

Proposal for an eSI Theme on “Modelling and Microbiology: using computational methods to understand how biological cells survive, proliferate and evolve”

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Synopsis (100 words or less): This theme will identify the key future research directions and challenges at the interface between computational modelling and microbiology. Development of ideas will take place via a series of three workshops focused on specific research areas. The results will be published in a roadmap document, which will be disseminated at a final workshop and ultimately as a journal article. This will act both as a rallying point and as a guide for future research. This theme builds on the work of the StoMP network, which has established contacts between microbiologists, physical and computer scientists and mathematicians over the period 2007-2010.

1. Theme topic and brief description

The potential contribution that computational modelling can make to our understanding of biological systems is enormous. Computer simulation allows quantitative testing of whether a proposed model fits the observed experimental results, and may also lead to completely new insights into a biological system, by allowing a whole range of “in silico” experiments which would be difficult, expensive or even impossible in the lab. Biological systems also have an important contribution to make to the computational, mathematical and physical sciences: presenting new problems and challenges to spur the development of new methodology. Facilitated by the activities of the StoMP network (see below), a sizeable UK community has developed over the last few years at the interface between microbiology and the computational/physical sciences. However, this community is scattered, both geographically and in its research activities. Much more could be achieved by identifying a small number of key topics as rallying points for this community and as nuclei for multi-investigator collaborations. This is the aim of our proposed theme.

Microbiology is the science of microbes. These are single-celled, microscopic, living organisms which exist in huge populations in almost every possible location on Earth, from hot sulphur springs to the human gut. As well as their well-known potential for causing disease, microbes are crucial for the functioning of the Earth’s biogeochemical cycles (and thus a key factor in predicting and mitigating global climate change) and are essential for many industrial processes such as fermentation and waste water treatment. Microbes are also an ideal starting point for understanding how biological processes work in higher organisms, populations and ecosystems, since they are small, fast-growing and easy to manipulate in the laboratory.

From a computational point of view, microbes present both opportunities and challenges. Because their populations are very large (typically $\sim 10^9$ individuals), high performance computational methods are needed to simulate, for example, spatially structured microbial communities. Moreover, microbial populations often display stochastic heterogeneity: genetically identical cells may show a range of different behaviours. As it is often the outliers in a population which survive environmental stresses such as antibiotic treatment, understanding the effects of heterogeneity on population dynamics is an important goal for computational modelling. Other challenges are associated with understanding the chemical reaction networks which control the behaviour of a single microbial cell: here one needs to find computationally efficient methods for determining the dynamical behaviour of many interlinked chemical reactions. Computational modelling of microbial systems also has great potential for furthering our understanding of evolution. For animals and plants, evolution acts on timescales of billions of years, making laboratory experiments impossible. However, microbes grow fast enough to evolve on laboratory timescales, making them ideal model systems for studying evolutionary processes. Large-scale computation has an essential role to play in guiding and interpreting such experiments, as well as in generating and testing new general hypotheses about evolution.

This theme will build on the achievements of the StoMP research network (Stochastic Modelling for Prokaryotes). This network was funded by a 3-year £80K grant from BBSRC under the MATSYB (Mathematical Tools for Systems Biology) initiative, awarded to Drs Allen, Stekel and Wood. Since 2007, StoMP has organised interdisciplinary events approximately once per year. From an initial membership of 15, StoMP has expanded to ~60 members, approximately half of whom are microbiologists and half mathematicians, computer scientists and physicists. StoMP activities have included organising a “meet and greet” workshop (York, 2007, ~20 participants), a training workshop involving lab-based and computer-based activities (Birmingham, 2008, ~45 participants) and a research conference entitled “Noisy Genes: Modelling and Microbiology” which was hosted by the eSI in July 2009, with ~80 participants. A second training workshop is planned for July 2010, in York. StoMP also runs a website (www.stompnet.org) and mailing list and sponsors small satellite meetings within the overall theme of modelling in microbiology. We have received excellent feedback on all these activities: for example, on a scale of 1-5, the average scores awarded by delegates at our eSI event were 4.5, 4.3, 4.5 and 4.5 for enjoyability, usefulness, talk quality and networking opportunities.

