical and coordinate bonding models to qualitatively predict the outcome of multiple phase synthesis	Enhanced complexity in solid-state assembly processes to produce synthetic targets	Enhanced structure prediction methodologies coupled with atom-by-atom and analogous molecular bond-making methods to allow more complex structures to be predictably isolated. Control over these classes of material will afford new heterogeneous catalysts, fuel cells, separation membranes and solar energy harvesting systems.	Property prediction for cooperative behaviour. The control of the assembly of complex solids.	The predictable assembly of complex solid-state materials with designed function.
Limited kinetic control of self assembly using templates with combinatorial libraries; 'sergeants and soldiers' chiral amplification; surface templating; interconversion between labile and inert states by redox reactions to 'lock' assemblies	Much greater use of kinetic methods to effect controlled self-assembly, e.g. selection of different parts of a library of functional components to make a different device just by changing template.	Use of surfaces to order multi-component functional assemblies in 2D (initially), then 3D by using the first layer of assembly as template for the second layer; temperature-based control of formation of surface assemblies; combination of existing deposition (MBE) methods with solution-based self-assembly on a 'designer surface'	Responsive assemblies, systems that allow components to unlock and rearrange under a specific stimulus, possibly changing the function in the process	Complete kinetic control of self-assembly of functional components using a wide range of techniques
Preparation of some useful materials (superconductors, ferroelectronics, NLO systems etc.) based on empirical trial-and-error methods; some understanding of how emergent function relates to structure	Better theoretical understanding of structure / function relationships and the origin of emergent properties. Better fabrication methods and control of crystallisation	Designed materials with pre-planned properties based on combination of crystal engineering and high-T fabrication methods		Atom-by-atom fabrication of 3-D arrays to give a pre-planned property based on full understanding of structure / function relationships; complete control of crystallisation of large number of components into functional solid-state assembly

A Collaborative Vision

It will be vital to promote industrial connectivity to drive changes in traditional manufacturing and develop new advanced manufacturing industries, based around molecular electronics and molecular factories.

The cross-over between disciplines, e.g. enabling chemists to learn from and improve upon the natural processes studied by biologists, and enabling knowledge to be developed and applied by the joint working of experimentalists, theoreticians and engineers will be vital. Thus continuing opportunities for these researchers to interact and work together must be provided through networking meetings, opportunities for inter-institutional visits and shared research projects.

Presenting academic expertise in a format easily accessible to industry and providing opportunities for interdisciplinary working will be simplified through the continuation of the Directed Assembly network and may also be facilitated through the development of a 'virtual institute' created by clustering the multidisciplinary knowledge contained within a group of institutions.

The creation of such a virtual institute also gives a strategy for training the future researchers in the field of directed assembly through the creation of a Doctoral Training Network and through enhancing the interaction and mentoring of early-career researchers.

Theme 2: A Roadmap for Controlling Nucleation and Crystallisation Processes in Pharmaceutical and other Fine Chemicals

The Grand Challenge Vision of Theme 2

Our aim is to revolutionise the production of solid forms of essential products, such as pharmaceuticals and agricultural chemicals, by significantly reducing cost and timescale for moving candidate molecules from approval into reliable and stable formulation for delivery.

For this to happen we need to be confident of being able to generate all possible solid forms of a substance, knowing how they can be interconverted and their properties. Alternative solid forms, such as amorphous or multicomponent phases must be similarly evaluated or designed for desirable properties. Both require a computationally driven design of a close to 100% reliable solid form screening and property evaluation experimental program.

With greater insight from enhanced models of nucleation processes, we will develop the ability to induce nucleation in both homogeneous and heterogeneous systems at will.

We must produce flexible, automated approaches that will allow particle shape and size to be dialled-up, modified and tuned in a flexible reactor system. We will be able to enhance the impact of additives and defects to produce flexible particle systems that can be engineered over a range of length scales and with a range of tuneable properties to allow delivery in a range of environments and stability ranges. In-line diagnostics and feedback must be available, allowing information on evolving physical properties to be utilised in the automated optimisation systems.

Development of these processes will enable us to take candidate molecules from the sister Grand Challenge "Dial-a-Molecule" Network for assessment and delivery into particle production and formulation

These broad goals define a research and development programme, which draws together industry and academia, which will revolutionise the way that pharmaceuticals are developed and will deliver a personalised healthcare regime that can only be dreamt of at present. In order to meet this Grand Challenge, a sustained effort is essential over the next three to four decades in order to overcome the scientific, economic and societal barriers.

Such breakthroughs will revolutionise the efficiency and cost-effectiveness of production facilities, reducing cost and waste for both manufacturers and consumers.

The Scientific Challenges

Introduction

Active pharmaceutical ingredients (APIs) are selected for their therapeutic effect. The challenge is to control the crystallisation (or encapsulation or other delivery mechanism) of the API so that the therapeutic effect can be delivered. At present, compromises need to be made in the selection of the physical form of these molecules for manufacture into a product. It may not be possible to turn the most therapeutically-useful molecule into a formulation for dependable delivery.

If the range of supramolecular structures for a given molecule could be known and along with all the associated physical properties that determine the performance of the possible pharmaceutical products, this would revolutionise the drug development process.

Personalised Healthcare
With efficient, flexible and responsive processes we can deliver on the aim of fully customisable production of pharmaceuticals, on-demand and in single-dosage formulation – avoiding stockpiling, waste, disposal of unused doses, etc. With our vision, and those of other Grand Challenge teams, a single seamless individualised chain can be created from the clinical prescriber to the delivery of specifically designed, formulated medication to the individual patient.

Understanding how the nucleation and crystallisation processes drive the formation of different polymorphs is vital to prevent manufacturing disasters such as occurred with Ritonavir and Rotigotine. More importantly, knowledge of the complete range of solid forms available to a molecule and the ability to control the crystallisation of the form with the best polymorph properties, e.g. solubility, may open up the opportunity of using different, perhaps more economically-favourable, manufacturing processes as well as enabling 'difficult' molecules to be turned into deliverable product.

In general crystallisation will occur from solution, but crystallisation from a melt should not be neglected. Multi-component forms, such as co-crystals, solvates, salts and amorphous forms must also be considered.

Nucleation and growth

The first step along the way is to understand and be able to model the initial nucleation and growth process, both to control manufacturing processes, but also to ensure we can produce the first samples of a desired product

- Given any molecule we need to be able to model feasible extended structures.
- We require thermodynamic & kinetic models of growth and inhibition processes. There is a lack of experimental data to ensure that these models are realistic.
- We need experiments to explore and validate the nucleation processes.
- This includes experiments to understand the effects of additives, whether deliberate or impurities, on seeding and templating, and to contrast behaviour over different time and length scales.
- These data can then be used to inform and improve the assumptions made in modelling nucleation and growth.

With a complete model of nucleation we can predict what will happen for a given molecule under given conditions, so can then control nucleation behaviour within the manufacturing process.

Agglomeration

After nucleation and growth into crystallites we need to understand how these agglomerate to form particles.

- Different surfaces of the crystallites generally have differing properties, so we must first understand the surface chemistry and physics of the exposed faces of the crystallites.
- We need to understand the extent to which we can vary the morphology of the crystallites
- We require experimental techniques to characterise the way the aggregates are bonded together – how the crystallite surfaces join, what remains between.
- We need to develop particle flow models to describe the behaviour of the crystallites and aggregates within the manufacturing reactors under different conditions.

- The end point will be control of agglomeration, enabling the creation of the ideal particle size and shape for product delivery. This will drive reactor and reaction design.

Solubility and dissolution rates

However, to define what the ideal particle would be, we also require a better understanding of particle solubility, not just under conditions that might obtain for delivery in the patient, but at any point along the production chain.

- We need to improve measurements of solubility against particle size and morphology.
- We need to understand how the surfaces of the particles and their microstructures affect dissolution rates.
- We need improvements in dynamical calculations of dissolution (as well as nucleation & aggregation), relating rates in pure solvents to those in vivo.
- Understanding this will enable the optimisation of solvent choice for particular conditions (e.g. temperature).

Understanding the phase diagram

Models can be checked by comparison of predicted states with the phase diagram (including polymorphs) built up through experiment. It should be recognised that phase dependencies on pressure and temperature are not simple, the path to a particular set of physical conditions is also important. Therefore, it is necessary to develop phase diagrams to include the time dimension (i.e. kinetic limitations). The importance of capturing all experiments into the phase diagram for a particular substance should be emphasised – null results are important too.

Defects and multicomponent systems

The effects on properties of missing molecules (defects) or substitution of other molecules (multicomponent systems over a range of concentrations) need to be understood if progress is to be made. We need to use multiple experimental techniques to characterise particles down to the level of defects to understand how a typical particle differs from the perfect crystal – data which can be fed into models. Characterising the types of defects (and at what point a system with many defects becomes amorphous) and controlling the extent of disorder and its effect on properties such as dissolution rate or mechanical strength, is a key step in extending the range of pharmaceutical materials.

Multicomponent systems, ranging from impurities to designed co-crystals containing active ingredients in a fixed ratio, again require experiments to determine effects and inform models that allow choice of other components.

