Directed Assembly Network

BEYOND THE MOLECULE

A Roadmap to Innovation

The EPSRC Directed Assembly Network

2017 Edition

EPSRC
Engineering and Physical Sciences Research Council

Directed Assembly Network

BEYOND THE MOLECULE

A Roadmap to Innovation

The EPSRC Directed Assembly Network

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2017 Edition

www.directedassembly.co.uk

"Our global scientific impact far exceeds our size as a nation, and our scientists and engineers stand tall on the world's stage." [1]

Jo Johnson MP
Minister of State for Universities and Science

"Through the EPSRC sponsored Directed Assembly Grand Challenge Network we have brought together over a 1000 academics and industrialists to form a community to tackle the grand challenges in chemistry and chemical engineering over the next four decades. The interdisciplinary collaborations are providing a new impetus in this research area and are making the UK the best place to develop innovative directed assembly techniques."

Professor Paul Raithby, University of Bath
Network PI
2010-2016

EXECUTIVE SUMMARY

The Directed Assembly Network, an EPSRC Grand Challenge Network, set out in 2010 to build a wide-reaching community of scientists, engineers and industrial members that includes: chemists, biologists, physicists, chemical engineers, mathematicians, and computer scientists, to name but a few.

This Roadmap has been constructed by the Network community over years of consultations and continuous engagement through: themed meetings, sandpits, Network awards (proof of concept projects) and strategic meetings. In 2010, the Network was tasked to look 20-40 years into the future, and to capture, short, medium and long term goals. Over the 6 years since its inception the Network has grown to over 1,000 members and hosts several highly acclaimed meetings each year.

Early career researchers are at the heart of the Network and benefit greatly from access to, and networking with our world-leading members, senior management team and Network Champions. The Network is now embedded into the culture of the UK landscape and continues to work at the leading edge.

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

The UK position and World challenges are set out in this Roadmap to highlight the importance that new materials provide when it comes to solving the *Grand Challenges* of this century. Challenges include: the development of medicine and implants tailored to each individual; the creation of green alternatives to scarce resources; discovering new energy sources; capturing pollutants; enhancing both crop production & the provision of clean water and developing exciting innovations, such as smart materials, new catalysts, organic computing and high-temperature superconductors that will transform society.

The Network has proven very successful in fostering this research, helping to maintain or propel the UK to the forefront of the research areas. £50 Million of subsequent grants are linked to and/or supported by the Directed Assembly Network.

The science is set out across 5 overlapping themes in this Roadmap, which encompass directed assembly and disassembly, and the translation and scale-up of the research towards manufacturing. Some examples of the Network-funded proof of concept projects are highlighted, showing advances in the short term goals set out in the 2012 edition of the Roadmap.

Areas for potentials calls or signposting, along with fundamental science topics for further development are discussed before structural recommendations are also made. Finally, conclusions and the Network Management team are presented.

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1. INTRODUCTION

1.1 UK Position and World Challenges

UK position:

"Today, for advanced nations such as the **UK** to prosper as knowledge economies, scientific **research is essential** – both to produce that knowledge and also the **skills and people** to use it." [2]

The foremost economic challenge facing the UK is the **productivity gap** and excellent research has been highlighted as crucial towards tackling it. [3]

World challenges:

- Antibiotic & drug resistance
- Increasing demands for energy
- Economic & political instabilities
- Depleting natural resources
- A changing climate
- An ageing and growing population
- Pesticide resistance and global food security
- Supplying clean water
- Epidemics and world health security

1.2 The Grand Challenge

New materials provide the key to solving these challenges through the development of:

- Bespoke medicines and implants
- Green alternatives to scarce resources & improvements in efficiencies
- Offering new energy sources
- Capturing pollutants
- Enhancing both crop production & the provision of clean water
- Developing new catalysts
- Research & innovation, leading to commercialisation
- And developing exciting innovations, such as smart materials, organic computing and high-temperature superconductors that will transform society

In 20-40 years, innovative manufacturing will enable us to **design**, **control** and **engineer** artificial and biological materials:

- Controlling manufacture from the molecular level upwards
- Harnessing and adapting methods from nature
- Drawing on advanced algorithms to run self-adaptive production systems

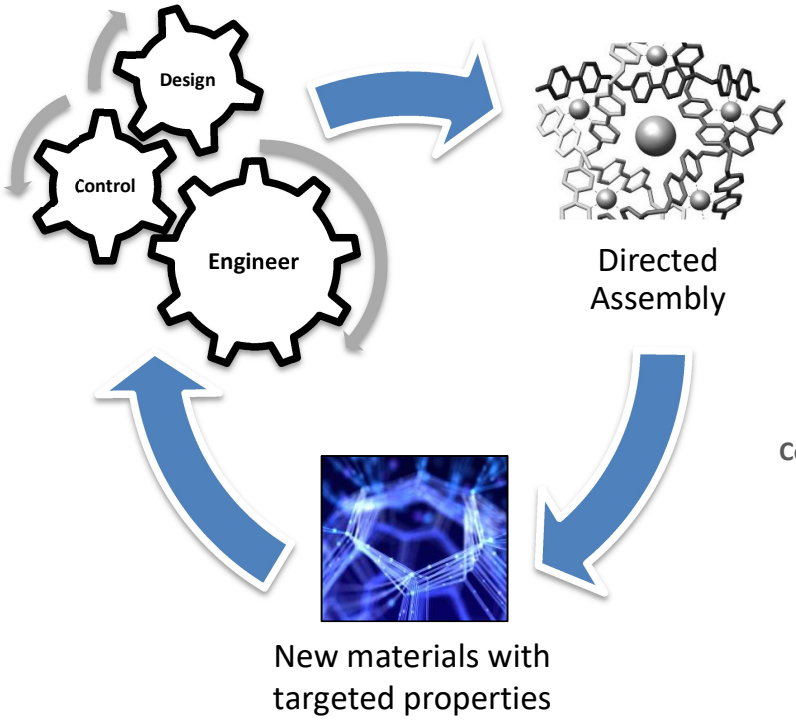


Figure 1 – Design, Control and Engineer

An inter-disciplinary community is vital to achieve such important breakthroughs:

- Our members have many areas of interest and expertise
- All share the aim of understanding and controlling intermolecular and supramolecular interactions to enable routes to synthesis of existing and new materials with bespoke properties

Leveraging the strengths of the UK's acknowledged world-class research areas, to combine knowledge across diverse scientific fields, is fundamental to success. The research communities and their end-users must be given opportunities to come together to develop adventurous joint programmes, encouraged to produce and share a grand vision of new technologies and to strengthen the expertise of all participants, particularly those at an early stage of their careers.

That is the Grand Challenge, and the role of the Directed Assembly Network.

"The data and track record we gained from the [pump-priming] project was instrumental in us securing an EPSRC grant"

Dr Paul Beales, University of Leeds, Network Member since 2012

1.3 The Importance of Understanding Assembly Processes

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 (RAE 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, structural chemistry, catalytic chemistry and the development of advanced functional materials.

- In industrial production, the Chemical Industries Association [4] 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 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 noted that 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 [5] 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

intermolecular 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.

"Network funding has led to a strong ongoing collaboration"

Dr Valeska Ting, University of Bristol, Network member since 2012

2. Network Overview

2.1 Vision

Recognising the importance of this research area, the 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 to draw up a roadmap to drive progress towards these goals.

Vision
The vision of the Network is to be able to 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, policy makers, the government and the general public.

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.

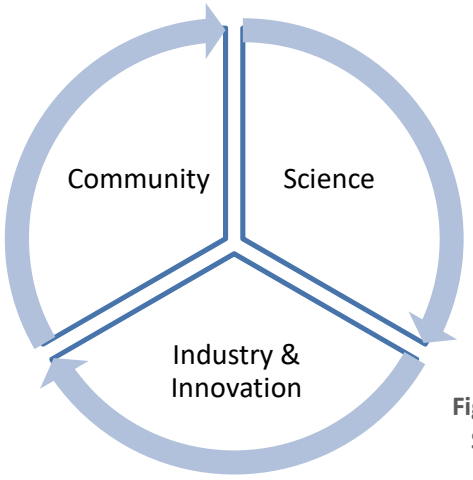


Figure 2 – Community, Science, Industry & Innovation

In this Grand Challenge we aim to gain unprecedented control of the assembly of molecules that are the building blocks of many functional materials, consumer and industrial products. We start by understanding the assembly of the very small, but methods we explore will allow production of new types of useful materials at a whole range of length scales from the nanoscale to the everyday. Such materials will have outstanding impact in areas of societal importance such as personalised healthcare and food production, clean and cheap energy, transport systems and fuel production, housing construction and consumer electronics.

Through this intelligent approach to design we will compete effectively with the USA, Japan and mainland Europe, as well as with the growing powerhouses of China and India, to place the UK firmly at the forefront of developments in the areas of manufacturing, healthcare and energy.

The added value that the Network provides is in gathering the widest group of internationally-leading expert scientists from across a range of disciplines in the UK, and providing them with a challenge, a focus and a vision that they help shape.

"The Network has succeeded in bringing together new PIs and successful senior PIs in a friendly and productive manner…

Everybody seems to be extremely open and excited about new ideas"

Dr Barbara Ciani, University of Sheffield, Network member since 2013

2.2 Directed Assembly Network

The Directed Assembly Network has nurtured and engaged a community of more than 1000 members consisting of chemists, physicists, biologists, biochemists, engineers, mathematicians, computer scientists and over 110 industrial members.