The activities of StoMP have created a sense of community among microbiologists and “modellers”. A number of leading StoMP participants have emerged who are actively engaged in interdisciplinary work. However, these research activities are not coordinated. The interdisciplinary community has now reached a critical mass where it could become much more productive and effective by identifying key future research directions along which to proceed in a collective manner. This requires an intensive series of discussions and dissemination of the outcomes, which is beyond the scope of StoMP. Achieving such coordination is the purpose of this eSI theme.

The central deliverable of this theme will be a roadmap document which will act as a rallying point for this community. This document will identify future research directions around which collaborative groupings can be built, focusing on three key areas: stochastic modelling, modelling of evolution and modelling of large-scale networks. The roadmap will also act as an information source on computational challenges in this area for computer scientists, mathematicians and physicists. Consensus on the contents of the roadmap will be achieved via a series of workshops (see Sections 5 and 8 below). The ideas arising from these discussions will be disseminated to and endorsed by the wider modelling and microbiology community at a larger workshop towards the end of the 12 month period.

2. Proposed leaders with brief description of their areas of specialisation.

The theme will be led jointly by Dr. Rosalind Allen (University of Edinburgh), Dr. Dov Stekel (University of Nottingham) and Dr. Jamie Wood (University of York), with Dr. Allen as primary contact.

Dr. Rosalind Allen (RJA) is a Royal Society University Research Fellow and proleptic lecturer in the School of Physics and Astronomy at Edinburgh University. She has extensive expertise in computer simulation of biological systems. Her research achievements include the development of the Forward Flux Sampling method for simulating rare events in nonequilibrium systems, which is widely used in soft matter and biological physics, and the discovery of intermittent wetting dynamics in hydrophobic nanopores, which is important in biological ion channel gating. Dr. Allen currently uses both computational and experimental methods to study microbial ecosystems and gene regulation.

Dr. Dov Stekel (DJS) is Associate Professor in Integrative Systems Biology at the School of Biosciences, University of Nottingham. He has a wide range of experience of mathematical, computational and statistical modelling, working in both industry and academia, in many biological systems from microbes to man. His current research is focussed on using mathematical and computational techniques to model transcription regulation in bacteria, with a particular emphasis on the evolution of stress responses. DJS is author of a leading book in computational biology (Microarray Bioinformatics, CUP).

Dr. Andrew James Wood (AJW) is an RCUK fellow in Biological Complexity at the University of York. He holds a joint appointment between the Mathematics and Biology departments as part of the York Centre for Complex Systems Analysis. AJW is establishing an inter-disciplinary research portfolio on the interface between mathematics, computer modelling and biology, with a particular focus on applications to microbiology. Current projects include modelling the respiratory pathway design and the anaerobic/aerobic switch in *Neisseria Meningitidis* (with James Moir, York), developing differential equation models of *E. coli* respiration to include the BD-I system (with Jeff Green, Sheffield) and modelling the impact of growth dynamics on gene networks, especially phase varying motifs.

RJA, DJS and AJW were co-PIs on the 2007 BBSRC grant which led to the StoMP research network.

3. Relation to e-Science.

a. Please describe the application areas that would benefit from the outcomes of this theme.

The main beneficiaries of this theme will be microbiologists who use computational modelling in their research and physical/computational scientists who work on microbial systems. The development of key ideas for future research, summarized in the roadmap document generated by this theme, will provide direction for collaborative research within and between these groups of scientists. Such direction is essential if the UK community at the microbiology-modelling interface is to be successful in proposing large well-supported collaborative research projects.

By raising the profile of research at the microbiology/modelling interface, and through the planned final larger workshop, this theme will also engage a wider community of microbiologists who do not yet use computational modelling in their research and physical/computational scientists not yet familiar with biological problems. By reaching out to these scientists, the theme will generate new members of the e-Science community as well as in the longer term, new e-Science applications and solutions.

b. Please list the technical areas that would be engaged and developed as a result of the theme.

Computational challenges that are central to this theme include:

- (i) Development and use of high-level stochastic computational algorithms to simulate molecular interaction networks. More efficient methods are required to supersede the widely-used "Gillespie Algorithm", which becomes inefficient when the system involves many chemical reactions. Other challenges include the need for new algorithms to analyse large reaction networks whose kinetic parameters are unknown.
- (ii) Development of multiple-timescale computer simulation algorithms, which include intra-cell, population and evolutionary dynamics. Such simulations present considerable computational challenges, especially if one also aims to simulate spatially structured populations.
- (iii) Computational challenges associated with metabolic modelling include the need for efficient multidimensional optimisation routines and databases in which metabolic models which have been developed for different organisms can be stored and made available to other researchers.