From molecules to process design by mesoscale models

Production may take place on many scales from large vats to micro-reactors. Different modelling techniques are used to represent these systems, from fluid dynamics to coarse-grained molecular dynamics models, complicated by the reactions and crystallisation taking place within the solution. Ideally there would be a seamless transfer of sufficiently realistic representations of systems from the molecular models of solid and surface structure all the way up to the bulk flows, but this is far from being achieved yet. This theme area is a particularly stringent test of the multi-scale modelling challenge of being able to go from adequate electronic structure to atomistic to particle modelling without eliminating the key molecule-dependent properties, because they depend on the balance between the molecule-specific inter- and intra-molecular forces. The range of applicability and level of accuracy of the assumptions used in existing models needs better definition, tied into

detailed observation, with studies focused on areas where the models developed for different, idealised systems, have broken down.

Zero-waste and on-demand bespoke functional chemicals
The same philosophy will hold, with similar savings in terms of waste, customisation and flexibility, in the wider fine chemicals domain to which our Grand Challenge theme is also targeted. For example in pigments, we aim not simply to "mix colour" on the shop floor, but to assemble, formulate and produce raw material efficiently and effectively at source, reducing overproduction, transport costs and other wasteful overheads and increasing flexibility and the potential for dramatically enhanced products.

Our emerging vision to achieve this is an essential and intimate academic-industrial collaboration, underpinned by the need to make profound scientific advances in both the pure and applied domains, in order to deliver this exciting and transformational outcome.

The Capability Roadmap

Progress in this area of Directed Assembly depends on

- experimental and modelling approaches developing hand-in-hand within academia. A clear balance must be achieved between the two areas and the limitations and advantages of both appreciated. There is much fundamental science that needs to be undertaken before there is sufficient information generally available to be drawn upon so that realistic modelling of complex systems can be carried out.
- The integration of publically-available databases that contain a range of physical and chemical information is essential if progress is to be made, and the inclusion of pre-competitive information from industry would enhance the value of this resource.

A Collaborative Vision

- Fundamental to achieving these challenging goals is the transformation of the way that academia and industry work together in partnership, to create a complete network of capabilities which are scientifically outstanding, easily accessible and support agile prototyping of innovative products.
- Supporting and facilitating secondments between academic and industrial partners will enable both scientific knowledge and an understanding of each other's culture to be shared.
- Inter-company partnerships, where competition is set aside and information shared to the benefit of all contributors, give a better definition of the critical gaps in understanding to which scientific expertise can be applied.

Science & capability development to match onto product roadmap

<table>
<tr><td colspan="5">Control of Crystallisation of Pharmaceuticals and other fine chemicals</td></tr>
<tr><td>Where are we now</td><td>Short term</td><td>Medium term</td><td>Long term</td><td>Goal</td></tr>
<tr><td>Empirical screening for variety of solid forms.</td><td colspan="2">Exploiting better understanding of nucleation and growth to access to a wider range of solid forms.
Risk of a thermodynamically stable form turning up unexpectedly eliminated.</td><td>Ability to determine full range of solid forms. Confidence in designing two component systems</td><td>Full control over choice of solid forms and properties.</td></tr>
<tr><td>Full experimental characterization of properties of solid forms only in favourable cases.</td><td>Advances in measuring properties for non-optimal samples.</td><td>Sufficient data for validating prediction of properties from structure</td><td>Adequate models for predicting key properties to allow targeting useful solid forms</td><td>Ability to concentrate resources on of forms with desirable set of properties</td></tr>
<tr><td>Solubility, dissolution rates and phase diagrams a matter of laborious experimentation.</td><td colspan="2">Better measurement methods and modelling provides more atomistic understanding of phase diagrams for different solvents, and levels of defects and other components.</td><td>All relevant phase diagrams (including metastables) can be generated from minimal designed automated experiments.</td><td rowspan="2">Controlled design of optimal crystallisation process. Automated feedback and monitoring methods readily adapted.</td></tr>
<tr><td>Particle characteristics from observation</td><td colspan="2">Understanding of surface chemistry and growth allowing control of shape and agglomeration.</td><td>Ability to tailor crystallisation process to desired particle properties</td></tr>
<tr><td>Modelling based on over-simplified theories and parameterisation.</td><td colspan="2">Extension of more realistic methods from small generic molecules to more typical modern pharmaceuticals. Meso scale modelling developed for anisotropic crystals.</td><td>Integrated multiscale modelling of crystallisation possibilities and resulting properties</td><td>Modelling tools to predict all possible solid forms and their properties.</td></tr>
<tr><td>Qualitative structure/property relationships.</td><td colspan="2">Increasing examples of properties by design</td><td>Extended to multicomponent systems</td><td>Confidence in production process to optimal product.</td></tr>
</table>

Theme 3: A Roadmap for Controlling Molecular Assembly in Biological and Biomimetic Systems

The Grand Challenge Vision of Theme 3

Our aim is to borrow from, learn from and directly interact with nature: understanding, adopting and adapting processes which have been optimised by natural evolution, and interfacing modern materials with biological systems, to create functional materials with transformative impact.

Using these same techniques will also enable us develop new processes for creating bulk renewable commodities and fuels, reducing pressure on land and water use currently imposed by bio-fuel, chemical and materials production.

At a time when we are looking to support an aging population, creating new functional materials which are compatible with use in the human body will bring breakthroughs in quality of life for many. At the simplest level, biocompatible surfaces and membranes (an area of overlap with Theme 4 on surfaces) can coat structural materials to be used as bioimplants; with increasing complexity we could design functional and responsive materials that reacted to changes in-vivo and could be used as bio-sensors or support structures onto which new organs could be grown through stem-cell technology.

Novel, efficient manufacturing processes for renewable materials and fuel production can be developed through a better understanding of the natural molecular assembly processes catalysed by enzymes. Enzymes can also be used to drive biofuel cells which, in combination with the biocompatible materials described above, could be used for powered bioimplants in the body. Biofuel cells running on enzymes, rather than catalysts of rare metal such as platinum, have the potential to provide low-cost, environmentally-friendly energy applications for the future.

The whole exciting field of bio-electronics is currently in its early infancy. We are learning how to assemble biomolecules into complexes and arrays which can conduct electricity, be addressable for information storage and readout and connect with biosensors. In the longer term such research (again overlapping with Theme 4) could lead to bio-molecular circuits which self-assemble onto surfaces.

With a growing world population, food security for the future is a global challenge, particularly as pressures on land are increased for growing biofuels and other bulk materials for manufacturing. This theme supplies two solutions to the problem, firstly by offering new methods for materials production which make less demand on natural resources and secondly by creating enhanced versions of assembly processes within plants to improve their yield.

This is a dynamic and rapidly-growing area which must be harnessed into UK competitiveness, developing a national advantage in biological manufacturing for the future. It has the potential for significant commercial exploitation, for example through the creation of spin-off companies exploiting the high added-value associated with modern functional materials

The Scientific Challenges

For advances in these areas to happen we need to understand how nature controls and directs molecular assembly processes through the use of proteins, enzymes and other bio(macro)molecules both in equilibrium and in kinetic processes.

In addition, we need to develop the understanding required for using templating molecules such as DNA and peptides for the construction of functional hybrid nanoscale assemblies. The principles underlying the bottom-up construction of designed responsive matter and the interactions of such matter with cells and tissues need to be developed. Analogously, these interactions influence the manipulation and application of biopolymers for use in bulk commodities and fuels.

We also require understanding of how functionality arises through the combination of properties of individual molecular components and how natural, responsive materials are created hierarchically to show a range of reactivities and interactions over different time and length-scales.

We can divide the scientific challenges into two categories:

1. Learning from nature's functionality;
2. Learning from nature's control of reactions.

Learning from nature's functionality

Biological tissues are set apart by their ability to react and to combine ordered and non-ordered systems. Even tissues we may think of as being static are continuously broken down and rebuilt by processes within the organism – whether animal or plant. Their responses may be driven by a range of physical or chemical variables: pH, light, *etc*. and range from simple processes, such as breakdown of redundant structures, all the way through to complex activities such as differentiation of stem cells.

Capturing this responsiveness into artificial, biomimetic materials transforms materials from being merely structural or "unifunctional" into being functional devices which, even at their most elementary level, can open up a world of applications, such as

- replicating natural processes:
    - e.g. an artificial scaffold for tissue repair must evolve with the changing system, supporting healing then breaking down when no longer needed
- improving on nature:
    - e.g. supporting photosynthetic 'mats' for carbon capture or chemical production
- or creating completely novel systems
    - e.g. DNA cages containing drug molecules which can enter biological cells, then break up harmlessly to release their cargo or, in the longer term, nanomachines to repair the body

In addition to advanced responsive materials, there is also a need for bulk renewable commodities. The use and manipulation of biopolymers requires an understanding of their properties as a result of self-aggregation. For example, starch, cellulose and other cell-wall polysaccharides adopt precise 3D interaction networks by virtue of self-assembly processes. Polyhydroxybutyrates are an example of current biodegradable plastics, the market for which is sure to grow. Analogously, the combination of carbohydrates, proteins and lipids dictates much of the bulk self-assembly of biomaterials that impact on food form and function.

To produce bulk, food-grade and medical grade products we also need to develop robust processes able to use complex, heterogeneous natural feedstock through environmentally-benign (bio)chemistries or synthetic biology. The design and development of new-to-nature biopolymers similarly requires an in-depth understanding of both biochemical processes and self-assembly properties. A greater understanding of how to exploit natural polymers will give new options in generating biomedical materials, for example smart wound dressing and biocompatible sensors.

With respect to food science, we are lacking an understanding in areas such as 1) the molecular basis of the impact of dietary fibre on the glycaemic index of our food, 2) the impact of food matrix structure and composition on availability of nutrients, 3) the pre- and pro-biotic effects of dietary polysaccharides.

