2.1 Topic

The methods of atomistic simulation at the level of Molecular Dynamics (MD) are becoming ever more powerful, both due to the increasing amounts of computational power available, and to the improvement of the algorithms that are used. Nevertheless there are many contexts where the length and time scales arising in the physical, chemical and biological questions of interest remain entirely beyond the capabilities of MD simulations, and will remain out of reach for the foreseeable future. Thus there is a need for reduced-order descriptions. Reduced-order models can provide insights and numerical simulations for larger length scales and longer time scales, but at the cost of discarding some level of detail. The issue is to retain the appropriate level of information so as to be able to address the fundamental scientific questions of interest in a meaningful way.

One possible avenue to such reduced-order descriptions is provided by the methods of continuum mechanics. If a problem can be cast into the general framework of a continuum model there is a large, mature and extremely powerful body of work involving mathematical analysis and computational methods that can often be applied to great effect. However the traditional domains of application of continuum models have been macroscopic, at length scales of millimetres or more. In recent years there has been much activity in the mechanics and applied mathematics communities aimed toward applying classical continuum mechanics techniques at smaller and smaller scales, from micro-structure and models of grain structure in crystals, down to truly atomistic scales.

The main mathematical issues in relating continuum models to atomistic systems arise in identifying the appropriate averaging or homogenization techniques to obtain effective models at the dominant length and time scales. Discrete atom locations must be appropriately "smeared" in space to obtain continuous displacement fields, while very fast small-amplitude oscillations must be appropriately "smeared" in time to leave only larger amplitude, longer time-scale motions. Appropriate notions of stress (i.e. the appropriate continuum measure of the forces acting), and of strain (i.e. the appropriate continuum measure of the deformations arising) must be identified. Most importantly the constitutive relations that relate the stresses and strains within any continuum model should be derived from atomistic level information.

The previous three paragraphs are, verbatim, the first three paragraphs of the Scientific Proposal for a previous Mte Verita conference ``Atomistic to Continuum Models for Long Molecules and Thin Films," which was held in 2001 (see http://lcvmwww.epfl.ch/~lcvm/ascona2001/index.html). The message of the previous paragraphs has only been reinforced in the five years since they were written. The fields of Nanoscience and Nanomechanics have taken on their own identities, numerous conferences and workshops have been held, and dedicated funding programmes established throughout the world. Single molecule experimental techniques applied to DNA and proteins involving various kinds of microscopy and manipulation techniques, such as optical and magnetic tweezers, as well as new observation techniques such as FRET, have generated large volumes of experimental data on the nanoscale properties of

individual large biomolecules and biomolecular complexes. The explosion in available data magnifies the need for detailed models of the systems being studied in order to allow passage to the quantitative study of the physical behaviour of large biomolecular systems. In the same time frame the power of computers has increased enormously, but still for bio-macromolecules full atomistic simulations can provide only partial answers, and there is an ever more pressing need for multi-scale models of the nanomechanics of biomacromolecules.

This proposal can be regarded as requesting a sequel to the 2001 meeting, but with the following changes in emphasis. First the focus will be shifted away from the mathematical techniques underlying a wide variety of systems, to the more comprehensive study of specific biomolecular systems, starting from experimental data, through analytic and computational modelling, to quantitative interpretation of the model predictions. Concomitantly the attendees will be drawn more equally between applied mathematicians, mechanicians, biophysicists, biochemists, and molecular biologists, and between experimentalists, analytical modellers, and numerical simulators.

The mechanics of DNA will continue to be a central theme in the second conference. Standard models of DNA predict that it is strongly resistant to significant bending over length scales shorter than a persistence length (~150 bp). Yet DNA in biology is often bent much more tightly, and this tight bending is essential for function. For example DNA is sharply bent in prokaryotic regulatory complexes, such as in the 113 bp loop between OE and OI in the gal operon of E. coli, which contributes importantly to gene regulation. And most of the genomic DNA of eukaryotes is sharply bent by structural proteins in nucleosomes (into 80 bp superhelical loops), which regulate the accessibility and proximity of other DNA functional sites. Double stranded DNA is also sharply bent when stored inside viruses.