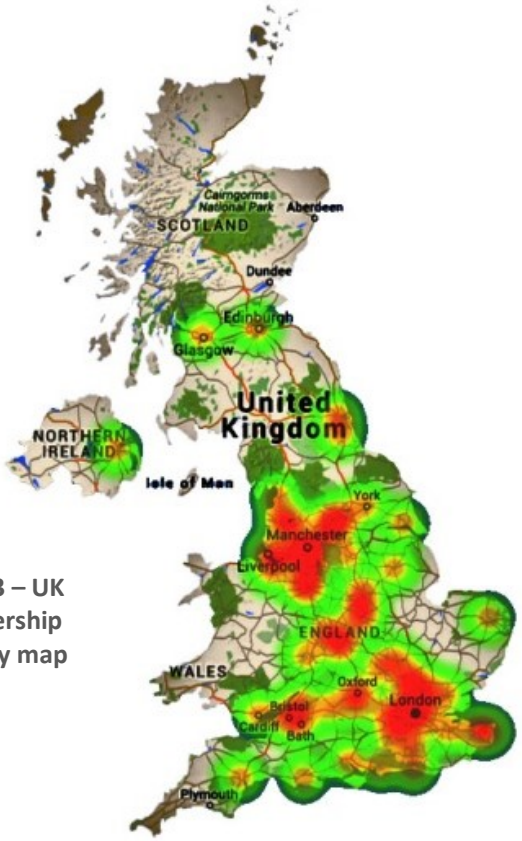


Figure 3 – UK Membership intensity map

- ✓ Focus on Networking
- ✓ Talent pipeline through Network
- ✓ Mobility
- ✓ Culture change
- ✓ Equipment & Lab sharing

Since the inception of the Network in 2010, consultative meetings have been held on each theme and on cross-theme issues. The Network has fostered debate through newsletters, the website, social media and direct emails, drawing input from researchers and end-users. This Roadmap reports on each theme area, based on the community input, in section 4 Roadmap.

Approximately 9 meetings are held each year, bringing together a plethora of multi- and inter-disciplinary members.

Figure 4 – Statistics 1

The Network has awarded over £325k in pump-priming, travel and seedcorn grants. Over 80 new collaborations have been formed and the Network has proved vital towards leveraging some £50M of other grant funding[1].

Figure 5 – Statistics 2

Early career researchers (ECR) are a key focus and as such, the Network has over 260 ECR members. Specific meetings are held to promote ECRs, along with a Network mentoring system. We have now seen many of the Network's ECRs develop and achieve more senior positions and some have now joined the Network Management Team.

Figure 6 – Statistics 3

"…the strength of the proposal is reflected in the fact it has already been reviewed and deemed suitable for pump-priming funds from the EPSRC Directed Assembly Network"

Anon. Reviewer for an EPSRC application submitted via responsive mode in 2015

[1] http://www.directedassembly.co.uk/Directed_Assembly_Network_GRANTS_LINKED.xlsx

2.3 Network Evolution

- Directed Assembly Network begins and sets out to build and engage a community
- Vision: In 20-40 years, innovative manufacturing will enable us to create, program and control new artificial and biological materials
- Roadmap (2012 edition) developed

- 300+ members
- 9 meetings a year, 23 pump-priming awards given, with 80+ new collaborations

- 1000+ members
- 260+ Early career researcher members, 110+ industry members
- £50 Million major grants linked to and/or supported by the Network

- 3 new Focus Streams encompassing the 5 Network Themes
- Early career researcher panel & Advisory panel
- Increased industry involvement
- Network expansion to include more: computer scientists and mathematicians

- 1500+ members
- European brand
- A sustainable Network

- Establish the Worldwide Institute for Directed Assembly (WIDA)

- Meet the original Grand Challenge
- Continuously evolve to reflect and serve the needs of the community
- Original early career researchers now at the top of their fields and internationally renowned, with each generation mentoring and supporting the next
- Regularly engage the community to develop a strategy towards solving the 'next grand challenge'; 2040-2080 and beyond

Figure 7 - Network Evolution

2.4 Network Themes & Challenge Streams

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

1. Controlling the assembly of designed molecular frameworks and hybrid materials with targeted properties. Short title: Functional hybrid materials.
2. Controlling nucleation and crystallisation processes. Short title: Nucleation & Crystallisation.
3. Controlling molecular self-assembly in biological and biomimetic systems. Short title: Biological & Biomimetic systems.
4. Controlling surface-based molecular self-assembly for applications in interface science. Short title: Surfaces & Interfaces.
5. Developing self-optimised chemical systems through self-evolution. Short title: Intelligent chemical reactors.

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.

Between 2010 and 2012, the Network ran 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. This work continued in the second phase of the Network between 2012-2016 and represents the ethos of the Directed Assembly Network. Reports on each theme area, based on that community input, appear in the following sections.

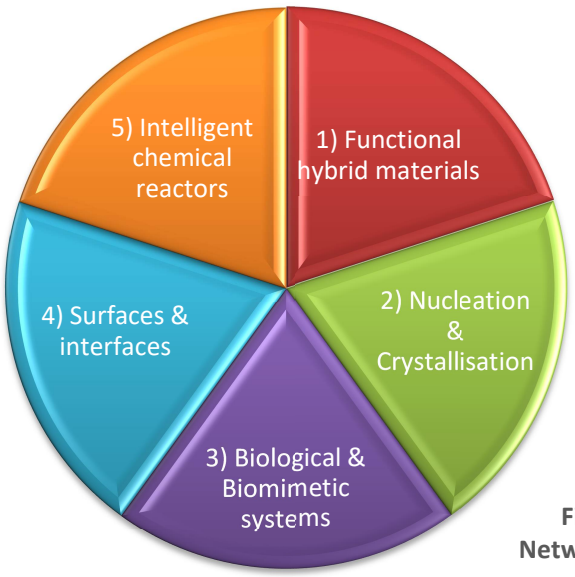


Figure 8 – Network Themes

The Network has developed and evolved, based upon the findings and inputs of the community, to expand and incorporate those working in all three of the following 'Challenge Streams':

A. Directed Assembly
B. Directed Disassembly
C. Translation and upscaling

Each stream encompasses the five original themes that were set out during the inception of the Network:

Figure 9 – Themes & Streams

Challenge Stream A: Directed Assembly (Led by: Paul Raithby) This stream continuously extends the existing findings and Roadmap of the Network on the assembly of molecular building blocks into pre-designed structures of condensed matter. The range of methodologies that are available or are currently being researched, together with future research directions for how such assembly processes work, will continue to be investigated, catalogued and recorded by the Network. This stream covers the range of molecular building blocks, from inorganic to biological systems, including materials from perovskites to polymers, for studies in the solid-state, in solution or on surfaces or at interfaces.

Challenge Stream B: Directed Disassembly (Led by: Chick Wilson) There are numerous applications where the condensed material must be dispersed or dissolved to release its components to deliver the desired functionality. Here we explore how to direct the disassembly of these materials into their constituent building blocks, releasing activity or action on appropriate triggering. As for stream A, we will record, catalogue and disseminate

the methods and future directions that can enable the controlled disassembly of suitably designed condensed materials for the range of building blocks considered above.

Challenge Stream C: Translation and Scale-Up (Led by: Harris Makatsoris, Andy Bayly)
Stream C involves translation and scale-up of newly assembled or disassembled materials to become of direct use to industry. New formulation methods and scale-up through flow processing will support existing and emerging industries, and there will be specific focus on material and device design for new high tech applications to support emerging technologies.

This stream started as part of phase three of the Network (2017-on) and is a crucial feature that reflects the broadening of the Network focus to include the translation of discoveries into applications. This Roadmap highlights certain short term capabilities and developments that are now moving rapidly towards the application phase, entering the higher TRL levels (3 to 4) and application domains.

Although the Network's core focus is within TRLs 1 to 3, with this stream, chemists, engineers and practitioners are brought together to explore and define the pathways for the translation of those scientific discoveries to potential future application domains. Prospective manufacturing routes for those materials will also be explored. However, this stream is not limited to such unidirectional exchange but rather embraces bidirectional interaction with end-users, allowing the development of multi-disciplinary collaborations to define applications or address particular engineering and industrial challenges.

This stream has two focus areas:
(1) Formulation, which entails the ability to control microstructures of multi component materials including complex fluid formulations, guest/host systems, polymeric materials etc, to deliver the range of functions that targeted applications demand.

(2) Scale-Up, which involves the understanding and the control that is required for manufacturing those materials at market scales. Ultimately, data-driven, mathematical techniques and design tools would be needed for manufacturing process design.

The range of materials and methods from the five Network Themes, which are now covered in conjunction with the three challenge streams, further help to place the Network in a position to cover a wide variety of potential future applications that will support the four key targets of Productivity, Connectedness, Resilience and Health that underpin UK prosperity [9]. Those include: drug delivery, sensors, photovoltaics, smart coatings, self-healing components and surfaces to name a few.

This provides opportunities to establish multidisciplinary collaborations to address larger, application-driven problems. For example, determining the optimal formulation and translation and manufacturing pathways for guest/host systems that can act as smart responsive coatings or sensing surfaces. Crucially, this evolved Network structure underpins the strategy for its growth and future sustainability, whilst reflecting its ability to adapt to the community and political landscape.

2.5 Aims & Objectives

In this Grand Challenge we aim to gain unprecedented control of the assembly of molecules that are the building blocks of many functional materials, consumer and industrial products. The Network aims to accelerate and form a focus for this process.

We start by understanding the assembly of the very small, but methods we explore will allow production of new types of useful materials at a whole range of length scales from the nanoscale to the everyday.

Such materials will have outstanding impact in areas of societal importance such as personalised healthcare and food production, transport systems and fuel production, housing construction and consumer electronics.

Fundamentally, the Network remains the provision of an environment for the research community that extends beyond Chemistry and Chemical Engineering, to establish multi-disciplinary collaborations, influence national research agendas and facilitate progress towards addressing the Directed Assembly Grand Challenge.

Through our evolution, the aim has been extended to reflect the translation to applications via the formulation of those materials into products through associated manufacturing routes. By linking together academic expertise and industrial requirements and helping develop an understanding of each other's operating cultures, the Network assists in speeding the uptake of new technologies into production processes, thereby maintaining the UK's industrial competitiveness.

Objectives:

1. Expand research community to include more disciplines such as: other Engineering areas, computer science and mathematics.
2. Extend the focus from pure fundamental science to the translation of discoveries to application by bridging the inherent gap that currently exists.
3. To continue to support and mentor ECRs.
4. To continue to influence National Research agendas, Decision and Policy makers and engage with current and future industrial thinking.
5. To further develop links with other Networks in the Physical and Life Sciences and to engage with the Global Challenge agenda, to provide a focus for the Physical Sciences community to support the world with new materials and processes, through targeted directed assembly.
6. Establish a sustainable model to secure the Network’s long-term future.