Assembling these functional systems and renewable commodities and understanding the effects of self-assembly on our food is problematic and faces challenges similar to those in the other themes. We are only just starting to understand how function is incorporated into complex biological molecules. Although individual molecular motifs can be identified, when they are assembled into larger structures the functionality resulting from combinations of components cannot be predicted. In addition, nature's preferred solvent, water, is not directly compatible with typical current approaches to supramolecular structures which focus strongly on hydrogen-bonding.

We thus set an equivalent fundamental target on the roadmap for biological and biomimetic systems - to develop an understanding of the nature of the intermolecular interactions, in particular the reversible bonds that give these biological materials their responsive and evolving nature. In biological systems, diseases such as CJD can be induced when the molecular bonding 'goes wrong', so the importance of understanding what is happening is more than just a question of academic satisfaction. Again, as in the other themes, progress can be driven by combining research across length scales – at the moment many studies are single-scale concentrating, for example, on molecular bonds, on micelles or on cm size systems without considering how functionality is hierarchically driven from the smallest scales upwards.

With the understanding of how function derives hierarchically from structure then comes the ability to create artificial systems. One illustration of the long-term impact of understanding biological, functional materials is to be able to create artificial tissues – structures built-up from cells with known function. Currently, the required actively supporting materials (scaffolds) for tissue engineering and the interactions required for efficiently supporting growing tissue are largely unknown.

The Artificial Heart

Heart disease is the leading cause of death in the UK and USA. The ability to grow a real replacement heart, not just a simple mechanical pump requiring an external energy source, using stem cell technology would revolutionise healthcare. Growing a replacement heart requires currently unavailable responsive materials which support and nurture the growing heart, in place of the human body. Developing the understanding required for the development of support/scaffold materials for tissue engineering is therefore a major challenge with potentially huge rewards.

Learning from nature's control of reactions

Valuable natural products are assembled through complex series of reactions – whether we consider the photosynthetic assembly of sugars from CO_2 and H_2O through enzyme-driven cycles or the synthesis of proteins and enzymes from amino acids directed by DNA but moderated through networks of interactions. Understanding the function of enzymes and templated reactions are therefore also fundamental targets for this theme.

Developing an understanding of how to direct and catalyse reactivity through bio-molecules will have huge impact for example:

- understanding the reactions of and creating enhanced versions of the enzyme RuBisCO could improve photosynthesis and hence yield for selected crop species
- photosynthesis could be adapted to create other useful end products such as fuels
- the 'molecular factory' described in Theme 1, where sequenced reactions take place in a functional material, could also be created through the use of bio-enzyme gradients created in gels
- bio-compatible functional molecules embedded into medical devices could enable the detection of and reaction to particular chemicals in the blood stream, for example reacting to enhanced levels of blood glucose to control diabetes
- new routes for delivery of drugs could be developed, such as the assembly of small molecules within the cell, rather than trying to deliver large molecules across the cell-membrane
- The development of green processes for the manufacturing of renewable materials and fuels from biological feed stocks.

Food Security for the Future

Major issues for food security are associated with increased pressure on both land and water use for the production of biofuels and renewable materials. We therefore need to be smarter about the generation of feedstocks for industrial biotechnology. Understanding the physical and biological properties of bulk renewable materials, foods and medical grade materials allows us to optimise these competing processes in order to provide for a growing global population.

DNA might be viewed as the ultimate directed assembly molecule, creating proteins by assembling amino acids according to encoded information. Manufacturing DNA sequences is now a commonplace process. With the recent synthesis of an entire artificial bacterial genome (Venter, 2010)[e], opportunities viewed over the 50 year timescale using DNA to control assembly seem almost limitless, from using manufactured DNA to synthesize required proteins (Dial-a-peptide) or non-natural amino acids all the way up to creating entirely artificial cells.

The UK is strong in the field of using DNA to direct reactions. However, chemists recognise that DNA is just one way of encoding information and many other ways of driving assembly are open to them – use of peptides, of charged species, combinations of hydrophobic/hydrophilic regions of molecules etc. Research into these other methods would broaden and further enhance the UK's competitiveness

The use of hybrid systems involving templating of building blocks for materials using the programmable structures of DNA, DNA variants and proteins, is particularly interesting and will require close collaboration between chemists and biologists.

The Capability Roadmap

This is a dynamic and rapidly-growing area, requiring considerable collaboration between various disciplines in both identifying and solving the problems currently holding back the enormous potential for transformative discoveries.

The interdisciplinary nature of the field requires the best creative and visionary researchers to cross the scientific boundaries. Overseas funders and institutions have recognised this and a significant amount of overseas investment is being directed into this area to create new bio-technology industries. There is a danger that the UK's talent will be attracted away. We must prevent this and attract other key researchers from overseas, be it permanently to posts in the UK or through international collaborations. By increasing UK recognition of the importance of the field we will recapture its potential and harness the knowledge into UK competitiveness, developing a national advantage in biological manufacturing for the future.

- Attraction and retention of appropriately-trained researchers able to work across traditional discipline boundaries will be vital for developing capability.
- Experimental programmes to gather data and understand the rules which parameterise how molecular structure drives large scale function are required to enhance prediction models.

A Collaborative Vision

To create any of the transformational materials, developments in bio-renewables and foods described above, the interdisciplinary collaboration of chemists, understanding molecular assembly processes, with biologists, looking at functionality on a larger scale, engineers, developing devices, food technologists, etc. will be vital for progress – for example in understanding how the chemical structure of biological membranes, such as the cristae of the mitochondria, gives rise to their functionality. Similarly, matching this understanding with that of engineers will enable creation of devices and process scale-up.

Therefore we need to facilitate and enhance the level of interaction between different disciplines, retain and rebuild the research community and create a science base that can react quickly to changing knowledge. We thus recommend:

- Continuation of networking meetings to build a new multi-skilled community from researchers who would not otherwise have opportunities to meet. This is likely to require collaboration across the traditional research council boundaries.
- Enabling very short placements aimed at exploring boundary-crossing projects and sharing knowledge between institutions.
- Creating flexible student training that can cross discipline boundaries and be directed in agile fashion towards areas of particular need.
- In times of reduced overall funding, it may be tempting for sponsors to retreat to funding their core activities. However, multi-disciplinary research such as this is vital to enhance the UK's future competitiveness, so cross-funder programmes must be encouraged.

Science & capability development to match onto product roadmap

Where are we now	Short term	Medium term	Long term	Goal
Control of interactions in non-aqueous solutions through hydrogen bonding is relatively successful.	Develop an understanding of interactions in aqueous solutions allowing the construction of designed supramolecular structures			Full control over interactions in any solvent or solvent mixture
For some systems, reasonable guesses regarding biomolecular interactions can be made using docking and simulations.	Improve predictability of interactions through improved computation across length scales.			Fully design interacting components in-silico.
Some approaches to the analysis of complex networks of equilibria and kinetic systems.		Improve predictability of interactions through improved computation across length and time scales.		Design networks of interacting compounds with predictable responsive properties
Interfacing materials with biology is restricted to the level of individual components	Develop materials with programmable, directionally sensitive conduction properties	Selective connection strategies for cell components and conducting materials		Create selective connections between electronics and living cells
DNA is a valuable building block for the construction of 3-D structures and these structures are beginning to be exploited.	Develop hybrid DNA – materials approaches to optoelectronically active materials. Bring proteins, lipids, sugars into play.	Combined structures consisting of DNA, proteins, lipids and sugars.		Create 3-D structures of any size with any functionality
Biofuels, bio-renewables and food sources all compete for the same resources and generate significant waste.	Suite of (bio)chemical processes for the production and processing of biopolymers	Integrated processing of biopolymers using biologically-compatible chemistry and chemically-resistant biochemical and biological processes	.	Balanced portfolio of designer crops and processes for the production of renewable materials, biofuels and food

Theme 4: A Roadmap for Controlling Surface-Based Molecular Self-Assembly for Applications in Interface Science

In discussing 'surfaces' or, more generally, 'interfaces' in this Theme, we do not constrain ourselves to macroscopic length-scales and uniform surfaces. Instead, it is vitally important to understand the non-uniform interactions that apply across interfaces on a molecular scale; a full appreciation of the application and variation of from the micro- to macroscopic scales is vital to our goal of a full molecular understanding and control of surface-mediated interactions and directed assembly across length and time scales.

Equally, the geometries of the surfaces commonly encountered are not smooth, certainly not on the atomic or molecular scale; being able to control interactions between molecular species on curved surfaces – such as those of micelles – is also critical. Recognising that functional materials may consist of mixtures of ingredients, it is not just the outer surface that is important, but all the interfaces between the components of a mixed material; for example for particle-particle interactions in fine preparations the surface area – and hence "active area" for surface-mediated interactions and processes can be very large.

The Grand Challenge Vision of Theme 4

We wish to exploit surface interactions in the design of formulations, microstructures, dissolution and crystallisation processes and wetting/drying phenomena for applications in the food, pharmaceutical, personal care, agrochemical and oil/gas industries.

This will include solid-liquid and fluid-fluid interfaces, polymeric microstructures and films, lyotropic and thermotropic structured fluids, surfactant solutions and complex fluid formulations.

A key goal within the whole Directed Assembly Grand Challenge is the tailored control of assembly (and disassembly) of a range of target active materials and formulations. Understanding how surface forces drive the interactions of the different components in a mixture is vital for successful product formulation, leading to a greater range of suitable ingredients and more exciting products with longer shelf-life.