4. Are there other similar projects to the proposed theme? What would be their relationship to/involvement in this programme?

We plan to apply to another funding body (most likely BBSRC) to support a series of training workshops for PhD students and postdocs. These would follow on from the StoMP training workshops of July 2008 (Birmingham) and July 2010 (York). If funded, these workshops would be complementary to the eSI theme, since they would be training-oriented while the eSI theme would focus on research.

To our knowledge, the only other UK grouping at the microbiology-modelling interface is the EPSRC-funded MMEMS network (Mathematical Modelling and Experimental Microbial Systems). MMEMS focuses on evolutionary ecology. We have already had positive interactions with the MMEMS co-ordinator Dr. Ivana Gudelj about linking the MMEMS network with our e-volution sub-theme. This would probably take the form of inviting leading MMEMS members to participate in the e-volution workshop. Several other UK research networks focus on different but complementary topics to that proposed here. The GENESYS network is concerned with genetic network inference (inferring the structure of gene networks from experimental data), while SIGNET focuses on cell signalling. StoMP has already developed close ties with GENESYS: their representatives have been present at all StoMP activities and *vice versa*. We would seek to maintain these interactions in the context of the eSI theme: for example, by inviting members of these other networks to attend our larger workshop, and the smaller workshops as appropriate.

Several web-based resources are available in this area. These include the Ecolihub database of information on the *Escherichia coli* bacterium (see Section 3); its founder Barry Wanner (Purdue University) has agreed to participate in this theme. Smaller databases also exist for other microbial species.

Productive interaction is also expected with the EPSRC-funded Centre for Numerical Algorithms and Intelligent Software (NAIS), who have agreed to fund 1-2 workshop speakers for this theme (see sections 9 and 13 below).

5. Identify a focus that will ensure the effort is most likely to be productive i.e. a specific test application domain/current unsolved research challenge.

The theme will focus on three specific research areas: modelling stochastic effects in microbial cells and populations (led by RJA), modelling evolutionary processes (led by DJS) and modelling large-scale

molecular and metabolic interaction networks (led by AJW). For each of these research areas, we will bring together a small number (~10-20) expert modellers and microbiologists in a workshop, with the aim of identifying the essential ideas, questions and challenges in the area. The results of these workshops will form the basis of the roadmap document which is one of the key deliverables of the theme, and may also nucleate collaborative projects between participants. Section 6 lists experts in each of the three areas who have agreed to participate.

Modelling stochastic effects in microbial cells and populations

It is now widely recognised that individual cells in a population are far from identical, even though they may all be descended from the same ancestor and be exposed to the same environmental conditions. This population heterogeneity arises from the intrinsic randomness (“noise”) in the chemical reactions that control cell behaviour. In some circumstances, this “noise” is believed to be disadvantageous, since it limits the resolution with which cells can detect and respond to their environment. However, in other cases, cells actively exploit noise to generate heterogeneous populations in which individual cells may be in any one of several different possible states at any time. Such heterogeneity is believed to be beneficial for microbial populations in changing and unpredictable environments, yet how the benefits are gained remains unclear. This is an area where computational modelling has an important contribution to make, since explorations of parameter and model space which would be extremely time-consuming in the lab are feasible in a few days using high performance computing. Computational challenges include how to simulate large assemblies of growing cells with several internal states, as well as the development of efficient simulation methods for large networks of stochastic chemical reactions. Biological challenges include the need to identify suitable model systems with which to test the possible benefits of population heterogeneity for microbial growth and survival.