2.6 Network Activities & Expansion

Network Activities

Networking, Support & Mentoring

The Directed Assembly Network is renowned for providing a forum that breaks down silos and barriers, by bringing different communities together helping to bridge the gap between academia and industry. This is evidenced by our diverse membership of over 1000 scientists and engineers with roughly 10% of members from industry, research institutes and National Facilities, e.g. Pfizer, iFormulate, CMAC, CCDC and the Diamond Light Source.

Further still, the Network also strives to ensure greater interaction between specific communities including experimental and computational scientists, chemists and chemical engineers, chemists and biologists. Early career researchers are mentored informally by senior, leading UK scientists and industrialists. The Network also strongly supports fellowship and grant applications.

Roadmap

The Roadmap represents the Network's knowledge repository, through which the shared and multi-disciplinary vision and research agenda of the Network is captured, developed and communicated. All activities carried out by the Network contribute to the Roadmap, which is continuously updated as the research directions are identified in the five themes and three challenge streams. The Roadmap highlights the progress being made by the Network community and is a knowledge capture tool, to aid future research.

Meetings & Workshops

Sandpit meetings and workshops attract a mixture of established academics and early career researchers; bringing them together to discuss the Grand Challenges facing science and what they can do to tackle them. Some meetings are focused on just one Network theme, whereas others are cross-themed. These take place over 2-3 days and significantly contribute towards successful future collaborations.

DREAMS meetings are designed for early career researchers and help to connect young scientists and engineers from different backgrounds, whilst fostering the development of skills, vital for an academic career, such as grant writing and writing for high impact journals etc.

Network Awards

Travel, seedcorn and Pump-priming (proof of concept) grants are awarded to multi-disciplinary projects led by academic investigators from across the Directed Assembly community, with the purpose of tackling well-defined barriers to progress. These projects provide the foundation for larger collaborative projects funded through the usual Research Council routes.

Network Engagement & Expansion

The Directed Assembly Grand Challenge Network is a highly respected brand across the physical sciences community. The Network and its five fundamental scientific themes are both attractive and powerful motivational forces to our members.

The Network's membership steadily expands year on year through meetings and conferences, the addition of scientists and engineers coming to work in the UK, and new early career researchers, coupled with the Network's ability to evolve and adapt. Furthermore, we proactively increase our membership through regular member-engagement and dissemination.

Alongside continuous engagement with members to advance the Network aims in discovery, and potential routes to the translation of discoveries to applications, we communicate the Network activities, progress and findings to the wider community. This includes via the Network website, the mailing list and expert directory, Network events, social media (LinkedIn and Twitter) and university press offices.

The Network attracts all those working in directed assembly, disassembly and materials design, development and scale up towards manufacturing. Additionally, the focus on translation and scale-up attracts even more diverse disciplines, including mechanical and process engineers and end users. These relationships help to foster routes to application and market.

"The proof of concept studies…funded by an EPSRC network demonstrates clearly that this team has the right balance of skills to deliver on the project objectives"

Anon. Reviewer for an EPSRC application submitted via responsive mode in 2015

3. IMPACT

3.1 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 accelerate 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, communication and transport. The Network ethos matches the ambitions from the EPSRC Delivery Plan of "A Productive Nation, A Connected Nation, A Resilient Nation, A Healthy Nation" [6]. For example, one key theme of the Network has focused on the biotechnology sector, which is projected to be a £150-360 billion global market by 2025 (with the UK share being £4-12 billion) according to the RAE [7].

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, medical sensors and even the growth of tissues 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.

Food supplies and security are now developing into a major global concern, and here directed disassembly will contribute substantially. The formation and control of amorphous materials, and the ability to prevent crystallisation are very important in the agrochemicals industry. Similarly, the prevention of the formation of solid deposits will provide new routes to prevent fouling, and support environmental clean-up.

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

Economic & Industrial Impact

Whilst the most obvious uses of a better understanding of molecular assembly and disassembly are around creating functional materials faster, with more efficient chemical synthesis fabrication 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 foodstuffs and drug production and delivery will be enhanced by better insight into nucleation, dissolution and 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.

The Network has already been credited as helping towards influencing a culture change when it comes to research within the pharmaceutical industry: rival companies now readily work together at precompetitive stages.

Academic Impact

The Directed Assembly Grand Challenge Network was set up, in the first instance, to benefit academic research into molecular and materials 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.

3.2 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 the UK. 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 US Materials Genome Initiative [8] targeted $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 continue to be strengthened.

The Network has directly influenced and/or supported £50 Million research grants and awards, following its vision and focusing on the 5-50 year targets identified by the UK community. Input from abroad is also encouraged so that the best of British can work with the best in the rest of the world to achieve our overall goal.

We aspire to the same vision as Jo Johnson, which he set out during his speech ‘Making Britain the best place in the world for science’, on 27 January 2016, at The Royal Institution: “Our global scientific impact far exceeds our size as a nation, and our scientists and engineers stand tall on the world’s stage.” [1]

It is also timely to take on the Global Challenges outlined in an EPSRC report [9] and extend the wealth of scientific knowledge in the UK to support developments overseas. The Network is well placed to use its knowledge of smart materials and innovative processes to support this initiative.

3.3 Benefit to UK

On-going 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. Society is challenged by a growing and aging population, and through declining natural resources. The goals we reach for will drive great breakthroughs in healthcare and offer alternatives to harvesting our limited reserves.

The potential for the global industrial biotechnology market is projected to be £150-360 billion by 2025, 'Engineering for a successful nation' from the Royal Academy of Engineering [7].

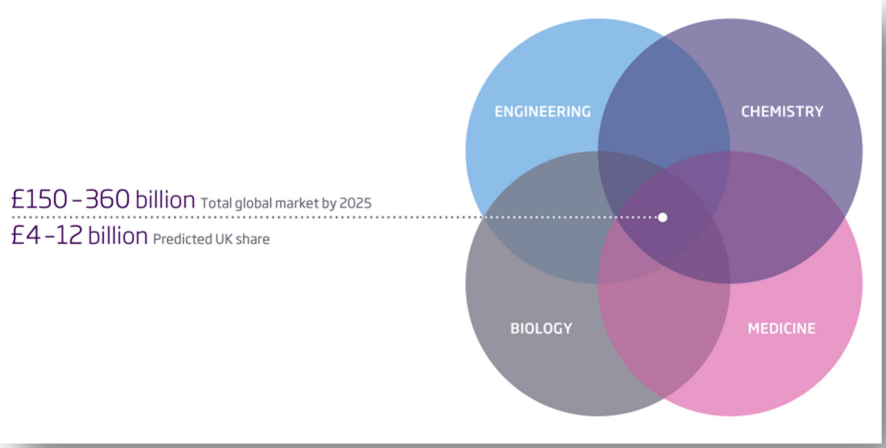


Figure 10 – Biotechnology market

The UK has already been identified as being world-class or world-leading in many of the individual disciplines needed to tackle these targets, but real breakthroughs will only be made by harnessing interdisciplinary excellence from across the UK - the Directed Assembly Network is key to the formation and maintenance of this interdisciplinary community. Other countries are already investing heavily in programmes to progress materials science; by adopting the recommendations above, 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.

Since its launch in 2010, the Network has become embedded into the culture of those working in Directed Assembly and is known as a place to go to for mentoring, advice and support. The Network awarded 23 pump-priming grants between 2012-2016. These, together with meetings, have been instrumental in leveraging approximately £50M of major grant funding. A community of over 1000 multi-disciplinary members from across the UK, including 10% industry members and 25% early career researchers has been engaged, nurtured and brought together with a common aim: the Directed Assembly Grand Challenge. During phase 2 of the Network (2012-2016) over 45 meetings were held, that have directly led to 80 new collaborations.

A culture change has been widely noted since the inception of the Network in both the way rival companies now commonly work together at precompetitive stages, and, different types of scientists now see each-other as invaluable towards achieving strong relationships and results. Researcher mobility through travel grants and pump-priming projects has contributed to both data and equipment sharing, whilst helping to nurture the skills development of the UK research base. The vast 1000-strong community has been engaged consistently and led to a Roadmap setting out the vision for the next 5-50 years.

The UK Government has already set out long term research and development goals, notably allocating £464 million to the 'Eight great technologies' [10]: advanced materials, energy, big data, space, robotics and autonomous systems, regenerative medicine and agricultural science.

The Directed Assembly Network directly encompasses five of the eight technologies and strives towards propelling the UK towards future growth, helping it to stay ahead in the global race [11].

Figure 11 – Eight Great Technologies

	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 and/or lipid-based compartments, 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). Use of compartmentalisation for the utilisation of energy and/or matter flow.	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. Multi-“cellular” functional materials.
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.

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

4. ROADMAP

4.1 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 [12]. 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.

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.

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. • Use of compartmentalisation strategies is in its infancy. • Systems utilising energy (“food”) to stay out of thermodynamic traps, i.e. systems displaying kinetic stability, are hardly explored, if at all.	• 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. • To develop “cells” with functionality provided by combinations of responsive functional (biomacro)molecules. • To develop and understand systems operating under conditions of kinetic stability.
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.