As an example, consider personalised drug delivery, a specific challenge within our Grand Challenge vision. Understanding surface assembly forces gives insight not just into the nucleation and crystallisation processes, analysed in detail within Theme 2, but also solubility and dissolution rates – a fundamental knowledge of which is required for understanding the behaviour of solid-state drug formulations within the body. In this context we note that it is important to understand how the surface characteristics vary with different faces of a crystal and how they change with time as the crystal forms or dissolves.

Turning to the implications and importance of "molecular-scale" surfaces, the Grand Challenge has major contributions to make in the study of porous materials. This is a well-established and extremely important scientific and technological area, based on the development and exploitation of zeolite and related microporous materials. There has been a recent explosion in new types of micro- and nano-porous materials, notably in areas such as Metal-Organic Frameworks, but also including gels and other less macroscopically-ordered materials. The high potential for engineering and control of assembly at the molecular scale offered by these naturally-porous systems requires further development beyond the more common chemical approaches being used to discover new systems.

By understanding how surface forces change during the molecular assembly process we will also be able to design processes which drive the transformation of a flat surface into a textured one, or even fold and curve a flat surface into a 3D object. The templating power of surfaces can be used to control the organisation and reactions of molecules assembling there, for example preparing analogues of graphene and related materials of single molecule thickness. Developing this method to integrate multiple molecular components will allow the preparation of complex structures – including the possibility of molecular circuit boards and sensing devices.

Better understanding of the processes of surface wetting and control of aggregation and viscosity will bring about revolutions in efficiency of oil extraction from porous rocks. It can also be used to develop smart coatings to help prevent 'destructive' self-assembly processes such as bio-fouling and build-up on the surfaces of pipelines and marine constructions.

Learning from nature and the molecular assembly processes forming biological materials, such as bio-mineralisation, we will be able to optimise surface-based assembly and produce bio-mimetic and bio-compatible surfaces and membranes. An understanding of these natural materials also helps target the actions of designed drugs within the body.

By harnessing the power of multiscale models we will be able to understand, direct and design the very different processes at solid/gas, solid/liquid, solid/solid and liquid/liquid interfaces. This will lead to improvements in the formulation processes mentioned above. It will also introduce a strong synergy between the activities of the Directed Assembly Grand Challenge and the vital and expanding area of catalysis. Once again we emphasise that while the immediate will be of benefits to heterogeneous catalysis, our enhanced understanding, modelling and control of interactions at the molecular scale will also extend our reach into important aspects of homogeneous catalytic processes.

The Science Challenges

To be able to achieve this vision we have identified a range of underpinning scientific challenges, in which we need to be able to characterise, understand and predict:

- polymer processing under different physical conditions, e.g. pH and temperature, and using different solvents and excipients, and its effect on the microstructure and morphology of the material;
- the kinetics of dissolution of solid formulations and gels, and its dependence on surface properties at different length scales;
- the kinetics and rheology of micellar aggregation in liquid formulations
- the structures that molecular aggregates will adopt in formulations under different conditions of salinity and temperature and be able to link these with surface and rheological properties;
- the competition and balance of surface forces on curved surfaces, such as nano-sized pores, fluid droplets and micelles;
- the templating and control of polymeric films, molecular monolayers and structured molecular assemblies on solid and liquid surfaces, including very short length scale "surfaces", for example in multi-component or heterogeneous materials.
- the directed design of the processes and products where surface interactions play a key role

To tackle these challenges we need to:

- develop enhanced experimental characterisation techniques – direct surface characterisation (neutron and X-ray scattering), surfaces forces (AFM) and composition

(atomic force spectroscopy) for particles such as pharmaceutical APIs - thermodynamics of adsorption, interfacial free energies and tensions, surface and bulk phase behaviour.

- enhance multiscale modelling methods with a direct link to the characteristics of the specific material and experiment – recognising the value of a range of methods based on different assumptions;
- develop these methods so they can be used to reliably predict outcomes - at present much modelling is carried out through empirical models used outside their range of validation where they are unreliable;
- closely couple experiment and modelling into enhanced engineering and process design, with directed molecular assembly as the key ingredient.

The Surface Templating Challenge

Surfaces have important roles as facilitators for multi-component self assembly, a crucial consideration if we wish to be able to control assembly of several different types of component with different functions.

The surface can play two key roles: (i) templating the structure of an adsorbed layer (which in turn can template additional layers such that the pattern of a surface can ultimately control later-by-layer assembly of three-dimensional arrays); and (ii) imposing kinetic inertness on a layer so that temperature-jump (annealing) techniques can be used to allow an assembly to form which is at a local but not a global minimum, and will remain that way under normal temperature conditions.

This overcomes two major problems associated with more conventional self-assembly in solution: how to control the spatial organisation of components, and how to obtain assemblies that do not have a thermodynamic minimum-energy structure. The work described in this section on modelling, measuring and understanding interactions of molecules with surfaces will substantially increase our ability to use the structure of a surface as a template for the combination of multiple atomic or molecular components.

Developments in Characterisation

For experiments to follow molecular assembly, we require surface characterisation techniques to be enhanced in resolution and extended from our current ability to examine the outer surface of materials to being able to probe sufficiently deeply to look at interfaces and defects within a material.

Among the challenges and required developments in this area are the following:

- Spectroscopy, diffraction and scattering – both neutron and X-ray – can be used to characterise surfaces, notably small angle scattering (SAXS, SANS) and reflectometry. It is also important that these techniques are adapted to examine our heterogeneous materials under “operational” conditions. We will necessarily be working with more complex multi-component materials, so data analysis and model building will have to become increasingly sophisticated to allow meaningful information to be extracted. With the availability of improved high-intensity sources (including synchrotron and neutron sources) together with more sophisticated and flexible sample environment, the experimental capabilities are evolving to allow these problems to be tackled. The associated data analysis methods must also evolve.

- We require not just analysis of the surface structure, but also to be able to use techniques such as scanning probe microscopy or surface processing techniques (e.g.

PEVD, CVD, etc.) to be able to manipulate and ultimately engineer surfaces with target properties by controlling for example adsorbate arrangements with atomic precision or manipulate surface reconstructions directly and selectively.

- Microscopy methods must also be applied to understanding how the surface characteristics template growth of structures. This will include both optical and electron microscopy, and again involves the examination of *in situ* growth processes, requiring real-time measurements. These time-resolved methods will enable the study of aggregation and growth of structures on surfaces. We must move away from integrated measurements to more subtle techniques in order to understand not just rates, but processes.

- Combinations of techniques must be used to allow the characterisation of self-assembled structure, composition and morphology across a range of length scales simultaneously.

Enhanced characterisation is particularly important in the study of the growth of biomaterials. Unlike, for example, drug molecules which often tend to crystallise around the stable or metastable polymorphic form that is achieved in the solid state, biominerals often pass through a state of amorphous solid or dense liquid as they form and the assembly processes are not well understood. The nucleation and growth of protein fibrils is similarly poorly understood.

Developments in Modelling

As is the case for other themes within the Grand Challenge, the greatest developments in modelling will come by linking the modelling methods which are used for at the different length scales: starting with quantum mechanical (QM) and molecular mechanical (MM) models moving upwards in scale through coarse-grained and meso-scale models of formulation behaviour up to computational fluid dynamics (CFD) for fluid flows in processing.

The accuracy of each scale of modelling can be improved by tying the models in to the experimental measurements of target properties and by cross-validating between length scales. We know that better models must be created – for example many models assume that all the particle surfaces have the same structure and properties. It is difficult to apply atomistic methods to complex molecules – but in order to move towards bridging these scales and tackling the modelling of the key physical properties we must recognise the value of semi-empirical models, particularly for use in the development of engineering processes.

As examples of the types of modelling methodologies that will be required, we have identified, for example, that squared-gradient theories for classical DFT must be extended from their use in liquids and smooth surfaces to be applicable for imperfect solid surfaces. It is also clear that modelling must be extended to cover not just liquid/liquid and liquid/solid systems but must encompass methods for adsorption of gases in porous media.

As yet we do not have good models of proteins on surfaces. The complexity comes about as both the protein and surface are heterogeneous objects – the surface will not be self-identical over its area and the biomolecules have several degrees of freedom. Conformational changes can take place on a range of timescales. DFT cannot cope with the scale of the system; atomistic models could, but need parameterising to accurately represent the protein-surface interactions. It is challenging to measure and understand what

is going on as measurements average out to heterogeneity. We need instrumentation with better spatial resolution so we can observe and measure the protein orientation on the surface.

A key target is the development and application of modelling approaches for transport properties and non-equilibrium situations (non-equilibrium molecular dynamics NEMD, dissipative particle dynamics DPD, lattice Boltzmann LB, etc.) where the parameters in the models are obtained from the microscopic description of the material either at the QM or classical level.

Another big challenge is understanding dissipative self-assembly – structures which are created by energy dissipation in living organisms – *i.e*., systems which are not in equilibrium. These can be understood as a sequential minimisation of entropy – an approach which could be adapted to synthetic systems

Developments in Engineering
Through better characterisation, understanding and prediction of surface properties, we will be able to control microstructures within a range of materials including molecular crystals, complex fluid formulations and polymeric materials, and understand the link between the microstructure surface properties, the rheology and stability of the phases and how these change with physical parameters such as salinity and temperature. This improved control will allow chemical engineers to design improved processes. For this we will require: rheological data, kinetics, to develop non-equilibrium and mixed-phase mesoscale and CFD models.