E-volution: modelling evolutionary processes for microbes

The organisms that we study today are the outcome of billions of years of evolution that cannot be replicated directly under controlled and monitored conditions in laboratory experiments. As a consequence, questions about the origins of diversity and complexity, or the relative importance of “chance and necessity” in explaining observations in biology, remain open, and explanations largely hypothetical. Such questions are important in many real-life applications, including facilitating the fight against pathogen evolution. Excellent progress has been made in recent years with evolution experiments on rapidly-growing microbial populations, aided by the advent of affordable high-throughput genome sequencing, which allows the rapid identification of mutations as they happen in the laboratory. Some very successful preliminary work combining such experiments with computational modelling has already been carried out, showing that this is an area where collaboration between experimentalists and modellers can yield significant additional insight. The e-volution subtheme will bring together experimental biologists who carry out laboratory evolution on bacteria with computer modellers who simulate evolution using high-performance computation. Specific challenges include: (i) Can we develop efficient computational methods, including the use of distributed and grid computing, that can simulate the evolution of bacterial gene networks on multiple time scales? (ii) Can we use *in silico* evolution to explain aspects of the diversity and complexity of real-life gene networks? (iii) Can we use *in silico* evolution as a method to predict evolutionary adaptation in laboratory evolution experiments? (iv) Can such modelling be used to predict how new pathogens might evolve?

Modelling large-scale molecular and metabolic interaction networks

Developments in large-scale molecular biology now mean that vast amounts of data on the genes and proteins present in different microorganisms are becoming available. A key challenge is predicting from this data how the organism will behave in different situations (eg is it pathogenic?). This often requires the modelling of very large interaction networks, in which few of the kinetic parameters are known. For metabolic networks (which control cell growth) this issue has been circumvented by flux balance analysis, which can predict the steady-state behaviour of the network, assuming the growth rate is maximised. If the system dynamics are important, the key aim becomes to determine which biologically relevant dynamical behaviours are possible for a given network. For small networks, this can be achieved by constructing a reachability graph (including all possible state-space trajectories). However, this is not feasible for large networks, for which new techniques are required. Challenges in the modelling of large-scale interaction networks, whether at steady state or not, include how best to include in the model what experimental data is available, how to refine models in the light of new data and how to store model information in an accessible way. The development and extension of techniques for modelling large-scale metabolic and molecular interaction networks has significant commercial, medical and industrial relevance, for example in predicting the response of human pathogens to different environmental conditions such as temperature or acidity, or predicting the

optimum treatment strategies from the genome sequences of newly evolved (eg antibiotic-resistant) variants of existing pathogens.

6. Please list any people who have agreed to actively collaborate.

The following people have agreed to actively collaborate (see Section 7 below for the workshops in which they will be involved).

Phil Aldridge (University of Newcastle), Ian Blomfield (University of Kent), Nigel Brown (University of Edinburgh), Albert Burger (Heriot-Watt University), Mike Cates (University of Edinburgh), Dominique Chu (University of Kent), Vincent Danos (University of Edinburgh), Gail Ferguson (University of Aberdeen), Chrisantha Fernando (University of Sussex), Richard Goldstein (National Institute of Medical Research), Igor Goryanin (University of Edinburgh), Mark Goulian (University of Pennsylvania), Jon Hobman (University of Nottingham), Charlie Hodgman (University of Nottingham), Martin Howard (John Innes Centre), Mustafa Khammash (University of California Santa Barbara), Andrzej Kierzek (University of Surrey), Laurence Loewe (University of Edinburgh), Pete Lund (University of Birmingham), Hongwu Ma (University of Edinburgh), JohnJoe McFadden (University of Surrey), James Moir (University of York), Conrad Nieduszynski (University of Nottingham), Bernhard Palsson (University of California, San Diego), Mark Poolman (Oxford Brookes), Wilson Poon (University of Edinburgh), Gail Preston (Oxford University), Mamen Romano (University of Aberdeen), Jon Rowe (University of Birmingham), Daniel Rozen (University of Manchester), Ian Stansfield (University of Aberdeen), Peter Swain (University of Edinburgh), Marco Thiel (University of Aberdeen), Gavin Thomas (University of York), Stratis Viglas (University of Edinburgh), Erik de Vink (Technische Universiteit Eindhoven), Barry Wanner (Purdue University), Patrick Warren (Unilever Research and Development), Pieter Rein ten Wolde (AMOLF, Amsterdam), Marjan van der Woude (University of York), Jeremy Zucker (Harvard University).

7. Sketch of who is probably working in the area, and/or might be interested.

Below we list leading scientists in our three chosen focus areas, and indicate with a star those who have already agreed to participate.