Table 2 - Research Issues and Aspirations

Where we were	Where we are now	Aspirations & Targets
• Physical scientists trained to a high level in small focussed areas. • Tendency towards a 'silo mentality'. • Experimentalists and theoreticians usually worked independently and often failed to communicate effectively. • The majority of chemists and engineers currently work in separate environments, looking at systems with different length scales. • Little interaction between biologists and inorganic chemists. • Academia and industry work independently to a large extent and there is a lack of understanding of the needs of each group. • Early career researchers (ECR) may be isolated with a greater need for supportive community. • 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.	• Physical scientists now more open-minded and aware of other areas, helped by over 45 Network meetings. • More interdisciplinary collaborations and more willingness to work across boundaries. • More experimentalists and theoreticians now exchanging knowledge, with bi-directional feedback. Over 80 new collaborations have been fostered by the Network alone. • Now closer interaction between chemists and engineers, working to bridge the length scale divide and study systems on the nanoscale together. This has started feeding into manufacturing materials with evolving properties across the length scales. • Facilitate interactions between biologists and inorganic chemists to develop biologically important multicomponent assemblies containing metals as sensors and for use in clinical applications. • Culture change attributed to Network activities: more industrialists involved, and working with academia. • People transfer technology: new relationships facilitated through industry engagement. • ECR's have flourished via the Network: meetings, awards, mentoring and support. • These future leaders are loyal and committed to the Network, striving towards the Grand Challenge targets. • Tens of exchange visits have taken place to other laboratories: sharing equipment, transferring knowledge and skills. • Summer schools have given cross-disciplinary training and helped form multi-skilled collaborations.	• Further develop multidisciplinary expertise. • Continue to facilitate the development of boundary crossing science in order to meet the Directed Assembly Grand Challenge. • Foster more collaborations between experimentalists and theoreticians, to exchange knowledge and to work on the same problems, providing iterative feedback in both directions. • Strive for even closer interaction between chemists and engineers. Feed knowledge into future manufacturing more quickly through **translation and upscaling**. • Facilitate interactions between biologists and inorganic chemists to develop biologically important multicomponent assemblies containing metals as sensors and for use in clinical applications. • Embed positive culture of the two-way relationship between academia & industry across the UK. • Facilitate more interactions between academics and industry through increased industry membership. • Consistently help and support ECRs to hone their skills, further their careers and support the following generations. • Embed the ethos into the culture of our Network and beyond. • Be a continuous and evolving presence, a 'go to' for support, fostering; cross-disciplinary training, solving real research problems, workshops, schools and networks; to build the multi-skilled workforce of the future.

Table 3 - Developing People – Sharing Expertise and Promoting Leadership

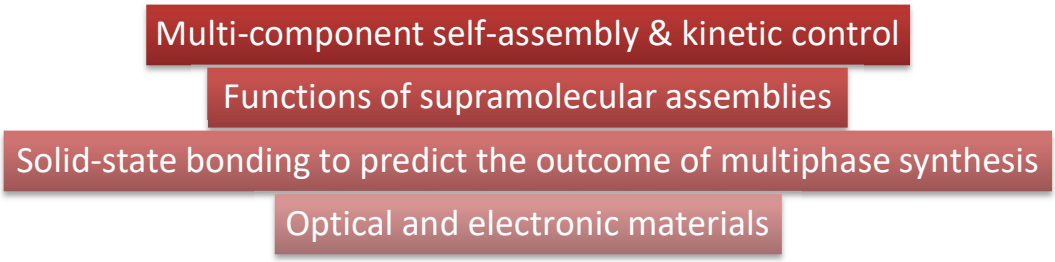
4.2 Theme Introductions

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.

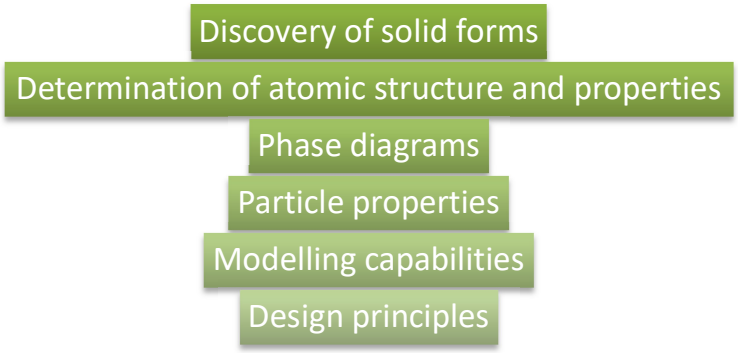
For each theme we describe why the area is important, the scientific challenges faced, where breakthroughs are needed to be made and what we can do to increase the capability of the community in the area. Table 4 gives highlights of key research areas for each theme – progress in these areas is described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

Theme 1



Theme 2



Theme 3
Control of interactions in any solution
Modelling methodologies for biomolecular interactions
Kinetics & time-dependence in biomimetic systems
Multi-component systems at the biology/materials interface
DNA structures & DNA hybrid materials production
Food, biofuel and bio-renewables production
Use of compartmentalisation
Exploitation of kinetically stable states of matter
Theme 4
Solid-liquid surfaces – solubility and dissolution
Fluid surfaces and structured liquid formulations
Polymeric functional materials and surface coatings
Surface-templated self-assembly
Theme 5
Computer directed assembly by control of multiple physical properties
Enable self-evolution in non-biological systems
Methods for measuring multiple properties simultaneously
DNA-based evolvable matter

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

4.3 Theme 1

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

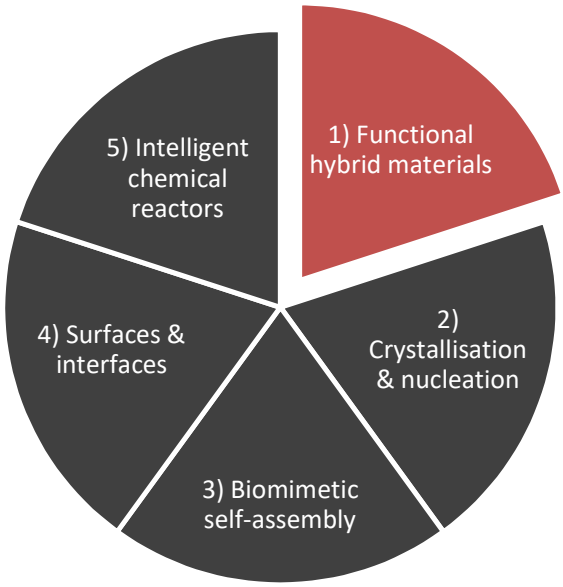


Figure 12 – Theme 1

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.

Network Award Example – Proof of Concept Project (Pump-priming)

Theme 1: Clean Synthesis and Characterization of Superstrong Metal-Organic Frameworks for Practical Applications
Pump-priming project, grant awarded in 2014.

Details at time of application: ***Forgan, R.*** *(Royal Society University Research Fellow, University of Glasgow),* ***Bennett, T.*** *(Research Fellow, Dept. of Materials Science and Metallurgy, University of Cambridge) and* ***Moggach, S.*** *(Lecturer in Inorganic Chemistry, School of Chemistry, University of Edinburgh).*

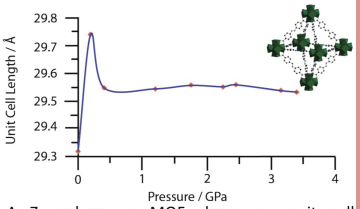
The Challenge
Metal-Organic Frameworks (MOFs) are of great interest because of their potential application in gas storage and separation, catalysis, sensing, drug delivery and harmful waste

storage. However, their mechanical stability, alongside the cost of synthesis, is a source of great concern.

Long Term Goal
To develop highly robust MOFs that resist change to their architectures: essential for industrial applications. The identification of structural motifs which confer extraordinary stability on these materials is an attractive prospect.

Work advancing the Roadmap
Discovered new routes to synthesise Zr MOFs in an efficient manner and as single crystals, which has allowed a study of their mechanical compliance in unprecedented detail by single crystal high pressure X-ray diffraction and nanoindentation. This results in dramatic improvement in crystallinity and access to otherwise unavailable MOF.

Nanoindentation has been made possible on a number of samples due to our ability to grow >50 micron single crystals of MOFs by our advanced synthetic protocols. We have begun to elucidate a series of design rules to control the mechanical compliance of Zr MOFs, through functionalization of the ligand before and after synthesis, to induce flexibility and thus pressure resistance.



A Zr-azobenzene MOF shows no unit cell compression with increasing pressure.

Impact
Papers
1. "Amino Acids as Highly Efficient Modulators for Single Crystals of Zirconium and Hafnium Metal-Organic Frameworks" R. J. Marshall, C. L. Hobday, C. F. Murphie, S. L. Griffin, C. A. Morrison, S. A. Moggach and R. S. Forgan* *J. Mater. Chem. A.* **2016**, accepted for publication.
2. "Geometric Frustration in UiO Frameworks: A Computational and Experimental Approach Linking Disorder, High-Pressure Behaviour and Mechanical Properties" C. L. Hobday, R. J. Marshall, C. F. Murphie, J. Sotelo, T. Richards, D. Allan, T. Düren, F. –X. Coudert, R. S. Forgan*, C. A. Morrison, S. A. Moggach and T. D. Bennett, *Angew. Chem. Int. Ed.* **2016**, *55*, 2401–2405.
3. "Postsynthetic Bromination of UiO-66 Analogues: Altering Linker Flexibility and Mechanical Compliance" R. J. Marshall, T. Richards, C. L. Hobday, C. F. Murphie, C. Wilson, S. Moggach, T. D. Bennett and R. S. Forgan, *Dalton Trans.* **2016**, *45*, 4132–4135

Beamtime and an EPSRC Application
Forgan and Moggach have won a number of days of beamtime on I19 at the Diamond Light Source, via four successful, peer reviewed applications, to carry out the research described in the proposal. These results contributed significantly to publication 2 and the results are underpinning a full proposal to EPSRC (responsive mode) where Forgan and Moggach are the two PIs.

Quotes from the Investigators
"The funding has been very beneficial to all three applicants, as we are all ECRs and have received a significant boost in our early careers when the funding landscape is considerably competitive. It has kickstarted a valuable collaboration, generated high impact publications which may be REF submitted (all are gold open access, including data), and given us results to underpin future larger proposals."
"We are developing links with Johnson Matthey to ensure that these breakthroughs are capitalized upon and built into long term research programs."

Theme 1				
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-	Better theoretical understanding of structure / function relationships and the origin of emergent	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 /**

and-error methods; some understanding of how emergent function relates to structure	properties. Better fabrication methods and control of crystallisation		**function relationships; complete control of crystallisation of large number of components into functional solid-state assembly**

Table 5 - Theme 1 - Science & capability development to match onto product roadmap

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.

Example of an EPSRC Grant directly influenced and/or supported by the Network

Theme 1:
Understanding and Engineering function in switchable molecular crystals
2013-2018

EP/K012576/1 (£486,532) **Raithby, P.,** EP/K012940/1 (£487,698) **Deeth, R.,**
EP/K013009/1 (£523,143) **Cooper, RI.,** EP/K012568/1 (£634,961) **Halcrow, MA.**

Program to improve our understanding of phase changes in crystalline materials, using spin-crossover compounds as a test-bed. We will establish new fundamental principles for engineering phase changes into molecular crystal, that occur under pre-defined conditions (of temperature and/or light irradiation), at different rates, and with the property of hysteresis. As well as synthesising these new materials, this apparently simple objective requires state-of-the-art methods for measuring these structure changes.

