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Introduction: statistical mechanics of molecular and cellular biological systems

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This issue of *Interface* contains a set of papers linked to a remarkable programme of research collaboration held at the Isaac Newton Institute for the Mathematical Sciences, Cambridge, UK in the first 6 months of 2004. The Newton Institute opened its doors for 'Statistical Mechanics of Biomolecular and Cellular Systems' (or 'SMC') after 3 years of preparation by the organizers to make sure that the ripest topics were raised, the right people were resident, and that the period contained a balance of workshops and unstructured time for discussing and thinking. The Institute's funding (from the Engineering and Physical Sciences Research Council and additional support from BBSRC and MRC, UK) allows each programme to host about 20 resident visitors at any one time, encouraging them to spend as long as possible at the Newton Institute so that major collaborative projects can be taken well beyond their initial conceptual stage. The building itself is highly conducive to this idea: all individual offices open to a roomy and well-lit *atrium* well-supplied with chalkboards and coffee! Many highly mathematical programmes work by concentrating the 20 experts in one field worldwide into the same place at a critical developmental stage of their subject. SMC was rather different. Conceived when the members of the community of 'soft matter physics' were beginning to apply methods from statistical mechanics to the complexities of molecular and cellular biology for the first time with some promise, it also had as a declared aim to sit very close to experiment, and to introduce biologists, mathematicians and theoretical physicists in a context that would allow time to develop a shared language. It sought to realise the direct etymology of 'interdisciplinary': to teach each other things.

We structured the programme around four broad themes of increasing complexity: (i) single molecule biophysics; (ii) molecular motors; (iii) membranes; and (iv) gene networks and signalling. No-one was prohibited from working on any area at any time of course, but a nucleus of people with special interests in each were invited at critical stages as the programme progressed. The six months also contained several memorable conferences and workshops: an open-ended question-poser during the first week, workshops on motors, membranes, consequences of evolutionary thinking and protein-folding. In addition, a NATO Advanced Study Institute was held as a satellite event in Edinburgh, covering the application of soft matter physics to biological problems at the graduate level. Holding the programme in Cambridge proved to present other strong advantages due to the presence of several leading centres of molecular biology embedded within the local University. Many local researchers became very regular visitors to the Newton Institute. On several occasions when a system of interest emerged unanticipated, we realised that to make progress we needed a thorough 'tutorial' from an expert biologist. In most cases, there was one on our doorstep and in most of those he or she was more than willing to come and discuss their great academic love—even with ignorant, if eager, physicists. The usual response to our thanks at the end of the day was intriguing: 'No, it was interesting—you asked questions that I've never heard asked before.' As one of our American visitors summed up, the programme introduced people 'who wanted to meet each other but didn't know it.'

It proved irresistible to find out what had happened one year on to the problems that the participants (over 100 in total) began working on in Cambridge. Equally tempting was the idea to gather some of the results together in an issue of *Interface*, since the new journal embodies much of the same philosophy as the SMC programme. It too is becoming a (virtual) place where biological and physical scientists feel equally at home, and where imaginative and novel ideas feed both disciplines. Of course, many of the programme's results have been and are to be published elsewhere, but the fascinating collection in this volume constitutes both a representative and highly stimulating selection.

Capturing the flavour of the 'single biomolecule' aspect of the programme in very different ways are the contributions of Hawkins and McLeish (2005) and of Cutello, Narzisi and Nicosia (2005). The first picks up the theme of allostery—a biomolecule's capacity to transmit information on substrate binding between distant sites. It is this feature that allows signalling networks to be constructed from allosteric proteins, each one acting as a logical element. Dennis Bray's research group in Cambridge regularly raised the issue during the programme, but the particular application

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to the dynein coiled coil arose when the authors heard about the puzzles of this system at a SMC workshop presentation given by Peter Knight, a biologist from their own university (Leeds)! The paper also introduces a constant theme of the programme: the question of what appropriate coarse-graining of biomolecular systems is appropriate for generating understanding. The contribution from Cutello *et al.* arises from the long-standing problem of protein-folding—or problems as the authors would have us realise. Although appearing at several points in the programme, protein folding was the subject of an intensive week where a very international mix of experts in the field took the opportunity to evaluate the search for a protein's native state from some fresh theoretical and experimental perspectives. Several fundamental issues were raised: whether the real surprise is that proteins fold as *slowly* as they do, the connection between kinetic and thermodynamic data, whether low-dimensional representations of the energy landscapes for folding are hopelessly naïve. The present paper takes up the theme of the best optimisation pathway for structure prediction, without necessarily assuming that this has anything to do with the real kinetics of folding.

The paper by Schilstra and Martin (2005) is a good representation of the advances made in modelling the behaviour of biomolecular motors during the programme. It shows again how a coarse-grained picture of a biomolecular system, in this case comprised of a motor (myosin V) and track (filamentous actin) may be developed to display subtle stochastic behaviour. It also raises by implication the issue of 'design' criteria for systems under cellular and functional constraints. The length and elasticity of motor arms was one example cited in the course of a memorable day devoted to evolutionary thinking during the programme, as candidates for 'fast' evolutionary variables that might be expected to optimize a functional aspect, such as processivity.

The other contributions to this volume introduce emergent phenomena in different ways. At the purely physical level, the fascinating rheology of inter and intra-cellular media was a focal point of several discussions (the advances in the theoretical dynamics and rheology of very stiff polymers that has emerged from biological physics is now well-known). The contribution by Oates *et al.* (2005) treats the remarkable case of synovial fluid, reporting on the experimental work of three US groups that was discussed in the programme. It seems to furnish a beautiful example of flow-induced aggregation that involves the subtle interaction of polysaccharides and proteins. At the same time, the work illustrates the power of rheological experiments combined with direct structural probes, in this case small-angle neutron scattering (SANS).

Protein signalling networks received increasing attention during the programme, each group of participants bringing their own perspective to the problem. Two such individually flavoured contributions are from Ogunnaike (2005) and from Radulescu *et al.* (2005), the first using the conceptual tools from chemical engineering, the second from graph theory. The first develops a model of coupled ODEs, then embeds it in an ensemble subject to stochastic forcing, to explain apparently contradictory data on a DNA repair system. The second takes a more abstract view yet of general biochemical networks, employing loop decompositions to make predictions about two important signalling networks, one prokaryotic and one eukaryotic. A surprising amount can be inferred from the topological properties of a regulatory network and its subnetworks, and the methods point towards a systematic way of simplifying very complex networks. The stylistic differences of these two closely related papers (the first contains a 'control system block diagram', the second structures itself around 'lemmas" and 'corrolaries') reminds us of how much 'interfacing' of language is also required in our task!

The final paper (Ben-Jacob & Levine 2005) marks the visit of Ben-Jacob to the programme, and reviews the even higher level organization of bacterial colonies in stressful environments. The theme of successive coarse-graining is taken a step further, in which the irreducible agents of the models are bacteria themselves. Ben-Jacob and Levine review the beautiful patterns exhibited by the colonies, and point towards the very topical application of evolved resistance to antibiotics.

The point of the Newton Institute programme was to allow interaction to both enrich but also divert (some would say subvert) individuals' research programmes. I hope that this selection of results one year on begins to illustrate how this happened. Readers who watch these pages carefully may be able to trace longer-term results from those fascinating six months in future issues, but in any case will by doing so be participating in the same stimulating activity that forces us to listen and try to understand another's language and questions, and by communicating our own to bring new light on the wonderful complexity of life.

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