Controlled formulation for efficient oil extraction.
When there is insufficient natural pressure to bring oil to the earth's surface, enhanced oil recovery techniques are used often including the injection of water at high pressure with other components such as surfactants. Understanding surface forces is vital for such a process: at the solid/liquid interface they control wetting of the rock and release of the oil, at the liquid/liquid interface they control the interaction of the oil and pumped fluid. The microstructure of the surfactant micelle surfaces controls the rheology of the flowing liquid under different pressures, temperatures and salinities which can be used to control the flow through the assembly and disassembly processes.

There is a pressing need to reliably design optimal formulations and their scaled-up manufacturing processes. We must develop new approaches, such as those envisaged in Theme 5, as well as new modelling techniques that span across multiple length and time scales. At the macroscopic or continuum scale multi-phase computational fluid dynamics models can describe, for instance, complex flows in continuous or batch formulation vessels driving process design decisions. The parameters entering the CFD models can be obtained from coarse grained and/or atomistic models at the microscopic scale describing component interactions at their interfaces and predict complex fluid properties at the output or during process evolution.

Liquid crystalline (LC) states with varying degrees of orientational and positional order can be designed by controlling the temperature (thermotropics) and/or composition (lyotropics) of the formulation. The link between the composition of the LC formulation and its properties offers both great challenges and opportunities in terms of designing ordered materials in a broad range of industries including the personal care, pharmaceutical, food, and oil exploration sectors. The key challenge is the extreme sensitivity of the structural,

thermodynamic and rheological properties of the material to the precise details of the molecular chemistry.

The Capability Roadmap

Community concerns expressed about developing capability in this area are around training and staffing issues and ensuring support for **fundamental** cross-disciplinary research is available.

Research problems in this area are very complex – we cannot jump to the top of Everest in one leap, but must progress step-by-step. Small, focussed projects addressing specific problems are vital before more complex systems can be understood. These could be explicitly supported through network funding of cross-disciplinary projects, of around a year, combining the expertise of network members across institutions. An alternative model sets these as individual milestones part of a much larger structured programme which provided the multi-disciplinary environment required within a real or 'virtual' centre – perhaps created by a multi-institution platform grant.

PhD students are very valuable in driving this area forward by carrying out cross-disciplinary research, but there is a concern about localisation – with single-site Doctoral Training Centres students may be continually focussed on the same single-discipline problem within the training environment. With a virtual DTC a greater range of research problems could be addressed, drawing on a multidisciplinary range of supervision, whilst maintaining the quality of the training.

A Collaborative Vision

Throughout this theme, the emphasis is on collaborative working:

- linking together experiment and theory is absolutely vital to a deeper understanding of surface processes and developing enhanced prediction;
- the same problems of understanding processes at interfaces occur in biological materials, organic and inorganic materials, working across these research communities can help share insights;
- cross-boundary working between chemists and physicists, particularly polymer physicists, will enable the transformation of models of interfaces, defined by macroscopic physical coefficients, into those based on a deep understanding of molecular forces;
- enhancing the overlap between the catalysis community and quantum chemists will benefit both disciplines facilitating the cyclic feedback as the two communities work together on solving common problems – putting relevant quantum chemical knowledge into real catalytic systems;
- connections with chemical engineers will help scale-up into process design which, in the long-term, will help cross the 'valley of death' identified between academic research and industrial uptake.

This is where Manufacturing for the Future will come from – the science base, particularly through the combination of expertise across disciplines, will generate innovation for UK plc. Fundamental research in this area is upstream of IMRCs and will feed into them for ongoing implementation into industrial processes.

Science & capability development to match onto product roadmap

Where are we now?	Short term	Medium term	Long term	Goal
Understanding of bulk phase behaviour and basic solid-liquid surfaces. Empirical description of solubility and dissolution.	Prediction of solubility for different solid forms in common solvents - experimental input of the heat of fusion (and its temperature dependence) and the melting point of the solid.	Predict of solubility for arbitrary solid formulations in solvents. Improved measurements of dissolution rates. The development of predictive approaches that go beyond the classical nucleation theory. Steady-state theories.	Understanding and prediction of dissolution in conditions far from equilibrium.	Bioavailability and targeted drug delivery (pharma sector).
Largely empirical or phenomenological of fluid interfaces and structured liquid formulations	Prediction of the fluid phase behaviour and interfacial. The link between chemical structure and the fluid microstructures.	Prediction of the microstructure from force fields developed for the bulk fluids. Understanding and modelling the link between the microstructure and the transport properties and rheological properties in the fluid.	Non equilibrium properties of the formation of glassy structures and gels.	Smart design of complex fluid formulations with targeted properties (e.g., personal care products and oil exploration fluids).
Characterisation and understanding of polymeric functional materials and surface coatings	Detailed experimental characterisation at the nanoscale. Basic physical understanding of the physics of the systems.	Link the physical understand with the chemistry of the functional materials and the processing conditions. Controlled surface templating.	Model the kinetics of the phase separation and spinodal decomposition to control the bulk and surface morphology. Model the non-equilibrium processing of polymeric surfaces.	Design of surface coatings with targeted properties (wide range of industries).
Surface-templated and controlled self assembly is in its infancy	Ability to form monolayers on surfaces with predictable structures but containing two or more components.	Rearranging components of monolayer using temperature-jump techniques to give kinetically stable non-thermodynamic-minimum assemblies.	Using the first layer to template adsorption of the second layer using different components in a different layer structures.	Stepwise fabrication of 3-D devices by layer-on-layer build-up of atomic or molecular components whose functions interface to give an emergent property.

Theme 5: A Roadmap for Developing Self-Optimised Chemical Systems through Self-Evolution

The Grand Challenge Vision of Theme 5

Our aim here is to develop entirely new scientific and engineering frameworks, borrowing ideas from naturally-occurring systems in the design and manufacture of new materials with arrays of sophisticated properties and function.

We will revolutionise manufacturing of such structures, by means of developments described within this theme, through the creation of methodologies and technology platforms mirroring the control, reliability and scale by which such naturally-occurring systems are produced.

Such developments will lead to game-changing, robust production systems able to manufacture consistent end products from variable feedstocks, creating flexible and resilient industrial processes with the ability to transform manufacturing in both the developed world and emerging economies.

We will explore how these rules, and evolution itself, can be applied to matter, to design and assemble soft and hard materials at market scales leading to highly-optimised, compliant, products.

We envisage that self-evolving materials can lead to innovative and intelligent manufacturing pathways exploiting dynamic conditions far from equilibrium.

We also aim, like nature, to harness the coding power of DNA and other biological molecules to drive assembly reactions, to capture information about conditions the reacting system passes through and to optimise the material output for particular conditions.

The Science Challenges

Introduction

It is first useful to explain how we might evolve materials with useful properties by replicating natural processes.

We make new materials to serve some particular purpose, so we are interested in how function arises from molecular or bulk properties, i.e. what materials do. Many useful functions of matter at the microscopic level depend on molecular structure, whilst more sophisticated functions or bulk properties depend on the arrangement of multiple types of molecular component. However, we currently do not possess a full understanding of the relationship between structure and function, nor are we able to exercise the precise control required to reliably assemble matter with the sophisticated functions we require to address the challenges we face.

In contrast, biological and naturally-occurring systems exhibit precisely this capability. They create complex assemblies with a rich variety of associated functions, reliably reproduced at large scales. Nature has created such sophisticated ‘machinery’ through the process of evolution.

Evolution takes place by the application of relatively simple rules, primarily at the molecular level. These rules are:

- reproduction,
- variation, comprising of two operators - mutation and crossover,
- selection.

Natural evolution is an adaptive process in which fitness to the environment drives the selection of those species with compliant phenotypes (function) that have sufficiently varied their genotype

(structure). Phenotype space and genotype space are related by means of complex mappings. The process in genotype space takes place in an environment that provides the right conditions enabling reproduction and variation. It is debatable at the moment whether reproduction and variation are properties of matter, or whether it is the environment which is exclusively responsible for enabling both to take place. Selection takes place in phenotype space and it can be conceived as a function that assesses fitness for compliance. This process always leads eventually to optimised, i.e., highly-compliant to the environment, structures and is dynamic, taking place under non-equilibrium conditions.

Learning from this natural process we can address three challenge areas in this theme.

1. The construction of the environment to drive self-evolution by directing an arbitrary chemical system within a fitness landscape towards some value representing a desired property or function. Potentially any material can be automatically discovered and assembled with this approach which, in effect, enables the simultaneous discovery of the manufacturing process too.
2. Like nature, we wish to be able to create 'intelligent' chemical building blocks that have the rules of evolution embedded. Upon certain environmental conditions being met, some signal received or simply specific building blocks brought together, the embedded reproduction and variation rules are activated.
3. How to robustly, and at commercial scales, exploit the molecular machinery nature uses. We need to be able to encode the design of the material and its assembly process in DNA and use that machinery to synthesise the material from available building blocks in the surrounding environment.

Meeting those challenges entails answering the following questions:

- Can we evolve the assembly of a material with a desired property, without understanding how its structure and property are related?
- Can we replicate nature and produce materials through naturally-evolving systems with embedded 'intelligence'?