This will be achieved using new X-ray diffraction techniques, for inducing phase changes in crystals in high yields under controlled conditions, and for interpreting the data that result from these experiments (to deconvolute contributions from the starting and product phases of the material, for example). We will also develop improved methods for simulating the phase change events using computer models, to provide new insight into how the design of the crystal affects the propagation of the phase change through its bulk.

The combination of expertise in our consortium will achieve real advances towards solving a problem that has only been successfully addressed up to now by trial-and-error.

http://gow.epsrc.ac.uk/NGBOViewGrant.aspx?GrantRef=EP/K012568/1

4.4 Theme 2

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

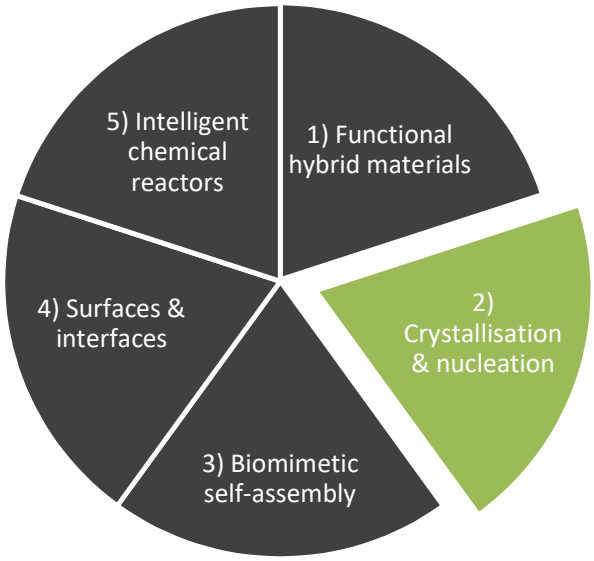


Figure 13 – Theme 2

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, 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.

Network Award Example – Proof of Concept Project (Pump-priming)

Theme 2:
Towards Smart, Sprayable Skin: Disruption of Crystallinity of Poorly Water Soluble Drugs for Long Lasting Continuous Dosage
Pump-priming project, grant awarded in 2013.

Details at time of application: ***Greenland, B.*** *(Lecturer, Dept. of Pharmacy, University of Reading) and* ***Shaver, M.*** *(Reader, School of Chemistry, University of Edinburgh).*

The Challenge
Pharmaceutical Efficacy – ensuring that the quantity of new drugs reaching the market increases. Many drug candidates have been identified that show excellent potency and selectivity during *in vitro* screening studies. However, potentially life-saving actives fail to progress to human trials as a simple consequence of poor water solubility. Dissolution in biological media is the rate-limiting step, severely restricting the bioavailability and efficacy of these compounds.

Long Term Goal
To develop (in)soluble block copolymers into a sprayable 'artificial skin' formulation that could be applied to cuts, skin grafts and burns.

Work advancing the Roadmap
Synthesised a series of new, functionalised degradable polymers based on hyperbranched PLA and poly(3-hydroxybutyrate) (PHB) with varying branching levels and functional side groups. Immortal ring-opening polymerisation and bifunctional chain branching monomer designs were used and model drug formulations produced. Degradable PLA polymers and copolymers were shown to modify drug crystallinity through supramolecular interactions and deliver a measureable increase on drug solubility in biologically relevant media.

Impact
Paper
MacDonald, J. P.; Parker, M. P.; Greenland, B. W.; Hermida-Merino, D.; Hamley, I. W.; Shaver, M. P.* "Tuning Thermal Properties and Microphase Separation in Aliphatic Polyester ABA Copolymers" Polym. Chem. 2015, 6, 1445.
Another manuscript is in preparation (2016).

Quotes from Investigators
"…having just moved from Canada to the UK, the most important part of it [the Network] was meeting people and getting a sense of the science being done"

"…the DA award cemented a relationship which then led to other things".

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

Table 6 - Theme 2 - Science & capability development to match onto product roadmap

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.

Example of an EPSRC Grant directly influenced and/or supported by the Network

Theme 2:
Molecules, clusters and crystals: a multi-scale approach to understanding kinetic pathways in crystal nucleation from solution
2011-2015

EP/I013563/1 (£1,013,295) **Davey, R.,** EP/I014446/1 (£1,299,408) **Roberts, K.**

We propose a novel approach to this problem in which we scrutinise the crystallisation of two related molecular systems in hitherto unprecedented depth, building on established state-of-the-art experimental and computational techniques, but combining these, for the first time, with in situ synchrotron radiation (SR) X-ray scattering and spectroscopy methodologies capable of probing long range and local electronic and geometric structure at molecular resolution.

We thus expect incisive structural information for every step of the nucleation process: measured molecular scale properties can be used to confront computational predictions at molecular, supra-molecular and solid-state levels, so that the structural and size parameters for the nucleation pathway are revealed. A step change in our understanding of this area of science is thus expected.

http://gow.epsrc.ac.uk/NGBOViewGrant.aspx?GrantRef=EP/I013563/1

4.5 Theme 3

A Roadmap for Controlling Molecular Assembly in Biological and Biomimetic Systems

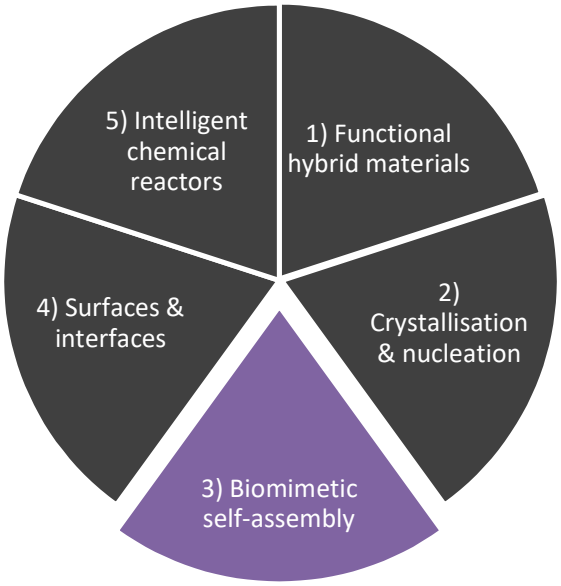


Figure 14 – Theme 3

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.

We note that nature is excellent in nanoscale organisation, which is of high interest in current science. For example, in this context, the coding ability of DNA suggests approaches for data storage and process control, enzymes provide inspiration for catalytic systems, proteins and peptides provide exquisite recognition elements, sugars provide building materials and energy storage, lipids allow for spatial (and possibly temporal) control through compartmentalisation, and these are complemented by a variety of messenger molecules.

Utilising these materials for their natural functions, but also complementing these functions through use of elements and components not in use by nature (e.g. palladium, ruthenium, extensively pi-conjugated molecules) opens a wealth of opportunities. We finally note that biological systems avoid the potential trap of thermodynamic equilibrium through energy conversion ("eating") allowing functional systems to remain in a kinetically stable state, away from equilibrium.

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 DNA, RNA, proteins, enzymes, lipids, sugars 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 reactivity's 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.

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 responsive 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 or in a series of cell-like structures.
- 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 [13], 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, or lipid-based structures 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.
- Coordination of facile access to specialist equipment and expertise on a collaboration basis.

Network Award Example – Proof of Concept Project (Pump-priming)

Theme 3:
Development of a bioinspired toolbox to dynamically remodel membranes for controlled chemical compartmentalisation
Pump-priming project, grant awarded in 2012.

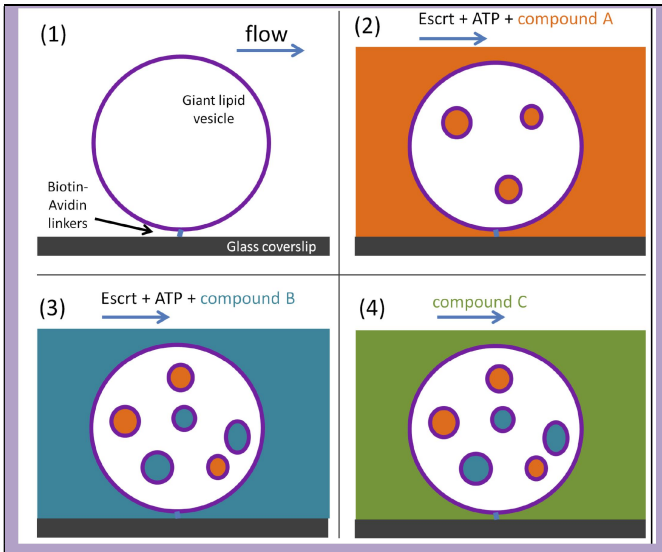
Details at time of application: ***Ciani, B.*** *(Lecturer, Dept. of Chemistry, University of Sheffield) and* ***Beales, P.*** *(Senior Research Fellow, School of Chemistry, University of Leeds).*

The Challenge
Nature compartmentalises its chemistry on microscopic lengthscales, which allows the maintenance of chemically incompatible environments (e.g. acidic/basic, oxidising/reducing) across short spatial lengthscales. Communication between compartments is rapid due to short diffusion distances and chemical mixing is rapid and efficient due to small confined volumes, where small quantities of substance are stored at high concentrations. These are auspicious features to mimic in soft, self-assembled materials for applications in diverse fields including nanoreactors, synthetic biology and nanomedicine.

Polymeric protein complex undergoes a continuous cycle of assembly and disassembly, propelled by ATP hydrolysis and mediated by the enzyme VPS4. Importantly, intraluminal vesicle generation happens only in the presence of ATP.

Long Term Goal
Harness the power of biology by learning to mimic assembly and disassembly processes. To develop a technology towards the design of complex nano-reactors and/or synthetic biological cells.