Modelling stochastic effects in microbial cells and populations

- * Dr. Phil Aldridge (University of Newcastle, Biological Science)
- * Professor Ian Blomfield (University of Kent, Biological Science)
- * Professor Nigel Brown (University of Edinburgh)
- * Professor Mike Cates (University of Edinburgh)
- * Dr. Gail Ferguson (University of Aberdeen)
- * Professor Mark Goulian (University of Pennsylvania, Physics and Biology)
- * Dr. Leendert Hamoen (University of Newcastle, Biological Science)
- * Professor Martin Howard (John Innes Centre, Systems Biology)
- * Professor Mustafa Khammash (UC Santa Barbara, Engineering)
- * Dr. James Moir (University of York, Biological Science)
- * Dr. Mamen Romano (University of Aberdeen, Physics)
- * Dr. Ian Stansfield (University of Aberdeen, Institute of Medical Sciences)
- * Professor Peter Swain (University of Edinburgh, Systems Biology)
- * Dr. Marco Thiel (University of Aberdeen, Physics)
- * Professor Barry Wanner (Purdue University, Biology)
- * Professor Pieter Rein ten Wolde (AMOLF, Amsterdam, Modelling Biochemical Networks)
- * Dr. Marjan van der Woude (University of York, Biological Sciences)

Professor Judy Armitage (University of Oxford, Systems Biology)
Professor Ian Booth (University of Aberdeen, Institute of Medical Sciences)

E-volution

- * Dr Dominique Chu (University of Kent, Computer Science)
- * Dr. Chrisantha Fernando (University of Sussex)
- * Dr Richard Goldstein (MRC National Institute for Medical Research, Mill Hill, London)
- * Dr. Jon Hobman (University of Nottingham, Biosciences)
- * Professor Charlie Hodgman (University of Nottingham, Bioinformatics and Systems Biology)
- * Professor Roberto Kolter (Harvard Medical School, Microbiology)
- * Dr Laurence Loewe (University of Edinburgh, Systems Biology)
- * Dr. Peter Lund (University of Birmingham, Biological Sciences)
- * Dr. Conrad Nieduszynski (University of Nottingham, Genetics)
- * Professor Bernhard Palsson (University of California, San Diego, Systems Biology)
- * Professor Wilson Poon (University of Edinburgh, Physics)

* Dr. Gail Preston (Oxford University, Plant Sciences)
* Dr Jon Rowe (University of Birmingham, Computer Science)
* Dr. Daniel Rozen (University of Manchester, Life Sciences)
Professor Uri Alon (Weizmann Institute)
Professor Richard Lenski (Michigan State University)
Professor Andreas Wagner (University of Zurich)

Modelling large-scale molecular and metabolic interaction networks

* Dr. Albert Burger (Heriot-Watt University and MRC Human Genetics, Maths and Computer Science)
* Professor Vincent Danos (University of Edinburgh, Informatics)
* Professor Igor Goryanin (University of Edinburgh, Informatics and Systems Biology)
* Dr. Andrzej Kierzek (University of Surrey, Systems Biology)
* Dr. Hongwu Ma (University of Edinburgh, Systems Biology)
* Dr. JohnJoe McFadden (University of Surrey, Biological Sciences)
* Dr. Mark Poolman (Oxford Brookes University, Life Sciences)
* Dr. Gavin Thomas (University of York, Biological Science)
* Dr Stratis Viglas (University of Edinburgh, Informatics)
* Dr. Erik de Vink (Technische Universiteit Eindhoven, Maths and Computer Science)
* Dr. Patrick Warren (Unilever Research Port Sunlight)
* Dr. Jeremy Zucker (Harvard Medical School)
Dr. Dany Beste (University of Surrey, Biosciences)
Professor David Fell (Oxford Brookes University, Life Sciences)
Dr. Jason Holder (MIT, Biology)
Dr. Chris Knight (University of Manchester, Systems Biology)
Professor Darren Wilkinson (Newcastle, Mathematics and Statistics)

We plan to disseminate the results of the theme to a wider community of modellers and microbiologists in the UK and abroad at a final theme workshop. Our recent StoMP conference, hosted by eSI, attracted ~80 delegates; we expect the final workshop to attract a similar number of people.

We are also keen to increase our interactions with industry. Dr. Patrick Warren of Unilever Research and Development has been an active member of StoMP and has agreed to participate in this theme. We would welcome suggestions from the Programme Committee / Science Advisory Board as to how we might further increase the level of industrial participation.