Evolving materials towards target properties

Just as, in natural evolution, phenotype space relates to genotype space by means of a poorly understood complex mapping, so structure/property relationships in materials are also insufficiently understood. That leads to an interesting debate over whether it is actually necessary to understand the structure/function relationships in the process of assembling functional materials. It is not *strictly* necessary to fully understand the relationship. It is the property, i.e. what the material does, that we are interested after all.

Therefore, one goal is to explore whether, by providing altering conditions, we can cause sufficient variation to the material structure such that we direct the chemical system within the fitness landscape to comply with a value of the physical property we are interested in. It is also necessary to explore whether we can then do the same for a range of molecular or bulk properties.

For the first class of challenge listed above, we wish to design and make a new material either completely theoretically, by applying the multiplication, variation and selection rules testing on the fitness completely *in-silico*, or practically, by combining model-based algorithms with suitably-designed reaction systems. Testing for fitness by means of property measurement probes radically differentiates this approach over conventional high-throughput discovery methods. This feedback drives selection and control of process parameters and, in combination, directs the system within the fitness landscape. The desired property is obtained by the material with the best fitness value. At the same time the process parameters are obtained.

A new scientific framework for manufacturing

The time and effort required to design and bring new materials to market is currently immense. What is required is an entirely new approach with an end goal to be automated and model driven, in contrast to existing high-throughput approaches. Such a production capability will be game-changing as it will revolutionise material assembly in the same way that numerical methods revolutionised mathematics.

For example we can consider evolving a material towards a target property of interest, such as a specific shade of blue, by directing a physical reactor through assessment of the output in terms of fitness parameters – closeness to the required colour – and feeding back control instructions to vary the reaction environment. This will have impact across the whole chemical manufacturing sector.

An evolving systems methodology can enable not only the discovery of unknown materials and their manufacturing process but also the discovery of optimal assembly processes for known materials. This methodology can also lead to greater understanding of structure/property relationships.

The fitness landscape can be defined by single or multiple parameters translating to multiple properties or complex function. Fitness parameters can include bulk properties of the assembled materials, such as compressibility, particle size distribution or even scale-up considerations or manufacturing cost, resolving manufacturing-related issues. One challenge here is whether the processes can take place concurrently in the same reaction vessel.

Even if we are successful in creating our desired functional material in this way, then we have not furthered our knowledge about the creation of the material including details of the assembly mechanism, thermodynamics or structure/function relationships. To progress the understanding of both products created and process-space explored, detailed data capture during the iteration process is vital. With theoretical models, capturing the intermediate stages is reasonably straightforward, but with experimental systems new instrumentation is required to monitor the assembly process, i.e. developing fast, time-resolved techniques for monitoring the process at each iteration observing, for example, metastable states, or capturing sufficient data to feed theoretical models.

These models also test and evolve the systems based on current conditions, rather than past knowledge. It is possible we can improve convergence time by combining the two, perhaps by computationally-predicting useful starting conditions.

We can thus outline the issues that must be addressed in this challenge area:

a) Design of reactionware within which the conditions for material evolution can be delivered, be it continuous or batch, or more exotic - borrowing from 3D printing technology and additive manufacturing, applicable to any phase of matter.
b) Developing computational methods to screen *in-silico* for feasible options as starting points to effectively direct the process within a physical reactor system
c) Developing the control algorithms to run the reactor systems.
d) Developing a range of property probes to feed back to a fitness function.
e) Developing new types of real-time analytical tools for time-resolved and *in-situ* measurement and monitoring for feedback control and process understanding

Developing such evolving systems methodologies and platform technology could have huge impact on future manufacturing both for improving the production of existing materials and for creating entirely new ones.

As examples, consider manufacturing:

- known fuel products with fixed characteristics from variable feedstocks, an evolving reactor would simply adjust itself, and the process within, to cope with the variation;
- alternative materials with substitutes for rare or under threat elements;
- new materials with optimised characteristics, such as better porosity for CO_2 uptake;
- new opto-electronic materials with specific and tuneable band gaps;
- efficient photovoltaics that absorb across a range of wavelengths and emit at one wavelength;
- personalised healthcare: optimise formulation, preparation and delivery of drugs tuned to the needs of individual patients;
- process robustness adjusting to variations in input quality for manufacturing.

Learning from naturally-evolving systems

For the second challenge we aim, like nature, to create matter that is intelligent enough to control itself without needing the assistance of algorithms or to be embedded into an engineered system such as a reactor. The natural processes we consider here include the manufacture of proteins by using 'molecular machines' to read the information contained within DNA and (self)assemble the required components from the surrounding environment.

Unlike the evolving reactor systems described above, here our manufacturing machinery is on the same molecular scale as the output products – the reactor and products are combined.

In fact nature itself does not necessarily embed all the required 'intelligence' into the system – external stimuli can also trigger changes through changing reaction conditions and epigenetics. Collaboration with biologists studying this field will bring about a greater understanding of these processes and how we might develop analogues in non-biological systems.

Evolving Biomimetic Bacteria

The role of bacteria is essential to the majority of life cycles on Earth and is, of course, the result of natural evolution. A huge challenge is the controlled evolution of biomimetic bacteria based on non-carbon feedstocks. The long term challenge is to create self-replicating evolving inorganic systems that can be used in a controlled manner in medicine and chemistry. Such inorganic systems would extend the potential range of properties exhibited by their natural counterparts because of the ability to build in additional functionality such as metal-based redox activity.

One goal is a better understanding of how to encode manufacturing information into DNA and other biologically-based coding molecules. Artificial DNA is now commonly created, even undergraduates have the opportunity through summer schools to design new genes to synthesize molecules.

As with Theme 3, we can study how natural enzymes drive reactions and perhaps use them to inspire new catalysts to speed up manufacture within these evolving reactor systems and make processes more selective.

We may even be able to use the coding potential of DNA to capture the conditions within the reaction, to fulfil the same requirements as the in-situ probes for the evolving reactors described above. A key challenge however here is how to enable such naturally inspired processes to take place rapidly leading to reduced time to innovation and time to market as well as eventually deliver market scale quantities.

The Capability Roadmap

Approaches that are algorithmic and based on evolutionary computation are not widely used in chemistry and materials science at present and could have a much greater uptake in the community.

Opportunities for training or cross-disciplinary workshops, facilitated by the Directed Assembly Network, could enable a wider use across the community.

Within evolving process it is essential to develop methods for sampling the dynamic environment as the process evolves, through multi-property measurements. In this way this information can be fed back into the computation to calculate fitness of members of a population at each iteration and enable selection and control of fittest candidates for the new generation in the next iteration.

For successful evolutionary processes to occur, that is to converge quickly and efficiently to populations with the fittest members within the fitness landscape, it is vital to utilise as much initial information as inputs as is available. In order to maximise this, the access to current knowledge by means of integration of databases that contain physical and chemical data into the iterative decision making events is crucial. Much work needs to be done gathering physical and chemical information from multiple databases around the world (both academic and commercial) to achieve this, or intelligent search engines capable of assimilating relevant information quickly and effectively need to be developed.

Also key to the control of the evolutionary processes is the ability to use multiple measurement techniques simultaneously in order to monitor the evolving properties and rapidly provide information to direct the subsequent steps of the process towards the designed target. Here, the development of multi-purpose probes and new in-situ and on line analytical tools must be developed.

A Collaborative Vision

This is a new area of research and is not yet well explored. It is also extremely challenging and highly interdisciplinary, requiring integration of knowledge from a variety of domains, ranging from manufacturing and chemical engineering, through systems and computer science to materials science. chemistry and mathematics.

The evolutionary algorithms discussed can be very computationally-intensive and may require many thousands of iterations to reach an optimised end point. Thus it is useful to combine them with other methods of reducing the explored parameter space. For example, new types of predictive models that can screen options quickly *in-silico*, coupled with physical material assembly and process scale-up platforms are essential. Coupled together, testing of a smaller number of more likely options predicted *in-silico* can be done rapidly and automatically. Furthermore, sensitivities can be explored and tested with such a coupled arrangement. Sharing of knowledge between chemical engineers, chemists and mathematicians will ensure the best mathematical methods are adopted into the manufacturing systems, in the most appropriate ways.

As with Theme 3, working across the boundary with biology will develop a greater understanding of the molecular-bonding processes optimised through natural evolution, enabling these to be brought into our production systems.

Developing these evolving reactor systems will be game-changing for UK manufacturing. It will require close collaboration with instrumentation and sensor manufacturers, to gain a better understanding of flow processes and with producers within the chemical sciences sector to enable scale-up.