Work advancing the Roadmap
Utilised ESCRT proteins to generate chemical compartmentalisation in vesicle-based systems. Expression and purification of ESCRT proteins were conducted and their interactions with the giant phospholoid vesicles (GLVs) investigated by confocal microscopy. Employed the ESCRT protein system as a tool for dynamic switching and reconstruction of membrane compartments for bionanotechnology purposes.



Impact

EPSRC Grant

EP/M027821/1 (Ciani, B., £307,479) and EP/M027929/1 (Beales, P., £342,200): 'Harnessing Nature's ability to create membrane compartmentalisation through redesign of a protein machinery'.

Theme 3				
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.	Intermediate systems involving multiple biomacromolecules can be simulated	Extensive systems involving multiple biomacromolecules in combination with hybrids and designer compounds can be simulated	**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, from any bioinspired macromolecule, with any functionality**

Vesicles can be made routinely, compounds can be encapsulated but there are only sporadic attempts at using compartment-alisation	Develop an understanding of the complementarity of peptides, DNA, sugars with lipid-based compartments	Design systems employing transmembrane processes for energy generation and transmembrane signalling		**Use compartmentalisation for the spatiotemporal resolution of designed processes occurring in multiple "cells"**
Biomineralisation in nature gives rise to highly complex structures; synthetic systems do not generate anything near this complexity, if any at all		Understand the processes directing the biomineralisation process	Design templates for biomineralisation of designed nanostructured solids	**Generate nanostructured solids of any complexity and on any scale.**
The process of "eating" allows living systems to avoid reaching thermodynamic equilibrium ("dying")	Photochemical processes to provide energy to drive a specific process	Photochemical processes and simple gradients of energetic compounds to cause directed movement	Autonomous self assembled nanostructures carrying out multiple tasks in response to available energy	**Life-like functionality of energy-consuming non-equilibrium structures**
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**

Table 7 - Theme 3 - Science & capability development to match onto product roadmap

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-funded programmes must be encouraged.

Example of an EPSRC Grant directly influenced and/or supported by the Network

Theme 3:
Harnessing Nature's ability to create membrane compartmentalisation through redesign of a protein machinery
2015-2018

EP/M027821/1 (£307,479) **Ciani, B.,** EP/M027929/1 (£342,200) **Beales, P.**

If we are to mimic this complexity within synthetic "nanoreactors", or even build synthetic cells capable of useful tasks within areas as diverse as medicine, environmental remediation, or energy capture and storage, we will need to develop ways of mimicking cellular compartmentalisation within synthetic man-made structures. This is the challenge we will address in this project.

A first proof of concept will consist of encapsulating a molecular machinery capable of converting genetic information into new protein molecules inside one single internal compartment, mimicking the function of the cell nucleus. Further work will be conducted to allow selective movement of chemicals between internal compartments within a single vessel. The ultimate product of this project will be a well-characterised, functional toolkit enabling researchers to create complex compartmentalised and communicating nanoreactors. These devices could be used as cell-sized vehicles that simultaneously produce, transport and deliver therapeutic cargo to specific targets in the body. Alternatively, they could be employed as chemical factories that can remove pollutants from water supplies.

http://gow.epsrc.ac.uk/NGBOViewGrant.aspx?GrantRef=EP/M027821/1

4.6 Theme 4

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

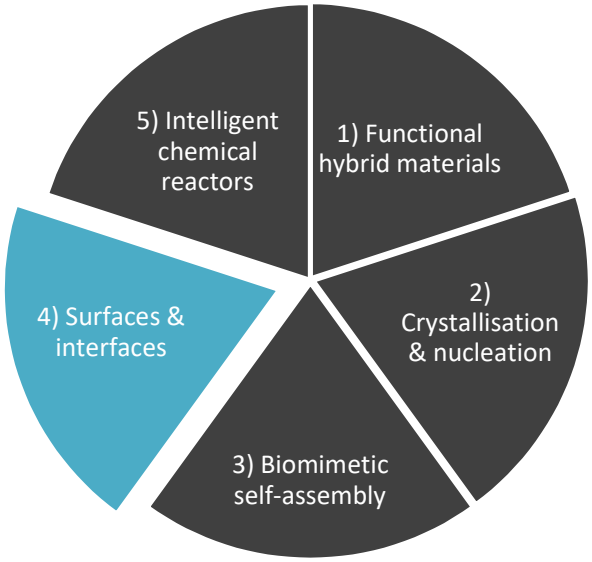


Figure 15 – Theme 4

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.

Network Award Example – Proof of Concept Project (Pump-priming)

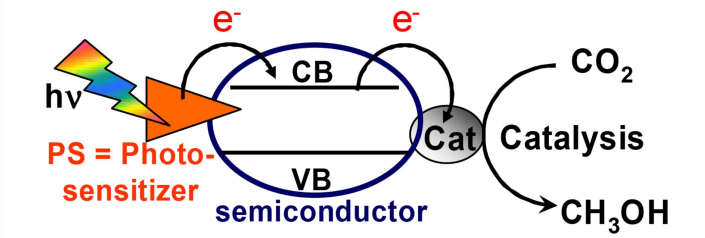
Themes 4 & 5:
Directed co-assembly of photosensitizer and catalysts for photoelectrochemical CO2 reduction into chemical fuels
Pump-priming project, grant awarded in 2013.

Details at time of application: ***Weinstein, J.*** *(Senior Lecturer, Dept. of Chemistry, University of Sheffield),* ***Towrie, M.*** *(Leader & Head of Molecular Structure and Dynamics Laboratory, RAL, STFC),* ***Haywood, S.*** *(Professor, School of Engineering, University of Hull).*

The Challenge
Reducing worldwide CO2 levels and preventing the potential corresponding irreversible damage to the environment. Despite numerous attempts, an efficient, robust and practical artificial system for CO2 reduction is yet to be developed.

Long Term Goal
To make significant steps forward towards the efficient conversion of CO2 in chemical fuels, namely MeOH, using the energy of light. The multielectron nature of the process is a major challenge and there is a lack of understanding of the electron transport between the surface of the electrode, the catalysts and the photosensitizer.

Work advancing the Roadmap
Development of a solar-powered photoelectrochemical cell for CO2 reduction where the components self-assemble on a surface of a semiconductor electrode. Known Re(I) photocatalysts were modified to be absorbed on the SC surface, as were Pt(II) photosensitizers.



Solar CO_2 reduction with surface-assembled photosensitiser and catalysts

Impact

Overall, the results of this Pump-Prime funding contributed to at least one large-scale EPSRC grant application; and 3 PhD studentships.

It also fed into the PhD program of a WhiteRose student, funded by a WhiteRose SolarCO2 consortium led by Prof S Haywood.

1. Data and expertise which were used, in parts, contributed to the Programme grant proposal “HydroGAN” (EP/N031865/1), which was selected for an interview.
2. Securing a University-funded studentship in CO2 reduction (commenced in October 2013), and a PhD student through CDT in “Molecular Scale Engineering”.
3. Initiated a collaboration with Prof P Hall, Faculty of Engineering, University of Sheffield, and a joint PhD student.
4. Support in developing a collaboration on photoelectrochemical CO2 reduction with Professor F Hartl, University of Reading; one joint paper in submission.

Theme 4				
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.**

Table 8 - Theme 4 - Science & capability development to match onto product roadmap

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 the UK. Fundamental research in this area is upstream of IMRCs and will feed into them for ongoing implementation into industrial processes.

Example of an EPSRC Grant directly influenced and/or supported by the Network

Themes 3 & 4:
New Enzymatically Produced Interpenetrating Starch-Cellulose Gels
2016-2020

EP/N033310/1 (£949,836) **Edler, K.**
EP/N033337/1 (£610,417) **Khimyak, Y.**
EP/N03340X/1 (£797,598) **Eichhorn, S.**
EP/N033167/1 (£402,975) **Field, R.**

The project aims to translate existing academic research to enable the production of interpenetrating network (IPN) gels of starch and nanocellulose fibres using side-by-side enzymatic and/or bacterial synthesis routes. These IPN gels will be produced with the end aim of use in the food and home care industries. The project will develop tandem enzymatic processes for the production of small fragments of starch, xyloglucan and cellulose, assembly of components into gels in the presence of water, and characterisation of the mechanical and physical properties of the gels. We will valorise waste, making new products, reducing costs and CO2 emissions for the companies we will support through this technology. Industrial input will guide development of the gels, targeting key industrial applications. No research has yet developed gels based on industrial biotechnology approaches to produce small molecules of starch combining them with cellulose fibrils.

http://gow.epsrc.ac.uk/NGBOViewGrant.aspx?GrantRef=EP/N03340X/1

4.7 Theme 5

A Roadmap for Developing Self-Optimised Chemical Systems through Self-Evolution

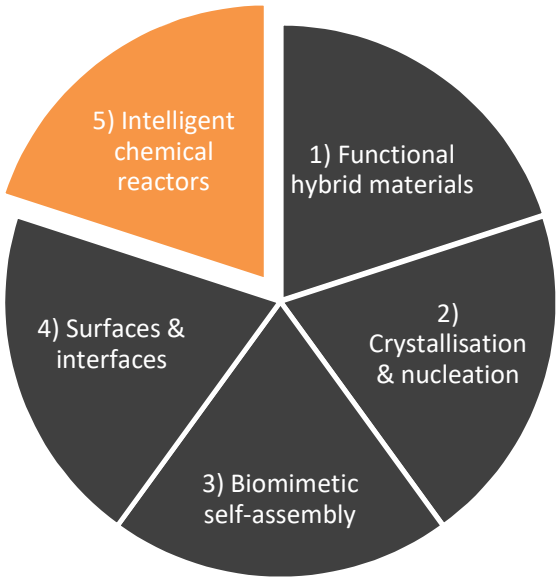


Figure 16 – Theme 5

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.

Network Award Example – Proof of Concept Project (Pump-priming)

Themes 1, 2 & 5:
Structural and Diffusion Characterisation of Soft Materials
Pump-priming project, grant awarded in 2012.

Details at time of application: ***Lloyd, G.*** *(Research Fellow, School of Engineering and Physical Sciences, Heriot-Watt University),* ***Khimyak, Y.*** *(Professor, School of Pharmacy, University of East Anglia).*

The Challenge
One of the key problems facing supramolecular chemists that work on soft materials such as gels is the experimental determination of atomistic models of the extended structures of the materials. These finely detailed structural models, if obtained, would provide incredibly important scientific knowledge allowing for further tuning of the properties of the materials, the design of the compounds that form these materials and the application of these materials in solving real life societal difficulties.