8. Identify the current key research challenges(s) in the area.

The key current research challenge in this area is to determine how the enormous power of computational modelling can be used to answer questions of real interest and importance to microbiologists. Computational approaches are often interesting to the “modelling” community, while failing to resonate with microbiologists. Conversely, microbiologists are often keen to model their system without understanding the range of tools / techniques available or without realising what new scientific questions might arise from a physical/computational approach. To overcome these barriers it is essential that microbiologists, computer scientists, physicists and mathematicians communicate with one another on an equal footing, and that specific directions are determined where modellers and microbiologists can work together most productively in a collective way. This is the purpose of the proposed theme.

For our three proposed focus areas, specific challenges are:

Modelling stochastic effects in microbial cells and populations: development of efficient stochastic simulation methodologies for large systems; integrating cell-level and population-level models; identifying suitable biological model systems.

E-volution: development of multi-scale algorithms for simulating evolutionary processes; determining to what extent *in silico* evolutionary algorithms are a realistic model for natural selection; finding suitable biological models for experimental tests of evolution.

Modelling large-scale molecular and metabolic interaction networks: developing flux-balance models for a new biologically and industrially relevant microorganisms; improving flux-balance models to incorporate known kinetic and expression data; developing new methods for determining possible behaviours of large systems out of steady state, where parameters are unknown.

9. What are the plausible outcomes (deliverables) from the theme? Journal papers, books, reports? Will they be entirely theoretical, or will there be some experiments and/or software produced?

The main deliverable of the theme will be a jointly authored roadmap document arising from the three targeted workshops. This document will contain the results of the development of ideas that has taken

place during the theme. The roadmap will identify a small number of key scientific questions around which community research can focus, and will also highlight areas where high performance computing and new algorithms are needed – thus acting as an information source for other programmes such as NAIS. The roadmap will be disseminated at the larger theme research workshop as well as at other conferences and workshops (see Section 10). We aim ultimately to publish the contents of the roadmap as a “perspectives” article, or as a full review article, in a major journal such as Molecular Systems Biology, PLoS Computational Biology, Molecular Microbiology or Nature Reviews Microbiology, to ensure its dissemination to the widest possible audience. Contributions to, and authorship of, the roadmap document will come from across the microbiology, computer science, physics and mathematical disciplines, so that this document will truly represent a consensus focal point for the emerging microbiological modelling community.

A second deliverable of the theme will be sustainable research collaborations. We expect at least one collaborative grant application to emerge from the theme in each of the three focus areas, although the timescale for actual submission of such proposals might be longer than the 12 month period of the theme. StoMP activities have already led to collaborative grant proposals between RJA and Ian Stansfield (Aberdeen) and between Marjan van der Woude (York) and Mustafa Khammash (UCSB).

We do not have specific plans to produce any experimental data or software. However, an outcome of the theme will be the nucleation of new collaborative projects and a strengthening of the research community at the modelling-microbiology interface, which will in the long term lead to both data and software production.

10. Sketch the kind of events (focus/scope) proposed, where they would be held and who would participate.

We propose to organise the following events:

- Three workshops, each focusing on one of the three research topics identified in Section 5. The “Stochastic modelling” workshop will be coordinated by RJA, the “E-volution” workshop by DJS and the “Modelling large networks” workshop by AJW. These workshops will bring together 10-20 expert microbiologists, physicists, mathematicians and computer scientists working in these fields (see Section 7 above), to identify key questions and future directions. To ensure that these workshops are effective in delivering content for the roadmap, an editorial group, consisting of the theme leaders and several other researchers, will meet together for 1-2 days before the workshop to generate a list of key questions to be answered during the workshop. Other participants will then join for a ~2 day programme of intensive discussions based around this framework. Following the workshop, the editorial group will stay behind for ~1 extra day to draft a report on the outcomes, which will be used in writing the roadmap. eSI would be an ideal venue for these workshops.
- One larger (~4 day) research workshop / conference, with a broader research agenda, at which the contents of the roadmap will be disseminated to and discussed by a wider community. This will take place towards the end of the 12 month period and is likely to attract ~100 participants. Again, eSI would be the ideal location for this meeting.
- Research visits by theme leaders and other participants to eSI to prepare the roadmap document and to discuss plans for collaborative projects.
- Presentation of theme results at other conferences and workshops: e.g. Society for General Microbiology meeting, International Conference in Systems Biology, European Society for Evolutionary Biology conference 2011, CCGrid conference, 2011 ESEB congress (European Society for Evolutionary Biology), BacNet 2010 (Spain), Society for Applied Microbiology, European Federation of Biotechnology.
- Opening and closing public lectures by theme leaders.