Existing computational models of DNA disagree both with each other, and with experimental data, in this biologically relevant, tight looping regime. These discrepancies may be explicable by particular sequences at the scales of 5--10 bp or longer with exceptional mechanical properties, such as intrinsic curvature, stiffness or proclivity to denaturation. A-tracts and TATA boxes are candidates for such mechanically special motifs, but even in these two well-known cases the pertinent phenomena are not clear, and the time and length scales are already such that multi-scale modelling is necessary. During 2004 there has been much work, both experimental, analytical modelling and numerical simulation, in a related direction namely considering the possibility of extremely localized DNA kinking (which was a phenomenon first suggested as perhaps being important in the biological function of DNA by Crick and Klug in 1975). One of the goals of the conference will be to establish interdisciplinary interactions between workers that can enhance understanding of the sequence-dependent nano-mechanical properties of highly deformed DNA fragments in specific contexts that are known to be biologically important.

One of the significant and concrete consequences of the 2001 meeting was the establishment of the Ascona B-DNA Consortium (or ABC) which is a collaboration of

ten (and growing) laboratories throughout the world concerned with the Molecular Dynamics (MD) simulations of DNA. The Human Genome project has provided a more or less complete listing of the approximately 3 *billion* base pairs of DNA that are present in each cell of your body. However current state of the art MD atomistic simulations of DNA are limited to a few *tens* of base pairs for some tens of nanoseconds. Thus to understand the biological function and intricate storage and replication mechanisms of DNA and RNA it is widely accepted that it will be necessary to develop models and simulations using coarse-grained or effective models at meso-scopic scales above the atomistic, but which retain the all important sequence information. But there are, for example, 136 independent possible tetramer sequences of the four bases, which means that comprehensive numerical simulations that scan all possible sequences for their mechanical properties are still prohibitively large for a single research group to achieve. The ABC consortium has as its objective the construction of a uniform database of MD simulations of DNA fragments containing multiple instances of all possible tetramer sequences, specifically in the first phase, simulations of 39 15-mers, which when divided between ten labs means that the necessary computational resources are no longer daunting. A first database (of around 0.5 terabytes describing 15 ns trajectories) has been established, and the analysis of this comprehensive set of data has already lead to surprising conclusions, described in multiple joint group publications, as well as additional individual groups'analyses exploiting the shared data base. The collaboration has continued and regular meetings have been held subsequent to Ascona in 2001, namely Lausanne in 2003, Como in 2004, and Minneapolis 2005. These short meetings have all been run in conjunction with a larger conference, and we would plan to devote half a day or so of the proposed meeting to the ABC 2006 discussions.

Many of the same experimental techniques that have yielded detailed information about the nanomechanics of individual biological macromolecules are also providing a wealth of information about the physical mechanisms by which cells divide, move and regulate their function. Rather than the study of individual macro-molecules, the emphasis then switches to the studies of assemblies of molecules that make up the filaments and molecular motors that make a cell work. Many of these assemblies are incredibly intricate nano-machines. For example various bacterio-phages pack viral DNA for storage in a very efficient and highly organized way, using a molecular motor at the neck of the head cavity to coil the DNA. Then, when the DNA is to be inserted into the victim cell, a neck injects itself through the cell wall using a phase transition in the material making up the neck, and the DNA uncoils itself at very high speeds once the restraining molecular motor is disengaged. Again there is a wealth of experimental information available on such systems, but the development is just beginning of the rigorous continuum mechanics models that seem necessary to provide a quantitative understanding of the phenomena.

Finally advances in the uses of fluorescent dyes and confocal light microscopy have allowed several groups to observe the three-dimensional dynamics of known points along the chromatin fibres in the nuclei of living cells. We propose to devote part of this conference to presentations describing these experiments and the development of models that will allow quantitative interpretation of the available data.