Long Term Goal
The problem of obtaining reliable atomistic structural models of gels pertains to the fact that the solid component of the material is highly diluted, often being less than 1 % by weight and often has only one-dimensional periodicity. This work will help towards the development of application of complex supramolecular gels for molecular recognition and host-guest chemistry.

Work advancing the Roadmap
The aim of this project was to use newly developed NMR techniques and probes suitable for studies of viscous liquids and soft materials to delve into the structural characteristics of a series of low molecular weight gels. The combination of advanced NMR (in solution, solid and gel states) with other experimental and computational methods led to the development

of characterisation methodology suitable for understanding of soft materials with different structural and dynamic domains.

Impact

EPSRC Grant
Development of NMR methods suitable for probing gels are different dynamic regimes was instrumental for application of such tools for other systems. Such methods will be expanded within the recently awarded project "New Enzymatically Produced Interpenetrating Starch-Cellulose Gels" (Industrial Biotechnology Catalyst, EPSRC grant involving UEA, Universities of Bath, Exeter and JIC - Total grant about £3.2 M, EP/N033337/1 project to start in June 2016) also facilitated by DA network.

Papers
The methodology developed in the project has enabled the following publications:
1. Francesca Piana, David H. Case, Susana M. Ramalhete, Giuseppe Pileio, Marco Facciotti, Graeme M. Day, Yaroslav Z. Khimyak, Jesús Angulo, Richard C. D. Brown and Philip A. Gale Substituent interference on supramolecular assembly in urea gelators: synthesis, structure prediction and NMR Soft Matter (2016), DOI: 10.1039/c6sm00607h.

2. Karol P. Nartowski, Jack Tedder, Doris E. Braun, László Fabian and Yaroslav Z. Khimyak Building solids inside nano-space: from confined amorphous through confined solvate to confined 'metastable' polymorph Phys. Chem. Chem. Phys., (2015), 17, 24761-24773.

3. Karol P. Nartowski, Susana M. Ramalhete, Peter C. Martin,Jamie S. Foster, Margaux Heinrich, Mark D. Eddleston, Hayley R. Green, Graeme M. Day, Yaroslav Z. Khimyak and Gareth O. Lloyd, The Plot Thickens, Gelation by Phenylalanine in Water and Dimethyl Sulfoxide (Manuscript in preparation).

4. Susana M. Ramalhete, Karol P. Nartowski, Nichola Sarathchandra, Jamie S. Foster, Jesús Angulo, Gareth O. Lloyd and Yaroslav Z. Khimyak, Supramolecular multi-component hydrogels: molecular level understanding on the addition of guest molecules using NMR spectroscopy (manuscript in preparation).

Fellowship
The DA pump-priming grant helped towards Dr Lloyd's completion of his probationary period and was awarded a Royal Society of Edinburgh/Scottish Government Personal Research Fellowship (5 year tenure track award) with gels playing a key role.

Other
The grant was beneficial in formulating directions for NMR facility in UEA. The combined application of structural and modelling tools along with NMR led to important methodological advances suitable for probing supramolecular systems at different time and length scales.

This contributed to achieving the major objectives of the DA network, i.e. gaining molecular level understanding of complex intermolecular interactions in materials where control of such properties is essential for directing their properties and, as a result, future applications.

Theme 5				
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**

Table 9 - Theme 5 - Table showing science & capability development to match onto product roadmap

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.

Example of an EPSRC Grant directly influenced and/or supported by the Network

Theme 5:
Advanced Flow Technology for Healthcare Materials Manufacturing
2015-2020

EP/M015157/1 (£2,482,246) **Gavriilidis, A, Makatsoris, H.** et al.

We focus on the manufacturing of gold nanoparticles (Au-NPs) and iron oxide magnetic nanoparticles (MNPs). These materials have existing applications in diagnostics and therapeutics. Bespoke monodispersed functionalised NPs offer new applications in antimicrobial surfaces (Au NPs plus dye) and in a new hyperthermia treatment for cancer (MNPs). UCL is at the forefront of the engineering approach to make nanoparticles as well as being world leading in magnetic hyperthermia and antimicrobial surfaces.

Using chemical engineering principles and systems engineering methodologies within a multidisciplinary framework, our research will demonstrate not only the need to consider key physical phenomena (mixing, heat transfer etc.) in nanoparticles synthesis, but also how to account and address related manufacturing challenges from the outset. In this way, an important benefit of this project will be to provide a paradigm shift in nanoparticle synthesis and production and bridge the discovery-manufacturing divide.

http://gow.epsrc.ac.uk/NGBOViewGrant.aspx?GrantRef=EP/M015157/1

5. 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, the community has made progress on the short term goals set out in this Roadmap. Progress has been driven by Network meetings, awards (pump-priming, travel, seedcorn) and major EPSRC grants. The Network has continuously engaged the community to evaluate and keep track of research targets and has focused on 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:

Theme 1

- Control of multi-component self-assembly in solution, on surfaces or in crystals
- Understanding emergent function and structure / functional relationships
- Understand and control the evolution of functions and properties across length and timescales

Theme 2

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

Theme 3

- A better understanding of complex biological functional materials
- Development of bioinorganic chemistry

Theme 4

- Control of processing conditions for templating and surface coatings
- Design of solid formulations for targeted and controlled delivery

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 from atomistic to coarse grain, including the nanoparticle regime
- Strengthen collaborations between experimentalists and theorists

Table 10 - Summary of Individual Theme Recommendations

5.1 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, have proven to be very successful vehicles for progress and may continue to open up new possibilities.

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 [14].

Nucleation, Crystallisation & Dissolution Methodologies for Making Better Pharmaceuticals and Agrochemicals, Faster and More Efficiently

This opportunity arises from progress and 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 across the diverse and extensive DA Network members and partners, using directed assembly techniques to produce and deliver active reagents, drawing on an intimate combination of modelling and experiment and a range of materials types. 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 EPSRC Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation (CMAC) in which Network members are heavily engaged, to the National Formulation Centre, and would provide strong experimental input to newly-established efforts in digital drug design such as

the ADDoPT (Advanced Digital Design of Pharmaceutical Therapeutics) project. 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, and offers complementarity and diversity of community engagement and access to research across a wide range of materials types, in support of a major UK academic-industrial priority domain.

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 envisaged in this opportunity area will offer the potential for the Directed Assembly Network to engage its diverse range of excellence and expertise on a wide range of research across a range of extended materials types that 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. Here there are close links with the Catalysis Hub, centred on the Harwell Campus, and several of the DTCs in chemistry, chemical engineering and sustainable technologies.

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.

5.2 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. The Directed Assembly Network awards have been deployed in flexible and cost-effective ways, delivering rapid progress in developing these topics through feasibility studies and pump-priming projects.

Projects funded through the Network has helped to drive Fellowships, including the development of links amongst the academic community and with industry, and formed the foundation work for larger, focused proposals for making progress in specific areas. They have helped steer research rapidly to maturity to feed into EPSRC priorities in a timely manner [15].

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.

5.3 Structural Recommendations

To deliver the potential of the research areas identified by the Grand Challenge, the 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. 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;

- Long-term aspiration: the development of the Worldwide Institute for Directed Assembly (WIDA), 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.

6. 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.

The Network's ethos to continuously engage, evolve and adapt is key to its success and will continue to underpin all of its activities. The evolution to include the three challenge streams: directed assembly, disassembly, translation & scale-up, reflects these values and helps towards ensuring that the Network adds great value to the community and the UK. Directed disassembly is becoming increasingly important and is fundamentally linked to our work on directed assembly. New and increasing relationships with practitioners and industry-based stakeholders will enable the Network to foster pathways to translation and further assist in the development of multi-disciplinary collaborations that address upcoming scientific, engineering and industrial challenges.

To achieve these goals, we must continue to 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 further 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 Network funding and subsequent Research Council grants:

- 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.
- 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.

7. NETWORK MANAGEMENT

7.1 Network Management Team

Prof. Paul Raithby was the PI on the Directed Assembly Grand Challenge Network for both Phase one (2010-2012) and Phase two (2012-2016). He is now Co-I for Phase three (2017-2020).

He is Chair of Inorganic Chemistry at the University of Bath. He successfully completed an EPSRC Senior Research Fellowship in December 2011. He has a track record of extensive funding (currently £5.4 M from EPSRC as PI and has over 800 published papers (h-index 60). PRR was President of the British Crystallographic Association (BCA; 2006-2009), a Member of EPSRC TOP/SAN (2010-2015) and is currently the Chair of Trustees of the Cambridge Crystallographic Data Centre. He was awarded the RSC Structural Chemistry Prize in 2008 and Corday-Morgan Medal in 1988.

Prof. Harris Makatsoris was Co-I on the Network for phases one and two (2010-2016). He is PI for Phase three 2017-2020.

He joined Cranfield University as Professor of Manufacturing in May 2016. He has extensive expertise in process engineering, manufacturing operations and control and has been developing intelligent reactor platforms for functional materials synthesis and scale-up for the last 10 years. His team is multidisciplinary with a ~£5m industry, EPSRC, EU research portfolio and has been a member of the steering group of the EPSRC Network Dial A Molecule. He has 70 peer reviewed papers, one patent and a book. He is a graduate of Imperial College, has a track record in programme management, technology transfer; several years commercial experience prior to returning to academia and ten years of experience working at the interface between chemistry and engineering.

Dr. Julian Rose has been the Network Manager since May 2015. He has a wealth of experience in research and knowledge transfer, graduating with a first class engineering degree and PhD from the University of Bath. He also has extensive experience in leadership, communications and strategy. Julian was awarded both the Westminster Medal and Engineering Medal at the Houses of Parliament at SET for Britain in 2010. He is passionate about innovation and communicating research, and is a natural and influential people person.

Dr. Jenny Woods was Network Manager between 2010-2014. Jenny is a physicist by training and has applied that scientific background widely, from managing peer review processes at the EPSRC to acting as 'Science Ambassador' at the University of Bath - enhancing impact by connecting physical sciences and engineering to social science and the humanities. She has a keen interest in the routes by which scientific evidence can be used to inform policy making. She now works for the University of Manchester, based at Diamond Light Source.