11. What difference will be generated by running the theme for 6 or 12 months?

This theme requires a 12-month timescale to achieve its goals. Even though a fledgling community has developed around the StoMP network over the last 3 years, getting people to work together towards a consensus roadmap on the future directions of the field will take time and require a series of focused meetings. For this reason the three small workshops and one larger meeting that we propose are really necessary; organising such a programme within a 6 month period would not be feasible.

12. Is the topic of the theme so specific that it can really all be "tied up" in 6 or 12 months time, or should there be some follow-on? If so how might the follow-on be funded?

This one-year programme should be enough to achieve consensus on a roadmap for future directions in the field, and to develop collaborations to a sufficient level to support coherent and credible multi-

investigator projects. We also plan a programme of biennial training workshops, for which we will seek BBSRC funding. We are not sure at this stage whether we will seek to continue research network activities after August 2011: if so, one option would be to apply for funding from the European Science Foundation.

13. Are there opportunities for co-funding from other sources?

We have agreed co-funding from NAIS for our workshop on modelling large-scale networks: NAIS will provide funding for 1-2 extra speakers to present a computational algorithms perspective at this event. It may also be possible to combine resources with the EPSRC-funded MMEMS network (see Section 4) – however it is unclear at this stage whether MMEMS will continue to be funded in 2010-2011.

14. Please provide a high level project plan with milestones and the resources being applied for.

Project plan

This theme will be structured in three parts:

Part 1: Detailed planning (August 2010):

During this period the leaders and editorial group members will (either in person or via virtual meetings) finalise arrangements for the workshops and plan the structure and organisation of the roadmap.

Part 2: Focus workshops (September 2010 – January 2011):

During this period we will organise three workshops to develop ideas for the roadmap. For the detailed organisation of these workshops see Section 10 above.

- (i) “Modelling stochastic effects in microbial cells and populations” (~20 people, ~2 days + 1-2 days pre-meeting and ~1 day post-meeting of editorial group, lead organiser: Rosalind Allen)
- (ii) “E-volution” (~20 people, ~2 days + 1-2 days pre-meeting and ~1 day post-meeting of editorial group, lead organiser: Dov Stekel)
- (iii) “Modelling large-scale molecular and metabolic interaction networks” (~20 people, ~2 days + 1-2 days pre-meeting and ~1 day post-meeting of editorial group, lead organiser: Jamie Wood)

Milestone: For each workshop, production by the editorial group of a report on key research challenges and future directions in this area. This report will be used in the roadmap document.

Part 3: Preparation of the roadmap (February - May 2011): Combination of the workshop findings into a roadmap document. This will involve at least one meeting of the combined editorial groups from all three focus workshops. At this stage the editorial team will also decide on a strategy for submission of the roadmap as a journal article.

Milestone: Completion of the roadmap document.

Part 4: Larger dissemination workshop (June 2011): Research workshop / conference (~100 people, ~4 days, to be jointly organised by RJA, DJS and AJW). This will include all the above three focus areas. This workshop will allow dissemination of the roadmap to the wider modelling and microbiology communities and allow us to seek endorsement from the wider community for the contents of the roadmap. This workshop will also provide an opportunity to consolidate plans for collaborative research projects and proposals arising from the smaller workshops.

Milestone: Report detailing the conference outcomes, to be publicised via the web, together with webcasts of the workshop contents, produced with appropriate technical help from the eSI team.

Part 5: Final editing of roadmap article and final reporting (July 2011)

Final editing of the roadmap document based on workshop outcomes and circulation among the community via the web and email lists. Appropriate formatting of the roadmap for journal submission (we note that depending on the choice of journal, final submission may take place after the end of the theme period).

Final report on theme activities, to be publicised via the web.

Resources

Theme Leader: Rosalind Allen (15% FTE for 12 months)	
Theme co-leader: Dov Stekel (10% FTE for 12 months)	
Theme co-leader: Jamie Wood (10% FTE for 12 months)	
Budget for theme leaders and visitor travel	£7000
Cost of 3 small focused workshops	3 X £6000 = £18000
Cost of 1 larger workshop	£20000
Budget for posters and advertising	£1500

Total: £58393