Table showing science & capability development to match onto product roadmap

Where are we now	Short term	Medium term	Long term	Goal
Demonstrated experimentally computer directed assembly of a complex molecular cluster by selection and control of a single physical property in flow conditions	Development of computer directed reactor platforms that by the selection and control of flow conditions in liquid phase can reliably evolve a variety of materials with multiple user selected properties	Development of computer directed reactor platforms that by the selection and control of flow conditions in solid or gas phase can reliably evolve a variety of materials with multiple user selected properties	Extend the development of evolvable platforms with multi phase multi property capability	Evolvable product and process design of complex, multi-component structured materials with application specific properties. A platform for future manufacturing A brand new scientific framework for the rapid design and scale up of new multi-component materials
Currently we debate whether evolution is a property of matter and can indeed embed the rules of evolution in non-biological material to allow it to self-evolve. The fabrication of hybrid inorganic chemical cells at the liquid-liquid interface has been demonstrated experimentally	Develop molecular building blocks confined within controlled environments that are separated by membranes can upon external triggers and the controlled passage of materials and energy allow sequences or reactions to take place		Develop libraries of such building blocks with targeted functionality and selectivity	Non-biological evolvable matter
Currently we have a range of analytical techniques which are mostly off line and can measure one property at a time. They are expensive and cannot take concurrent measurements	Evolve data analysis methods and develop physical interfaces to current analytical instruments to collect multiple measurements for feedback control and fitness assessment	Develop multi-property probes for in-situ and online measurement of physical properties such as rheology, particle size and size distribution etc. Develop multi-parameter probes capable of a range of techniques concurrently including spectroscopy, diffraction, scattering etc to monitor in situ and in a time resolved manner assembly processes		Advanced analytical tools for rapid, in-situ and online monitoring and assessment of multiple properties concurrently
Limited number of DNA-based directed assemblies	Developed complex DNA-based directed assemblies	Develop bacteria mimics	Combine bacterial and non-biological assemblies.	DNA-based evolvable matter

Recommendations

In the previous thematic sections we have described the current state-of-the-art and routes to progress in the Directed Assembly Grand Challenge area. Those progression routes cover a vast research space and the picture thus developed could be thought of as being gathered by the Directed Assembly Network in its formation and divergent information-gathering phase. We sought out and engaged with a wide community; their input has helped us define the key areas and identify the key issues that form our Grand Challenge.

We view the desired goals within this research space as a "many-pointed crown". Each of the targets achieved is of great value in itself, as well as helping progress along the road to our ultimate goal – that of being able to *predict and control the assembly of matter with sufficient precision to be able to design and fabricate materials with any required function and property*.

In the second phase of the Network we turn from divergent information-gathering towards convergence on research targets, by driving forward the science that underpins the short, medium and long-term goals listed in each theme.

We summarise our research recommendations below, relating how EPSRC might support the envisioned progress within its own current priority areas of Manufacturing the Future, Healthcare Technologies, Energy and Living with Environmental Change. We give examples of well-defined areas suitable for calls and/or signposting, and within which smaller, focussed projects can drive progress. We also list other areas in which the Network can coordinate feasibility studies and pump-priming projects, from which future, larger collaborative projects can be developed.

It should be pointed out that, although these are scientific priorities distilled by the Network Champions from wide community input, our promotion of these does not imply rejection of other projects. We hope this document has shown that progress in this area is not simply a linear 'roadmap' progressing in an easily-defined manner from A to B; it is instead a research landscape through which many paths can be taken and where breakthroughs can be made on many fronts. Other teams may wish to drive trails through the space in different ways.

We also make recommendations on structural issues which have arisen time and again in the community discussion meetings across all themes. Best progress in the Grand Challenge will be made by freely sharing knowledge amongst appropriately-trained researchers who are able to draw on the best available data, the best experimental techniques and theoretical methods in their work. We discuss how this could be achieved by putting in place appropriate supporting measures.

Summary of Individual Theme Recommendations

As described in earlier sections, the main scientific areas that are recommended for development within each theme are

From Theme 1:

- control of multi-component self assembly in solution, on surfaces or in crystals
- understanding emergent function and structure / functional relationships

From Theme 2:

- development of nucleation, crystallisation and dissolution methodologies
- knowledge-mining methodologies for making more of existing data (also applies to other themes)

From Theme 3:

- a better understanding of complex biological functional materials
- development of bioinorganic chemistry

From Theme 4:

- control of processing conditions for templating and surface coatings
- design of solid formulations for targeted and controlled delivery

From Theme 5:

- development of intelligent reactors for synthesising and fabricating new materials
- development of analytical techniques (also applies to other themes)

Other Cross-Theme:

- development of multiscale modelling methodologies

Areas for Potential Calls or Signposting

Through the course of discussions with the Network membership we have identified several key areas that are ready for potential calls or signposting, and in which significant progress can be made over the next 5 to 10 years. The Network believes that these areas are ripe for immediate action by EPSRC to maintain and enhance the momentum generated by the Grand Challenge activities. Supporting large projects within these identified areas will allow the considered community recommendations outlined in the previous sections to drive EPSRC's strategy and portfolio development. Smaller, focussed, pump-priming projects, targeted at breaking through individual barriers to progress in these areas, may also be appropriately funded under a continuation of Network through the NetworkPlus model or through an analogue of the Knowledge Transfer Account.

Development Of Intelligent Reactors For Synthesising & Fabricating New Materials

This area arises from discussions around Theme 5, on evolving systems. It falls primarily into chemical and chemical engineering disciplines, supported by the mathematics of evolutionary algorithms. The evolving systems methodologies described, working with both adaptable reactor designs and evolvable molecular assemblies, could be used in an iterative, intelligent assembler system to produce new materials with pre-designed properties.

As well as linking closely with the Manufacturing the Future EPSRC priority, promoting this area will strengthen the ties across the chemistry/chemical engineering interface, as recommended in RAE 2008, by building upon and extending work funded previously across this boundary and adopting IDEAS Factory outputs such as the CHELL project.[e]

Nucleation, Crystallisation & Dissolution Methodologies For Making Better Pharmaceuticals And Agrochemicals, Faster And More Efficiently

This suggestion arises from discussions in both Theme 2, covering nucleation and crystallisation, and Theme 4, covering dissolution, and would drive progress in EPSRC's Manufacturing for the Future and Healthcare priority areas.

We envisage chemistry and biology-centred projects using directed assembly techniques to produce and deliver active reagents, drawing on an intimate combination of modelling and experiment. This approach gives strong complementarity in tackling the fundamentals of crystallisation, including in more dynamic environments. A key task will be the design of targeted delivery strategies involving the solubility of the formulation, the kinetics of dissolution, and the triggering of these effects with chemical and physical factors.

Work in this area offers strong and distinct complementarity to the recently-established EPSRC Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation

(CMAC) in which Network members are heavily engaged. This area provides added value by driving the underpinning research that fits into CMAC's more targeted work on crystallisation under flow. It also builds on the success of RCUK basic technology projects, such as those supported through the CPOSS Network.

Theme 2, and the complementary work in Theme 4, have the most immediate and evident industrial engagement of all the Grand Challenge areas, reaching beyond pharmaceuticals into a range of functionalised materials. The academic research outlined above is critically important in underpinning the future development of UK fine chemical and pharmaceutical manufacturing industries.

Developing A Better Understanding Of Complex Systems Of Biological Functional Materials

This area, emerging from Theme 3's discussion of biological and biomimetic systems, combines work across the boundary of chemistry and life sciences.

We envisage projects that involve enhancing understanding and developing new directed assembly techniques for producing designed templated or biomimetic functional soft matter, typically in aqueous or water-rich solutions.

Such materials could be employed, for example, for growing organs on demand. Predictable self-assembly (or self-manufacturing) of nanoparticulate complexes containing patient-specific combinations of biologically-active compounds allows targeted medical intervention. Other uses of functional, biological hybrid materials are in biosensors, creating links to medical technology and the manufacturing of medical appliances.

The development of compatible strategies for the delivery of food, biofuels and biorenewable commodities similarly requires an understanding of the interactions between biopolymers, as well as their processing through chemical and biological means. This in turn will drive the development of biotechnology and food technology industries.

This work thus helps promote EPSRC's Manufacturing for the Future and Healthcare priorities and complements activities in the new EPSRC Physics of Life Network and BBSRC's Synthetic Biology Networks.

Hybrid Materials For Environmental & Catalytic Applications

This is another initiative working across the chemistry and chemical engineering boundary and emerges from Theme 1's analysis of molecular frameworks and hybrid materials.

Projects in this area will enable the development of "smart" hybrid materials that can, for example, abstract specific gaseous pollutants from exhaust flues and, within the same material, engender chemical processes to convert these gases to useful chemical feedstocks.

Similarly, projects could be targeted on the design of hybrid materials containing dynamic catalytic centres to facilitate a series of chemical processes within a single material or on dynamically-evolving materials to generate reagents for the chemical industry. Materials to be developed include both nanoscale arrays, formed by unit-cell by unit-cell assembly processes, and molecular assemblies.

These projects promote EPSRC's priorities of Manufacturing for the Future, by providing low cost, energy-efficient catalytic systems to drive more effective manufacturing, and Living with Environmental Change through reducing environmental pollution.

Developing Strategies for the Design of Soft-Solid & Fluid Formulations

This area emerges from Theme 4's discussion of how the interfaces between the various components of a formulation control its overall behaviour and properties.

Projects here involve the control of the morphology of the nanoscopic aggregates and microphases (micelles, lamellar phases, gels, etc.). A key target will be developing an understanding of and being able to predict the link between the structures of the aggregates and the kinetics and rheology of micellar aggregation in liquid formulations.

Applications have relevance to the future manufacturing of, amongst other examples, personal care products, food, drugs and smart drilling fluids.

Polymeric Films & Templating

This is another area arising from Theme 4, particularly the discussions around the potential of surface templating.

Projects studying the control and design of microstructures and the properties of polymeric films and other organised surface phases will be key to being able to control the function of surface coatings. This will enable directed design of the processes and products where surface interactions play a key role.

Fundamental Science Topics For Further Development

These topics are wide-reaching areas of great potential and, at this stage, our recommendation is for targeted efforts facilitated through continuing and enlarging the Network's activities. We believe the allocation of an appropriate level of follow-on funding to the Network could be deployed in flexible and cost-effective ways, delivering rapid progress in developing these topics through feasibility studies and pump-priming projects.