7.2 Core Team

The Core Team will undertake the duties to support the development of the Network, including attracting wider industrial participation, fostering international links, supporting the PI, Co-I and the Network Manager. They will spend on average 2 hours per month on the project.

Prof. Andy Bayly (AB) Chair in Chemical Engineering at the Institute of Particle Science and Engineering (IPSE) at the University of Leeds. Prior to this he spent 18 years working for Procter and Gamble, designing, developing and scaling up particulate products. In particular, he was known for the development of pilot plant, experimental and modelling techniques which improved the predictability of scale-up of complex formulations for P&G that led to awards.

Dr Niek Buurma (NB) obtained his degree and PhD in physical organic chemistry, both cum laude, from the University of Groningen. Following postdoctoral work in chemical biology and biophysical chemistry at The University of Sheffield, he was appointed to a Lectureship in physical organic chemistry at Cardiff University in May 2006. He has been a DAGCN Champion since 2011.

Prof. Neil Champness (NC) was promoted to Chair of Chemical Nanoscience in 2004, University of Nottingham. He is Head of Inorganic and Materials Chemistry, Faculty of Science. He is a Royal Society Wolfson Merit Awardee (2011-2016) and a Fellow of the Learned Society of Wales, IUPAC and the Royal Society of Chemistry. In 2011 he was named as one of the top 100 most cited chemists of the previous decade and in 2014 he was recognized as a Thomson Reuters Highly Cited Researcher. He has been a DAGCN Champion since 2012.

Prof. Chris Frampton (CF) is Professor of Structural Chemistry and Crystal Engineering within the Wolfson Centre for Materials Processing at Brunel University. He has 24 years' experience in the pharma sector, including Roche Discovery being integral part of the teams that launched drugs such as the Tamiflu® and an HIV protease inhibitor Invirase®. Then he co-founded Pharmorphix Ltd., a CRO company, until its acquisition in August 2006. In 2008 he co-founded Nuformix Ltd., a company exploiting cocrystal technology for pharma and other functional crystalline materials. He has authored over 130 peer-reviewed papers (h-index 23).

Prof. George Jackson (GJ) is Professor of Physical Chemistry in the Department of Chemical Engineering at Imperial College London. A major achievement of his career has been a seminal contribution to the development of a highly accurate equation of state for the thermodynamic properties of complex fluid mixtures: the statistical associating fluid theory (SAFT), placing the UK at the leading edge and has contributed to his ranking in the ISI 1% most cited chemist listing since 1997. He is the PI of a £3.6M EPSRC grant, Molecular Systems Engineering: (EP/E016340/1). He has been a Directed Assembly Network Champion since 2010.

Prof. Yaroslav Khimyak (YK) was awarded a Chair in solid-state NMR spectroscopy in the School of Pharmacy in UEA in 2011. Before, he was a Senior Lecturer at the Department of Chemistry in the University of Liverpool. Yaroslav graduated from Ivan Franko Lviv State

University in the Ukraine with an M.Sc. in Chemistry, an M. Phil. and a Ph.D. from the University of Cambridge and held a position of Oppenheimer Research Fellow in Chemistry at Cambridge.

Prof. Panos Louvieris (PL) is Professor of Information Systems and leads the Defence & Cyber Security (DCS) research group in the Department of Computer Science at Brunel University London. His research interests are data and information fusion and data analytics and his research is funded by EPSRC. He is committee member of the EPSRC Digital Personhood Net.

Dr Anna Peacock (AP) was appointed as a Lecturer in the School of Chemistry in 2009, University of Birmingham. Anna's research interests lie in the field of bioinorganic chemistry and de novo peptide design. In particular, her research is directed at the development of novel metallopeptides with potential therapeutic applications. She has been a DAGCN Champion since 2012.

Prof. Chick Wilson (CCW) is Chair of Physical Chemistry and Associate Dean for Research at the University of Bath; previously (2003-2010) Regius Chair in Chemistry at the University of Glasgow, Director of the WestCHEM Research School and Head of Department. He led the Crystallography Group at the ISIS neutron source for 12 years (1992-2004), was Visiting Professor at the Univ of Durham (2001-2006), President of the British Crystallographic Association (BCA; 2003-2006) and Adjunct Professor at the Univ. of Tennessee, USA. He has published over 310 research papers and has been one of the leaders of the Directed Assembly Network since 2010.

In summary:

First Name	Last Name	Position
Andy	**Bayly**	Chair in Chemical Engineering at the Institute of Particle Science and Engineering (IPSE) at the University of Leeds
Niek	**Buurma**	Lecturer in physical organic chemistry at Cardiff University
Neil	**Champness**	Chair of Chemical Nanoscience, University of Nottingham
Chris	**Frampton**	Professor of Structural Chemistry and Crystal Engineering within the Wolfson Centre for Materials Processing at Brunel University
George	**Jackson**	Professor of Physical Chemistry in the Department of Chemical Engineering at Imperial College London
Yaroslav	**Khimyak**	Chair in solid-state NMR spectroscopy in the School of Pharmacy, University of East Anglia
Panos	**Louvieris**	Professor of Information Systems and leads the Defence & Cyber Security (DCS) research group in the Department of Computer Science at Brunel University London
Anna	**Peacock**	Lecturer in the School of Chemistry in 2009, University of Birmingham
Chick	**Wilson**	Chair of Physical Chemistry and Associate Dean for Research at the University of Bath

Table 11 – Core Team

7.3 Early Career Researcher Panel

A panel comprised of early career academics from a wide range of disciplines relevant to the Grand Challenge, who have shown strong support and dedication to the Network, includes:

First Name	Last Name	Position
Niek	**Buurma**	Lecturer in physical organic chemistry at Cardiff University
Barbara	**Ciani**	Biophysical Chemistry, University of Sheffield
Tim	**Easun**	Royal Society URF, University of Cardiff
Jonathan	**Foster**	Department of Chemistry, University of Sheffield
Saurav	**Goel**	School of Mechanical and Aerospace Engineering, Queen's University Belfast
Tom	**Hasell**	Department of Chemistry, University of Liverpool
Neal	**Hopkins**	Research Fellow, DSTL
Kim	**Jelfs**	Royal Society URF, Imperial College London
Lars	**Jeuken**	Biophysics, University of Leeds
Jon	**Kitchen**	Inorganic Chemistry, University of Southampton
Helena	**Shepherd**	Department of Chemistry, University of Kent
Valeska	**Ting**	Reader, Chemical Engineering, University of Bristol

Table 12 - Early Career Researcher Panel

7.4 Advisory Committee

The Advisory Committee reflects the relevant disciplines and comprises of academics and industrialists, world leading in their fields. The majority of members have been champions of the Network since 2010. The Committee includes:

First Name	Last Name	Position
Chris	**Bowen**	Professor of Materials Science, Department of Mechanical Engineering, University of Bath
Lee	**Brammer**	Professor of Inorganic and Solid State Chemistry, Chemistry, University of Sheffield
David	**Calvert**	Director, iFormulate Ltd
Bob	**Docherty**	Pfizer
Asterios	**Gavriilidis**	Professor of Chemical Reaction Engineering, Department of Chemical Engineering, UCL
Neil	**George**	Science and Technology Fellow, Syngenta Crop Protection
David	**Leigh FRS FRSE FRSC**	Sir Samuel Hall Chair of Chemistry School of Chemistry, University of Manchester
Panos	**Louvieris**	Professor of Information Systems, Department of Computer Science, Brunel University London
Sally	**Price**	Professor in Computational Chemistry, Department of Chemistry, University College London
Julian	**Rose**	University of Bath (Network Manager 2015-on)
Matt	**Rosseinsky FRS**	Professor of Inorganic Chemistry at the University of Liverpool
Joe	**Sweeney**	Professor of Organic Chemistry, University of Huddersfield
Nguyen	**Thanh**	Professor of Nanomaterials, Department of Physics and Astronomy, University College London
Aron	**Walsh**	Professor of Materials Theory, Department of Materials, Imperial College London
Mike	**Ward**	Professor of Inorganic Chemistry & Head of Department, Department of Chemistry, University of Sheffield
Chick	**Wilson**	Professor and Associate Dean for Research, Department of Chemistry, University of Bath
Jenny	**Woods**	University of Manchester (Network Manager 2010-2014)

Table 13 - Advisory Committee

ACKNOWLEDGEMENTS

The Directed Assembly Network Management Team would like to thank all of the Network members who have contributed their thoughts to the production of this document, whether at community meetings or through written feedback and input.

We also express great thanks to the Core Team, Early Career Researcher Panel and Advisory Committee. In particular, we would like to thank the original Network Champions (in no particular order): Sally Price, Chick Wilson, George Jackson, Mike Ward, Lee Brammer, Matt Rosseinsky, Sophia Yaliraki, Neil Champness, Kevin Roberts, Niek Buurma and Anna Peacock; many of whom continue to play a very active role within the Network.

Further thanks goes to the industrial and academic advisors who added their theme-specific expertise to that of the Champions: Professor Gill Reid, University of Southampton, Dr Robert Docherty, Pfizer; Prof Chris Frampton, Brunel University (formerly at Pharmorphix); Dr Chris Price, University of Strathclyde (formerly at GSK); Dr Richard Storey, AstraZeneca, Professor Neil Hunter, University of Sheffield, Professor Rob Field, John Innes Centre and Professor Lee Cronin, University of Glasgow.

We would also like to thank the partnering organisations that helped draw our community together through promotional activities and provided invaluable advice at the interfaces with industry and other academic disciplines: Academy of Pharmaceutical Sciences, CPOSS network, BBSRC's Synthetic Components Network, Chemistry Innovation Knowledge Transfer Network, the Intelligent Formulation Network and the Diamond User Network.

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Note: The molecular assembly picture used as the Directed Assembly Network logo is generated from a crystal structure reported by Jean-Marie Lehn and coworkers in Angew. Chem., Int. Ed. Engl. 1996, 35, 1838-1840 and is used under Creative Commons Licence. Originally uploaded to en.wikipedia by M Stone.

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