Smaller studies could be supported via the NetworkPlus model, but more significant work could be funded via the Network in an analogous way to that in which Knowledge Transfer Account money is used to fund collaborative pump-priming business development projects in Universities. Projects funded through follow-on Network funding could drive Fellowships for development of links amongst the academic community and with industry, or form foundation work for larger, focused proposals for making progress in specific areas. They will hence help steer research rapidly to maturity to feed into EPSRC priorities in a timely manner.

The Development Of Multicomponent Systems

Most functioning chemical and biological systems are made up of three or fewer active components. This focus topic, based in the research space of Themes 1 and 3, will progress the fundamental science that will allow for controlled development of systems containing four or more components. This will facilitate the development of new material properties that may evolve hierarchically as the length scale changes.

The Development Of Bioinorganic Chemistry

This focus topic, based on work in Themes 1 and 3, involves the expansion of biological processes to non-carbon based systems (sometimes referred to as 'inorganic life') and to the manipulation of metal-based systems within the biological regime to produce new functioning systems.

Knowledge Mining Methodologies For Making More From Existing Data

This focus topic draws from right across the physical and life sciences, pulling together disparate information from databases, to produce an interactive, comprehensive source of physical data for theoreticians and experimentalists to use in the design of new materials. This area underpins not only development in all the Grand Challenge Theme areas but also the key EPSRC priorities of Healthcare, Energy, Manufacturing and the Environment. Such a project may also draw collaboratively on expertise within EPSRC's IT programme or from other funders, such as JISC.

The Development Of Modelling Methodologies

Multiscale modelling across all length scales is essential if the planned design of new materials with desired properties is to be achieved. It underpins progress across the whole of the Grand Challenge and wider fields of research.

Electronic and atomistic methods for molecular systems and coarse-grain modelling for dealing with macroscopic systems are developing, but there need to be major improvements in *meso*-scale modelling if a key area of materials design is to be addressed. Developments at all scales must also be coupled closely with experimental efforts; to design both process and product reliably requires a fully-integrated approach.

This is a huge aspiration, which encompasses major areas of engineering and physical sciences, including mathematics and ICT, so these efforts must be staged to be manageable. We first need to ensure that modelling methods are available to reliably predict properties for related systems and difficult-to-measure properties and that they are properly understood by the communities adapting them for use in their areas of interest.

The longer term goal must be to integrate all the available modelling techniques for the range of properties required and to define the acceptable loss of accuracy induced by method choice. To achieve this requires closer collaboration between the electronic, atomistic and coarse-grain modelling communities. Experimentalists from the areas of chemistry, materials science and chemical engineering also need to be engaged closely in the process to ensure stringent validation. This is where the Network will be invaluable in building on collaborations already formed under its aegis and in bringing new groups of people together.

The Development Of Analytical Techniques, Particularly For Simultaneous Measurement Of Different Properties.

Whilst experimental methods for analysing materials across a range of length and time scales have developed considerably over the past decades, a major drawback remains. These measurements are generally made on different samples of the same material at different times and under different conditions.

If the assembly process is to be explored in detail and a full understanding developed, it is essential that methods are improved so that a range of analytical measurements can be made *simultaneously* under the same experimental conditions. It is important that comprehensive local and time-dependent measurements are made, as well as ensuring correct part of sample is analysed.

Pump-priming projects for developing these techniques will drive forward progress and understanding across all the Grand Challenge Theme areas and beyond.

Structural Recommendations

To deliver the potential of the research areas identified by the Grand Challenge Network requires a range of actions with different levels of funding and over different timescales. Some of these, involving targeted calls and pump-priming research projects, have been outlined above. However, other structural activities, for example facilitating knowledge transfer and skill development through simple exchange schemes, will also be beneficial to driving progress across the whole of the Grand Challenge research space. To this end, we recommend:

- The provision of ongoing Network funding, using EPSRC's NetworkPlus model. This will facilitate collaborative work not just by providing opportunities for classical networking activities and sandpits, but also allow short-term inter-institution visits, follow-on funding to help embed new skills and knowledge in collaborating institutions and small, focussed projects in well-defined areas;
- Additional funding to be provided to the Network in the form of a "Research Primer Account", to be managed in analogous style to Knowledge Transfer Accounts. This will enable short-term pump-priming and feasibility studies, of up to a year, to be funded by the Network in member institutions in an agile and timely manner, to drive progress through knowledge-sharing and research, and facilitate the development of larger projects;
- Investigate the availability of existing measured data across academia and industry and scope the possibility of a shared database project, perhaps guided and funded through JISC or one of the national database centres;
- Whilst the research recommendations outlined above will help the current generation of researchers drive forward this field, there is a deep concern within the community about how the necessary range of skills will be embedded in future generations with the currently-available training opportunities. We therefore recommend that suitable schemes are put in place to train researchers in the Directed Assembly area for the future, by developing a Doctoral Training Network or Centres;
- The creation of a National Centre for Self-Assembly and Functional Materials, whether by forming a virtual institute through combining complementary skills from different institutions or co-locating researchers with equipment and support into a dedicated space.

Conclusions

We have shown how immensely valuable the societal impact of learning to control molecular assembly is, and will continue to be over the coming decades. Breakthroughs will advance areas currently challenging society – finding alternatives to scarce resources, assisting an aging population and developing highly energy-efficient, low environmental impact modes of living.

We have also described how ongoing economic prosperity in the UK is critically dependent on having a competitive, high-tech manufacturing industry. Some areas of the Directed Assembly Network's activities address barriers to progress in existing industries, others will create the transformative industries of the future. Other countries are already investing heavily in programmes to progress materials science; by adopting the recommendations in this roadmap, the UK can enhance its scientific capability and keep pace at international levels, develop absorptive capacity and retain the competitive advantage needed to be a world player in the field of future manufacturing.

To achieve these goals, we must build collaborative research programmes - drawing on the best of UK talent, absorbing knowledge from overseas and developing a multi-skilled, multidisciplinary workforce for the future. We must breakdown the structural problems that prevent research progress - building a cultural understanding between traditional disciplines, and between theory and experiment; overcoming the 'valley of death' between academia and industry, encouraging high-risk, high-return activities at all project scales.

Such breakthroughs are best supported through a flexible funding system that the community can choose to engage with at whatever level seems appropriate for a particular project, from exploratory discussions across disciplines, through exchange visits, targeted projects or large research programmes. We recognise that a significant amount of focussed, fundamental research needs funding, as well as more complex projects. We make suggestions here for suitable funding methods, but recognise that community views may evolve over time.

The main scientific areas that we feel are ready for project development through calls or signposted areas for EPSRC funding, and for smaller pump-priming activities targeted at individual problems within the identified research space are:

- Nucleation and crystallisation methodologies for making better pharmaceuticals and agrochemicals more quickly and efficiently.
- Developing a better understanding of complex systems of biological functional materials.
- Hybrid materials for environmental and catalytic applications.
- Development of intelligent reactors for synthesising and fabricating new materials.
- Developing strategies for the design of soft-matter and fluid formulations.
- Polymeric films and templating.

In addition to the above, we also recommend the following areas of fundamental science be supported through extension of the Network funding:

- The development of multicomponent systems.
- Knowledge-mining methodologies for making better use of existing data.
- The development of bioinorganic chemistry.
- The development of modelling methodologies, from better modelling of intermolecular forces through to mesoscopic processes and across different timescales.

- The development of analytical techniques, particularly for simultaneous measurement of different properties.
- The development of methodologies and fabrication technology to engineer surfaces with atomic or molecular precision.

To support and accelerate the scientific progress, we recommend that the following structural issues be addressed:

- Consolidate community building and & facilitate short-term projects through Network continuation under the NetworkPlus model.
- Provide agile funding for larger pump-priming projects of around a year's duration through an analogue to the Knowledge Transfer Account, managed by the Directed Assembly Network.
- Ensure schemes are in place to train the new generation of researchers in this area, including summer schools and Doctoral Training Centres or Networks.
- Facilitate training and knowledge transfer through short-term exchange schemes between academic institutions and between academia and industry.
- Facilitate sharing of existing data and fill gaps across industry and academia, perhaps through a JISC-funded project or via one of the national database centres.
- Create a National Centre for Self-Assembly and Functional Materials, whether in a single location or as a virtual establishment across several sites.

We, as the Network Management Team, are inspired by the transformative vision depicted in this roadmap document and look forward to facilitating the collaborative activities required to turn that vision into reality.

Paul Raithby – Principal Investigator
Harris Makatsoris – Co-Investigator
Niek Buurma
Lee Brammer
George Jackson
Sally Price
Kevin Roberts
Matt Rosseinsky
Mike Ward
Chick Wilson
Sophia Yaliraki
Jenny Woods – Network Coordinator

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References

a) Chemical Industries Association Campaigns Report 2010
http://www.cia.org.uk/Portals/0/Documents/downloads_pdf_27_Campaign%20brochure_Sept2010_LR.pdf

b) EPSRC International Review of Chemistry Report 2009
http://www.epsrc.ac.uk/SiteCollectionDocuments/Publications/reports/ChemistryIR2009.pdf
c)
http://www.whitehouse.gov/sites/default/files/microsites/ostp/materials_genome_initiative-final.pdf

d) Venter, 2010
http://www.ted.com/talks/lang/en/craig_venter_unveils_synthetic_life.html

e) Cronin, et. al. EPSRC Grant EP/G026130 and *Nature Biotechnology*, 2006, 24, 1203.